The Economic Burden of Extended—Release Pharmaceuticals in Minnesota

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Abstract

Many drugs come in two forms, immediate—release and extended—release, that are differentiated by the way the drug is released. Immediate—released formulations of drugs release the active ingredient immediately after administration. On the other hand, extended—released formulations have a prolonged release period. Compared to immediate—release formulations, extended—release formulations reduce patients' dosing frequency but are often more expensive. We examined spending on a sample of drugs where extended—release formulations of the drugs offered no novel therapeutic benefit and decreased daily dosing frequency by no more than one pill compared to immediate—release formulations of the drugs. We projected potential cost savings for patients and insurers under four hypothetical scenarios involving switching some portion of extended—release formulations to either branded or generic immediate—release formulations using 2012 and 2016 data from the Minnesota All Payer Claims Database. We calculated total days supplied, insurer spending, and patient spending by formulation, adjusting for estimated insurer rebates. Our analytic sample included over 272 million days of therapy for 18 drugs across the two years of data. While the use of extended—release formulations varied across payers and years, extended—release formulations made up a disproportionate amount of total spending for different payers and patients. Overall, we found that patients and insurers could reduce their spending by up to 35% and 58%, respectively, by substituting extended—release formulations with therapeutically equivalent and minimally burdensome immediate—release formulations. Motivated by our results, we propose a pilot program allowing pharmacists to replace extended—release formulations with therapeutically equivalent immediate—release formulations for the 18 drugs in our sample.

Introduction

The United States spends approximately twice as much as other high—income countries on prescription drugs, and this spending is primarily driven by the high prices of brand—name drugs [1]. The state of Minnesota is no exception. In 2017, Minnesota spent approximately $5.2 billion on retail prescription drugs [2]. The high cost of prescription drugs financially burdens both patients and payers, and can be a major barrier to medication adherence [3]. In a 2019 survey of Minnesota residents, 15% of respondents reported not filling a prescription due to expenses, and 51% expressed "deep concern" over high prescription drug costs [4].

A recent paper published in *JAMA Network Open* by Sumarsono et al. (2020) proposed a novel approach to reduce prescription spending: switching patients from extended—release (ER) drug formulations, which release active ingredients over a prolonged period, to therapeutically equivalent immediate—release (IR) formulations, which release medications immediately and require more frequent dosing but are also less expensive [5, 6]. The authors found that Medicare and Medicaid could save $13.7 billion between 2012 and 2017 if all patients who received ER formulations switched to generic IR formulations [5]. The objectives of our study were to examine the spending on ER formulations in Minnesota and estimate the potential savings to insurers and patients associated with switching from ER to IR formulations, focusing on the subset of drugs specified by Sumarsono et al. (2020).

Many drugs exist in both IR and ER dosage formulations and, when taken correctly, ER and IR formulations generally achieve the same clinical benefits [7—9]. With

ER formulations patients take fewer pills compared to the equivalent IR formulation, due to the slower release associated with ER formulations. Accordingly, ER formulations are often touted for enhancing medication adherence and improving quality of life, especially for patients with chronic conditions that require frequent doses. However, the evidence supporting these claims is mixed and drug—specific [7, 8]. For example, there is no difference in adherence between once—daily dosing and twice—daily dosing of carvedilol in patients with heart failure, while ER quetiapine fumarate is associated with improved adherence in patients with major depressive disorder relative to its IR formulation counterpart [7, 9].

ER formulations are often priced much higher than IR formulations, even when their effects are therapeutically equivalent [6]. The high prices of ER formulations often result from pharmaceutical manufacturers' ability to obtain a new patent related to the same molecule – but in an ER form of the drug. This strategy allows manufacturers to prevent generic competitors from entering the market and maintain market exclusivity, enabling them to charge brand name prices even after their IR drug patents expire [1, 10, 11]. The higher costs associated with ER formulations can offset any potential benefit from improved medication adherence associated with lower dose frequency, and may even increase nonadherence if patients cannot fill their prescriptions due to cost [3, 12]. The cost barriers created by ER formulations may disproportionately impact low—income populations, who report the affordability of prescription drugs as one of the main barriers to accessing medical care [3, 13].

This study provides some of the first estimates of the potential reductions in spending for patients and insurers associated with switching from ER formulations to therapeutically equivalent IR formulations. Prior work in this area has not differentiated savings to patients and insurers, and has focused only on patients enrolled in Medicare Part D and Medicaid [5]. However, given the complexity of prescription drug benefits, patients and insurers may not experience similar savings when patients switch to cheaper prescriptions [14]. Additionally, since government—sponsored insurance plans differ in their benefit design compared to commercial plans, this prior work may not be generalizable to patients with commercial insurance. We address these two gaps by calculating savings using newly released data from an all—payer claims database (APCD). Unlike most publicly available claims databases, APCD collect detailed data from many different insurers [15]. This allowed us to separate savings both by patient vs. insurer and across insurance types (including both government—sponsored and commercial plans).

Most states do not allow pharmacists to substitute ER formulations for IR formulations—even in cases when the two are therapeutically equivalent and the IR formulation is less expensive— due to safety concerns for some drugs [16]. Based on the findings of this study, we propose a policy that allows pharmacists to substitute ER formulations with IR formulations for a subset of drugs where the two formulations are therapeutically comparable, to relieve the financial burden of ER formulations.

Methods

Data

Our data came from the prescription drug public use files from the Minnesota APCD from calendar years 2012 and 2016. Minnesota APCD collects administrative claims data from almost all insurers in the state, with a few exceptions (i.e., TRICARE, Indian Health Services, Veterans Affairs, self—insured employers, and prescription purchase without the use of insurance). The prescription drug files aggregate information associated with national drug codes in the APCD to the year—payer level for three distinct payer groups: commercial insurers, Medicare, and insurers for Minnesota Health Care Programs (MHCP), which include both Minnesota's Medicaid program and a basic health care plan for patients between 138% and 200% of the federal poverty guideline [17]. The files include information on total quantities, patient spending, and insurer spending for drugs at the payer—year level.

The different payer—years represented in the Minnesota APCD public use files vary substantially both across payers and over time. Patients covered by different payers vary in terms of demographic characteristics, given that Medicare primarily provides insurance for the elderly while commercial payers are more likely to cover children and working age adults. These patients also experience different cost sharing structures; patients enrolled in MHCP have almost no co—pay or co—insurance requirements to access prescription drugs compared to patients enrolled in commercial plans or Medicare. Furthermore, the patient composition in these groups has also varied across time, due to Gobeille vs. Liberty Mutual decision on claims data submission to APCD as well as changes in eligibility for different programs due to the Affordable Care Act [17]. As such, the data from the APCD public use files do not facilitate meaningful longitudinal comparisons.

ER and IR drug formulations

Given that switching all ER formulations to IR formulations would be unrealistic and clinically inappropriate in some cases, we only examined a specific group of drugs identified by Sumarsono et al. in their 2020 study [5]. The ER formulations of the drugs included in this analysis are not used for treating a particular disease and do not offer novel therapeutic benefit compared to the IR formulations, as determined by a physician review of existing clinical evidence [5]. In other words, a patient would be no better off from a clinical perspective by taking the ER formulation of the drug as opposed to the IR formulation of the same drug. In addition, the ER formulations of the drugs in this study save at most one additional daily dose, meaning there is not a substantial difference in dosing frequency between the ER and IR formulations. Lastly, we excluded drugs that entered the market after 2012, since 2012 is our first year of data. The final list of drugs for our analysis included 18 drugs across two broad therapeutic areas, including carvedilol, fluvastatin, glipizide, isosorbide mononitrate, pioglitazone, metformin HCL, propafenone HCL, dexmethylphenidate HCL, dextroamphetamine sulfate, fluvoxamine maleate, galantamine hydrobromide, lamotrigine, lithium carbonate, memantine HCL, paroxetine HCL, quetiapine fumarate, topiramate, and zolpidem tartrate. Cardiometabolic drugs (drugs with cardiovascular and diabetes indications) and central nervous system drugs represented 61% and 39% of the total sample, respectively.

Data analysis

To estimate total cost savings, we calculated quantities of ER and IR formulations in terms of total days of supply ("days supplied") for each payer—year. Using days supplied instead of a count of prescriptions or total units of supply allows for direct comparisons of quantities between ER and IR formulations. Under the assumption that patients continued to receive the same quantity of drugs but at the average cost associated with IR formulations, we then calculated savings to patients and insurers by estimating reductions in spending using the following formula [5]:

$$\textit{Estimated savings} = (\textit{Average cost of ER formulations} - \textit{Average cost of IR formulations}) \times \textit{Total days of supply of ER formulations}$$

Given that ER formulations are more likely to be patent protected than IR formulations and thus less likely to face generic competition [11], patients who switch from ER formulations to IR formulations may be newly able to switch from brand—name to generic drugs as well [5]. Thus, we simulated insurer and patient savings projections in four different potential cost saving scenarios: (1) if patients were to switch 25% of ER formulations to IR formulations while maintaining the same proportions of branded and generic drugs, (2) if patients were to switch 75% of ER formulations to IR formulations while maintaining the same proportions of branded and generic drugs, (3) if patients were to switch 25% of all drugs other than generic IR formulations to generic IR formulations, and (4) if patients were to switch 75% of all drugs other than generic IR formulations to generic IR formulations.

While we observed insurer spending on drugs at the point of purchase, administrative claims data do not incorporate rebates later received by insurers from manufacturers. Therefore, simply summing insurer spending would overestimate the true cost borne by insurers. However, data on pharmaceutical rebates are rarely disclosed by manufactures and insurers. Accordingly, we reviewed relevant literature to generate approximate rebate percentages for different payers. We relied on a report from the Government Accountability Office that found rebates accounted for roughly 12% of total Medicare Part D spending in 2012 and 20% of spending in 2016 [18]. We accordingly assumed rebate percentages in 2012 and 2016 were 12% and 20% of prescription drug costs at the point of purchase, respectively, for both the Medicare population and the commercial population. The estimation of the rebate percentages for MHCP was more complicated because the programs include both Medicaid programs that employ the basic federal rebate formula and the selected programs for seniors. Under the basic federal rebate formula, the rebate rate is 13% of the average manufacturer price for generic drugs and the greater of 23% of average manufacturer price or the average manufacturer price minus the best price for brand—named drugs. MHCP also require additional rebates for brand—named drugs if the price of the drug increases faster than the consumer price index. Furthermore, Minnesota has negotiated supplemental rebates beyond the basic federal rebate with manufacturers who want their drug to be placed on a preferred drug list [2]. For simplicity, we assume a 23% rebate percentage for all branded drugs and a 13% rebate percentage for all generic drugs for MHCP in both 2012 and 2016.

Results

Use of ER drug formulations

The 18 drugs included in this analysis represented over 272 million total days of therapy. The use of ER formulations

varied across payers and years, ranging from 16% to 27% of total days supplied for different payers and years (**Figure 1**). Seven of the 18 drugs in our sample did not have a generic ER formulation available in 2012, and three of the 18 did not have a generic ER formulation available in 2016.

While ER formulations accounted for a small portion of total days supplied, they contributed substantially to total insurer spending, as seen in Figure 2. In 2012, 20% of Medicare spending, 34% of MHCP's spending, and 43% of commercial insurers' spending on the drugs in our sample were attributed to ER formulations. In 2016, ER formulations made up over 60% of total insurer expenditures on prescriptions, ranging from 61% for Medicare to 74% for commercial insurers.

After adjusting for rebates, ER formulations represented more than $80 million in insurer spending and a disproportionate share of insurer spending relative to their total quantities. Similarly, patients experienced higher costs associated with ER formulations, and the relative cost burden increased over time as seen in Figure 2. In 2012, ER formulations accounted for 21% and 32% of spending for Medicare and commercial patients, respectively. In 2016, ER formulations were responsible for 50% and 46% of spending for Medicare and commercial patients, respectively. Patients enrolled in MHCP had little cost burden associated with the drugs because of the plans' low cost—sharing. While ER drugs still accounted for a disproportionate amount of cost in patients relative to their days supplied, the gradient was less stark compared to the role of ER drugs in insurer spending.

Cost savings to insurers

Insurers could reduce spending by switching patients from ER formulations to IR formulations, with savings increasing as the proportion of drugs switched to IR formulations increases. Assuming no substitution to generic drugs, switching 75% of ER formulations to IR formulations would reduce insurer spending on the drugs in our analysis for commercial insurers by 12% in 2012 and 35% in 2016, and for MHCP by 2% in 2012 and 23% in 2016, as seen in **Figure 3**. Medicare would realize little cost savings by transitioning from ER to IR formulations without also substituting brand name formulations for generic formulations. All payers could realize greater savings if generic substitutions occurred concurrently with IR substitutions. If 75% of all non—generic IR formulations in our analysis were administered as generic IR formulations, commercial insurer spending would decrease by 45% in 2012 and 58% in 2016, Medicare spending would decrease by 41% in 2012 and 48% in 2016, and MHCP spending would decrease by 50% in 2012 and 51% in 2016.

Cost savings to patients

Patients would also save by switching to IR formulations, with greater degrees of IR substitution associated with greater savings; however, their potential savings would be smaller in both absolute and relative terms compared to insurer savings. Assuming no substitution to generic drugs, switching 75% of ER formulations to IR formulations would reduce patient spending on the drugs in our analysis for commercial patients by 6% in 2012 and 15% in 2016 and for Medicare patients by 3% in 2012 and 16% in 2016 **(Figure 4)**. Patients enrolled in MHCP face less cost sharing and would experience relatively small savings even with a large degree of IR substitution. Medicare and commercial patients could increase their savings if they switched from brand name to generic formulations in addition to switching from ER formulations to IR formulations. If 75% of all non—generic IR formulations in our analysis were administered as generic IR formulations, commercial patient spending would decrease by 23% in 2012 and 2016, and Medicare patient spending would decrease by 35% in 2012 and 26% in 2016.

Discussion

Using an all—payer claims database from Minnesota, we calculated potential savings to insurers and patients from switching patients from ER formulations to IR formulations of therapeutically equivalent drugs. Consistent with prior work suggesting that pharmaceutical firms use extended release formulations as an "evergreening" strategy to preserve market exclusivity and maintain higher prices [5, 10, 11], many of the extended release formulations in our sample did not have generic alternatives available. We found that insurers could reduce their spending by up to 58% and patients could reduce their spending by up to 35% by switching from ER to IR formulations on a subset of drugs previously studied. The greatest cost savings could be achieved if 75% of all drugs other than generic IR formulations were switched to generic IR formulations. These findings suggest that such substitutions are a possible tool for reducing spending for both patients and insurers.

This study is an important contribution to the prior work on the financial burden associated with ER formulations. Prior studies have characterized overall spending on ER versus IR formulations, without specifically considering how different stakeholders would be affected [5]. In this study, we were able to estimate savings to payers

(commercial, Medicare, and MHCP) and patients separately. We were also able to observe actual insurer spending on drugs at the point of purchase and accounted for insurer rebates. While we found that insurers would benefit the most from increased use of therapeutically equivalent IR formulations, we also found that patients would experience sizable financial benefits by switching from ER to IR formulations, especially by substituting drugs other than generic IR formulations for generic IR formulations. Reducing prescription costs is critical for addressing disparities in access to prescription medication. The high cost of prescription drugs is a major reason for underuse of medications in low—income populations and racial and ethnic minority groups, which could result in adverse consequences such as higher rehospitalization risk and unnecessary medical expenditures [19—22]. Hence, substituting expensive ER formulations with therapeutically comparable IR formulations can promote equitable access to effective medical care.

Based on the findings of this study, we recommend that policymakers in the state of Minnesota consider altering the current prescribing policy to allow pharmacists to substitute ER formulations with IR formulations for the 18 drugs examined in our analysis, conditional on discussing that decision with their patients. Currently, pharmacists can switch patients from branded prescriptions to a generic equivalent, but they cannot switch ER formulations **to** IR formulations, since ER and IR formulations are different molecules, and for some drugs (not included in our analysis) there are meaningful clinical differences between ER and IR formulations [23]. We propose that Minnesota begins by allowing this switch from ER to IR formulations for the 18 drugs in this study, since the IR formulations of these 18 drugs are as therapeutically effective as the ER formulations and do not substantially increase patients' dosing frequency For some patients, the benefits of taking one less pill per day may outweigh the additional financial cost associated with ER formulations. Pharmacists' discussions with patients should be framed around helping patients understand and weigh the financial costs associated with ER drugs relative to their benefits, with the ultimate goal of allowing patients to choose a formulation that best fits their needs. Increasing studies have demonstrated that patient—centered approaches that incorporate a patient's preferences and barriers can improve medication adherence, patient safety, and health outcomes [24—26].

We recommend that Minnesota roll out this policy across the state in a staggered fashion, progressively enrolling more counties over time**.** To improve equity in the rollout, the state should randomly assign counties different dates to adopt the policy, with the goal of eventually enrolling all counties. Similar staggered schedules have been used widely to introduce new health policies in Minnesota and other states [27—29]. Staggered implementation designs enable effective research and evaluation of new policies while minimizing ethical concerns associated with denying patients potentially beneficial treatments [30, 31]. This design would enable researchers to use data from the Minnesota APCD to directly evaluate changes in drug utilization, spending, and medication adherence associated with the introduction of the program. Conditional on observing a decrease in spending without a decrease in medication adherence, the state could then consider expanding the scope of the program and adding more IR formulations to the list of allowable substitutes to further increase savings.

This study has limitations. First, the Minnesota APCD prescription drug public use files do not capture prescription drug use from federal programs, limited—benefit plans, and uninsured patients. This limits our ability to generalize these results to other insurance populations. Substituting ER formulations for IR formulations of therapeutically equivalent drugs may benefit limited—benefit plan participants and uninsured individuals more because they are more likely to skip necessary drugs due to high out—of—pocket costs [32]. In addition, the public use files are only available for two non—consecutive years, 2012 and 2016. However, the fact that we observed similar magnitudes of savings in these two non—consecutive years despite the substantial change in the health care system between 2012 and 2016 suggests the high cost of extended release drugs is an enduring policy challenge.

Second, the estimated savings may underestimate the actual savings from switching to IR formulations more broadly. We drew on a prior study that carefully defined a set of drugs for which IR formulations could replace ER formulations. There may be many other drugs where IR formulations could reasonably substitute ER formulations, allowing for more savings for both patients and insurers. Third, the results aggregated at payer—year level may mask variation within the data, limiting our understanding of which specific drugs contributed most to savings. Fourth, while we believe the rebate percentages we applied are reasonable for our specific analyses and data setting, future research would benefit from a more careful and detailed accounting of rebates. Finally, our study only used data from Minnesota. The results might not be generalizable to other states**.**

Conclusion

This study sheds light on the potential cost savings associated with substituting ER formulations with IR formulations of therapeutically equivalent drugs. We found that switching patients from ER formulations to therapeutically equivalent IR formations with similar dosing frequency can significantly reduce Minnesota's spending on prescriptions. While insurers are likely to have greater benefits from this change, both insurers and patients could realize substantial savings. Allowing pharmacists to recommend IR substitutes may ease the financial burden resulting from expensive ER formulations for patients and insurers.

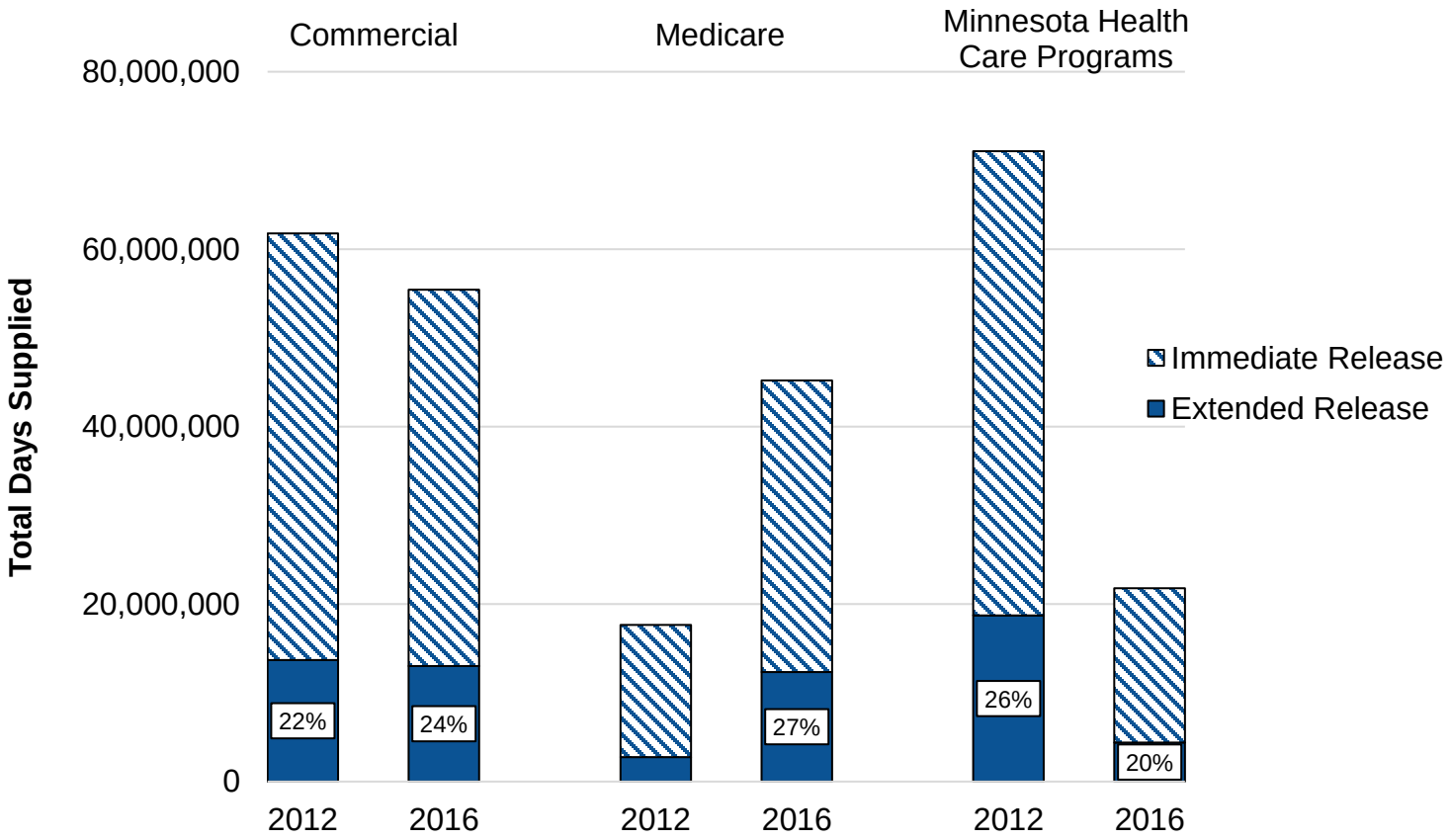

Figure 1: *Total days supplied of extended—release vs immediate—release formulations in Minnesota in 2012 and 2016 by payer.*

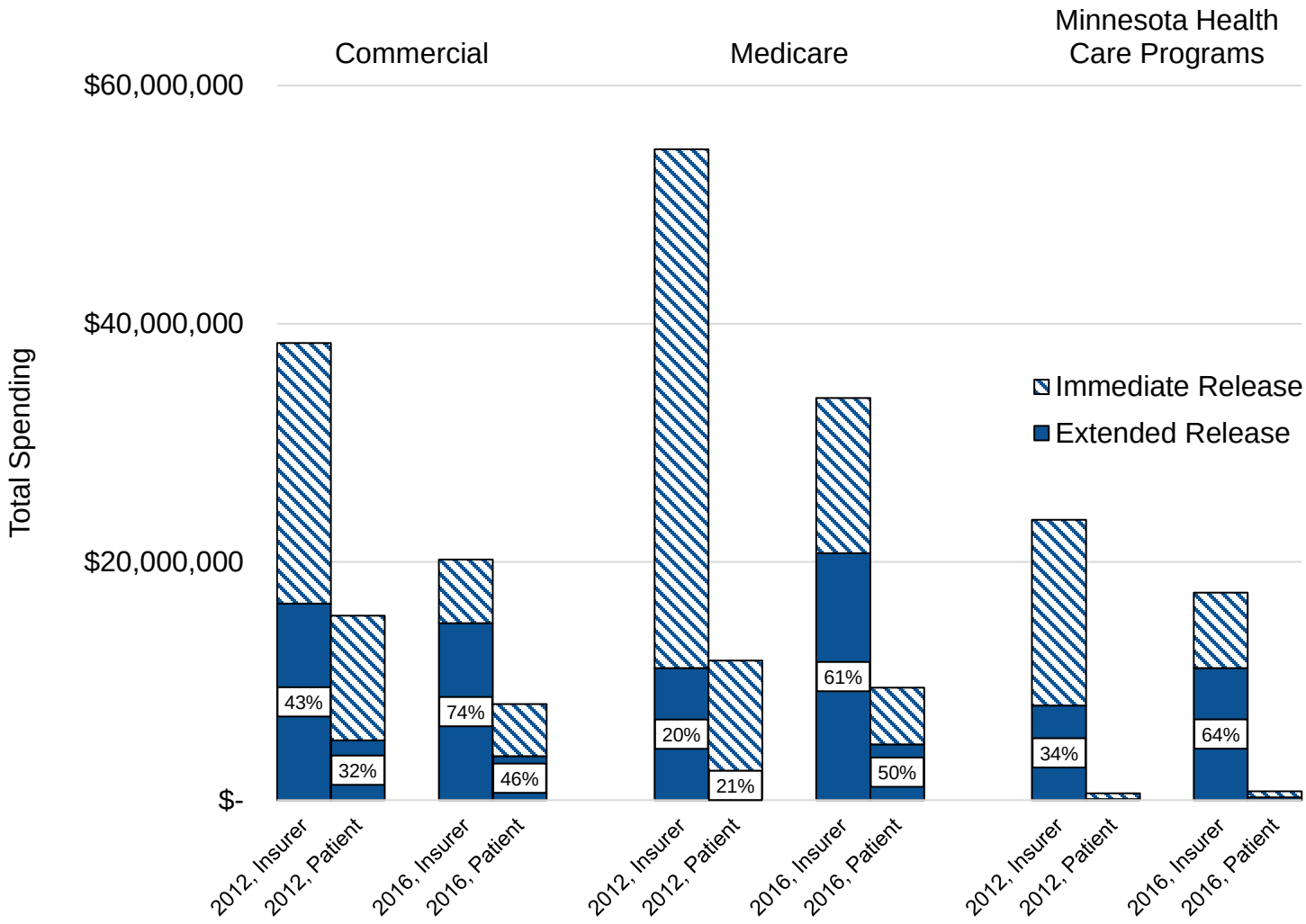

Figure 2: *Total spending on extended—release vs immediate—release formulations in Minnesota in 2012 and 2016 by payer and source of spending.*

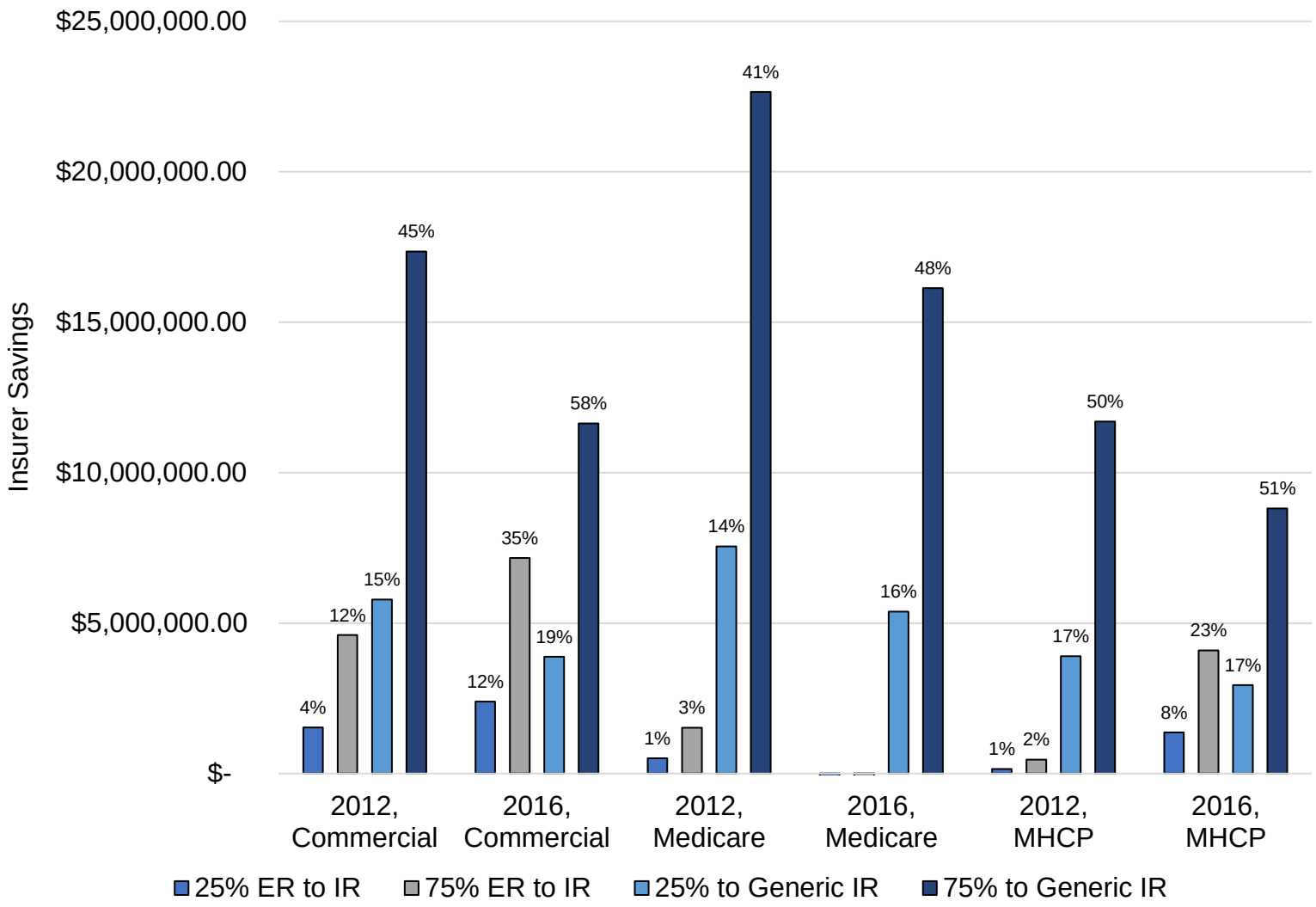

Figure 3: *The cost savings to insurers from switching extended—release formulations to therapeutically equivalent immediate—release formulations*

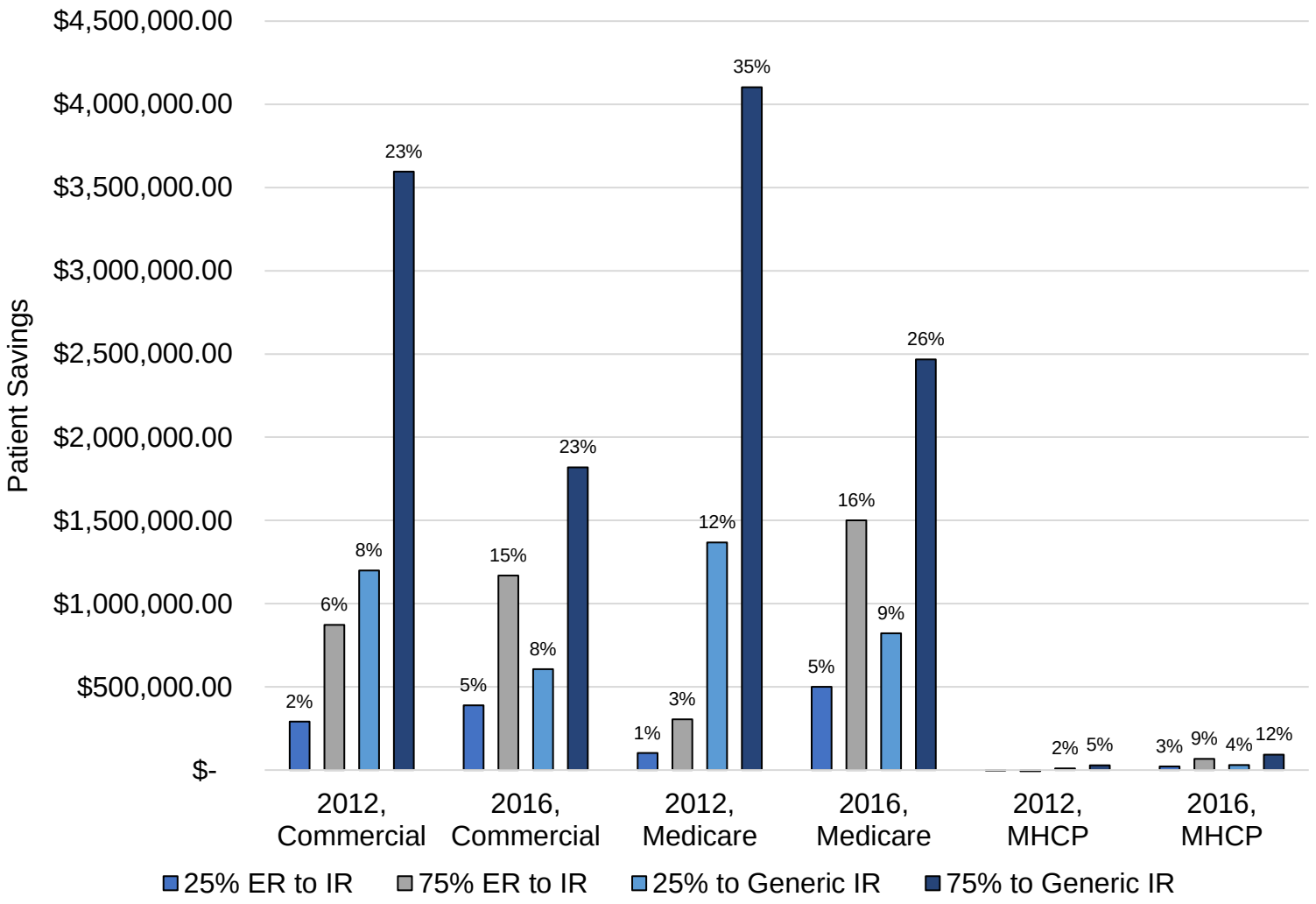

Figure 4: *The cost savings to patients from switching extended—release formulations to therapeutically equivalent immediate—release formulations.*

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