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LEADING ARTICLE

Restrictive Reimbursement Policies: Bias Implications for Claims-Based Drug Safety Studies

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Abstract Restrictive reimbursement policies—including those based on non-formulary drug status and prior authorizations—can create situations in which patients' use of prescription medications is not fully captured in administrative claims data. This can create bias in drug safety studies that depend solely on these data. An analysis in two Canadian provinces found that primary administrative databases captured only 61 % of dispensations of drugs for which restrictive reimbursement policies were in place. A subsequent simulation study found that, in certain circumstances bias due to exposure misclassification resulting from restrictive reimbursement policies can be quite large in analyses comparing outcomes between drug exposure groups. Investigators need to be knowledgeable about the data they analyze and know whether restrictive reimbursement policies are in place that might affect the capture of drugs of interest. It is also critical to understand the mechanisms by which restrictive reimbursement might cause bias in claims-based drug safety studies, the direction and magnitude of the potential bias, and strategies that could be used to mitigate such bias.

Key Points

Restrictive reimbursement policies can lead to substantial under-ascertainment of prescription drug use in administrative claims data

Under certain conditions, this missing information can cause or increase biases arising from misclassification and confounding in drug safety studies that rely on claims data

By understanding the mechanisms by which restrictive reimbursement might cause bias, investigators can anticipate the direction and magnitude of the potential bias and implement strategies that could be used to mitigate it

1 Introduction

Every observational study can produce valid results provided that all necessary study variables—including exposures, outcomes, and confounders—are measured accurately. However, observational drug safety studies are often criticized because of the potential for bias arising from unmeasured confounders [1]. Unmeasured confounding is a particular concern in studies based on administrative claims data, which are commonly used in drug safety research [2]. These data reflect transactional records of paid billing claims that healthcare providers submit to third-party payors for reimbursement for care provided to their beneficiaries [3]. They capture healthcare utilization information across a spectrum of care delivery

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settings, reflect "real world" care delivery processes and utilization patterns, and generally reflect data on large populations, enabling the study of rare adverse drug effects [4]. However, these data often lack information on potentially important confounders that do not generate billing claims, such as smoking status and body mass index.

Missing or imperfectly measured exposure and outcome information can also produce bias in observational studies. Administrative claims data are generally thought to provide fairly accurate drug exposure information [4]. However, a blind spot can occur in a payor's claims data when patients use drugs that the insurer does not reimburse, including over-the-counter drugs, such as aspirin, for which patients pay out-of-pocket. Prescription drugs are also sometimes paid for out-of-pocket and not reimbursed by the insurer. For example, for the past few years in the USA, several major chain pharmacies have been offering low-cost generic drugs for flat fees (so-called '$4 generics') [5]. Many patients fill prescriptions for these drugs without generating claims to their insurance companies. Free samples of prescription drugs also do not appear in claims databases, which may apply particularly to the first use of a drug so that outcomes occurring soon after initiation might not be appropriately attributed to the drug [6].

2 Overview of Restrictive Reimbursement

Restrictive reimbursement policies can also create situations in which patients' use of prescription medications is not fully captured in administrative claims data [7]. As a strict form of restrictive reimbursement, some insurers maintain formularies, or lists of drugs, that they reimburse, and do not pay for drugs that are not on the formulary. Prescription fills for non-formulary drugs usually do not appear in administrative claims databases. In these situations, patients still receive the prescription medication but either pay for it out-of-pocket or use another means of payment, such as supplemental insurance. When the Medicare prescription drug benefit was implemented in the USA in 2006, participating plans were required to cover "all or substantially all" drugs in certain categories, including antidepressants, antipsychotics, anticonvulsants, antineoplastic drugs, immunosuppressants, and antiretrovirals. However, many plans did not cover brand-name versions of certain drugs, including gabapentin, bupropion, and fluoxetine [8].

Less strict forms of restrictive reimbursement include limited use and prior authorization policies, which require patients to meet pre-specified clinical criteria before coverage approval (e.g., treatment failure or intolerance with first-line therapies) [9]. For example, prior authorization policies may require health providers to call, fax, or mail a detailed account of the patient's clinical history, justifying the use of the medication. Limited use policies are less restrictive than prior authorization policies, usually requiring a pharmacist to include a specific code when billing the third-party payor [10]. In 2009, Oklahoma Medicaid implemented a prior authorization policy for montelukast in which they required children to have tried treatment with an oral antihistamine for 14 days before reimbursing montelukast for allergic rhinitis [11].

While missing drug data due to restrictive reimbursement is a well recognized limitation of administrative claims data [4], little is known about the magnitude of under-reporting. In a recent analysis, Gamble and colleagues found a clever way to measure the extent to which administrative databases from two Canadian provinces miss use of prescription medications that are subject to restrictive reimbursement policies [12]. The investigators used administrative claims data in Manitoba and Saskatchewan to determine how many prescriptions for each of 75 drugs of interest were reimbursed in each province. They compared these figures to IMS sales data in these provinces, which provide an estimate of how many total prescriptions for these drugs were dispensed in these provinces, regardless of who paid for them. The investigators found that restrictive reimbursement can result in considerable under-capture of prescription drugs. Overall, the administrative databases captured only 61 % of dispensations of drugs for which restrictive reimbursement policies were in place. On a reassuring note, these databases captured 100 % of dispensations for drugs that were not affected by restrictive reimbursement policies. As expected, capture of drugs with the more stringent prior authorization policy was lower than capture of drugs with limited use policies. While it is not clear whether similar results would be observed in other healthcare systems, these findings provide compelling empirical evidence that administrative data can miss a large proportion of prescription fills for drugs that are affected by restrictive reimbursement policies.

3 Impact of Restrictive Reimbursement on Drug Safety Studies

Although Gamble and colleagues' [12] results are seemingly alarming, it is critical to understand the mechanisms by which restrictive reimbursement might cause bias in claims-based drug safety studies, the direction and magnitude of the potential bias, and strategies that could be used to mitigate such bias.

Restrictive reimbursement can cause mis-measurement of any study variable that relies on drug information. The following discussion will focus on the implications of

restrictive reimbursement when drug data are used to define exposures, but under-capture of drug information can also result in misclassification of confounder and outcome variables that rely on definitions involving drug use as a proxy for clinical conditions. For example, a commonly used claims-based definition uses diabetes drug prescriptions to define the presence of diabetes [13]. When confounder misclassification is non-differential with respect to exposures and outcomes, residual confounding will persist after adjusting for the mis-measured confounding variable. In some situations, differential confounder misclassification can actually increase bias after adjusting for the mis-measured variable [14].

In a second study, Gamble and colleagues conducted a simulation to assess the impact of the two key forms of restrictive reimbursement described above on bias due to exposure misclassification [15]. The authors based the analysis on a prior study comparing mortality among users of metformin versus sulfonylureas and among users of combination metformin and sulfonylureas versus sulfonylureas alone [16]. In the non-formulary scenario, the authors deleted all metformin prescriptions for a random sample of patients, creating a situation in which some patients were truly exposed to metformin but their metformin prescriptions were not captured in the claims data. In the special authorization scenario, the authors selected a random sample of patients and deleted their initial metformin prescriptions so that these patients appeared to be metformin users in the database but with misclassified metformin initiation dates. The authors found modest bias in the non-formulary scenarios, even under the fairly extreme situations where 50 % of metformin users were affected by the policy. Bias was much more extreme in the special authorization scenarios, yielding results for the most extreme parameter settings that were in the opposite direction of the original study results for the metformin versus sulfonylureas comparison.

While these results are very illustrative, and provide an assessment of the net bias that each scenario causes in each comparison, the results are also specific to the underlying study on which the simulation was based. Thinking through the various biases that misclassification can cause can help investigators assess the expected direction of the magnitude of bias that could result in their own studies. Figure 1 displays prescription filling patterns for five hypothetical patient types in Gamble and colleagues' study. Panel A represents the patients' actual prescription filling patterns. Type 1 patients are metformin monotherapy users and type 2 patients are sulfonylurea monotherapy users. Type 3 patients are combination therapy users. Type 4 represents those who initiate treatment with a sulfonylurea and switch to metformin and type 5 patients are those who initiate treatment with metformin and switch to sulfonylureas. Panel B reflects the observed prescription claims patterns for those patients affected by the metformin non-formulary policy, and panel C reflects the observed claims patterns for those affected by the special authorization policy.

By making explicit the actual versus observed prescription filling patterns of patients involved in each comparison, the potential biases become clear, but it also becomes clear that they depend on the design of the study. Let us assume that patients enter the respective studies at treatment initiation, as observed in the claims data, and contribute person-type only to the initial exposure category. For simplicity, let us also assume that combination therapy users (type 3 patients) initiate both drugs at the same time. Patients are censored when they add or switch to the other drug or discontinue the index drug. For example, if data were fully observed, types 1, 2, and 3 patients would contribute four prescription time units since

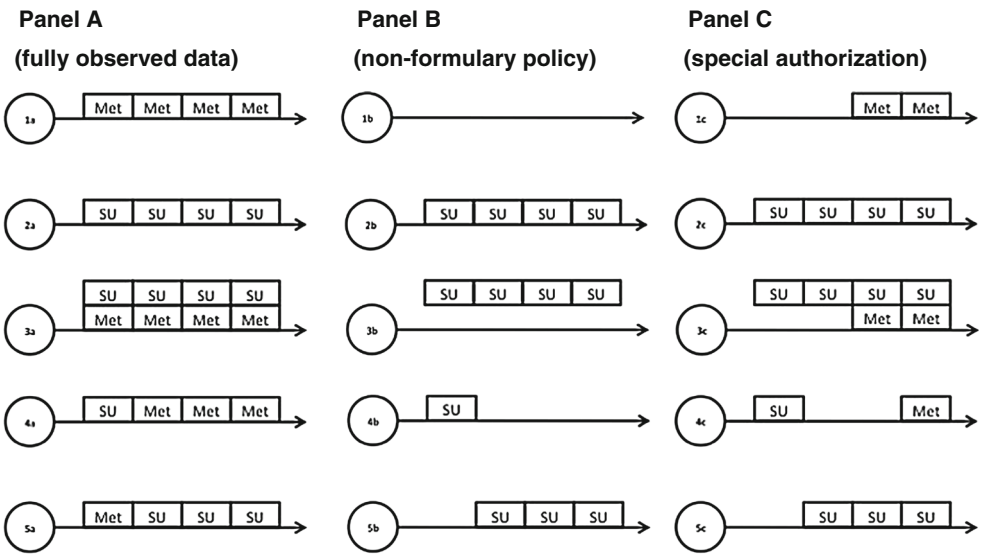

Fig. 1 Illustration of five patient types in hypothetical drug safety studies comparing metformin to sulfonylureas and combination metformin and sulfonylureas to sulfonylureas alone. *SU* sulfonylureas, *Met* metformin. *Panel A* shows hypothetical prescription filling patterns under fully observed data. *Panel B* reflects prescription claims patterns for patients affected by a hypothetical metformin non-formulary policy. *Panel C* reflects prescription claims patterns for those patients affected by a hypothetical metformin special authorization policy

they initiated treatment and remained on that treatment for four observed prescriptions. Types 4 and 5 patients would contribute a single prescription time unit because they initiate treatment but switch drugs after the first prescription.

3.1 Metformin Monotherapy versus Sulfonylurea Monotherapy

Under fully observed data, a study comparing metformin monotherapy to sulfonylurea monotherapy would involve comparing type 1 and type 5 (for only one prescription time unit) patients to type 2 and type 4 (for only one prescription time unit) patients. Under the non-formulary scenario, in which no metformin prescriptions are captured for some patients, some type 1 patients would appear in the database as non-users and would not contribute to the analysis. This would not cause bias, assuming that these patients do not differ on unmeasured factors from patients for whom metformin prescriptions are observed, but precision could be reduced because of a loss of true metformin-exposed patients.

Some type 3 patients, who should not be in the analysis because they are actually combination therapy users, would be classified as sulfonylurea monotherapy users. This could create bias if combination therapy and sulfonylurea monotherapy have differential effects on the outcome. In Gamble and colleagues' study, combination metformin and sulfonylurea therapy users had higher rates of mortality than sulfonylurea monotherapy users, likely due to differences in disease progression at the start of follow-up between the groups. The misclassification of the combination therapy users as sulfonylurea monotherapy users would therefore result in an expected downward bias in the comparison of metformin to sulfonylureas. In addition, some type 5 patients, who previously contributed one prescription time unit to the metformin group, would contribute three prescription time units to the sulfonylurea group because they would appear to be sulfonylurea initiators. This is potentially problematic for several reasons. First, in order for type 5 patients to start on the sulfonylurea treatment, they must have survived the first metformin prescription time unit. By omitting this immortal person time from the metformin group, it would inflate the estimated mortality rate among metformin users, leading to an upward bias in the comparison of interest. Secondly, follow-up for these patients would now begin later in the course of their diabetes disease process. Unless disease severity is carefully accounted for in the analysis, this could create downward bias due to confounding. With two sources of downward bias and a source of upward bias, the net effect of bias could go in either direction. In their analyses, Gamble and colleagues found a modest downward net bias. The base case analysis with no misclassification yielded a hazard ratio of 0.88, which drifted monotonically to 0.82 with increasing misclassification.

Under scenario 2, in which metformin prescriptions are observed in the data only after certain criteria are met, type 1 patients would be correctly classified as metformin monotherapy users but would pose risks of immortal time and confounding, since the initial metformin prescriptions would not be identifiable. In this case, both issues would potentially result in upward bias. Type 3 patients would pose the same problem as described above under scenario 1, but to a lesser extent since they would contribute time to the analysis only for the first two sulfonylurea prescription time units. Again, this bias would be downward. Type 5 patients would potentially affect the analysis as described above, creating both upward and downward biases. In Gamble and colleagues' analyses, the net bias was upwards and, in the more extreme parameter settings, actually changed the direction of the finding, with a hazard ratio of 1.34 in one analysis.

3.2 Combination Metformin and Sulfonylurea Therapy versus Sulfonylurea Monotherapy

Under fully observed data, a study comparing combination metformin and sulfonylurea therapy to sulfonylurea monotherapy would involve comparing type 2 and type 4 (for only one prescription time unit) patients to type 3 patients. Under scenario 1, some type 3 and 5 patients would be classified as sulfonylurea monotherapy initiators. As above, the type 3 patients would cause bias if combination therapy and sulfonylurea monotherapy had differential effects on the outcome. However, in this case, the expected bias would not necessarily be in an absolute direction, but rather towards the null because it would make the patients in the two treatment groups more similar. When biases occur in an absolute direction (i.e., upward or downward), they move the point estimate in that direction regardless of whether it starts above or below the null. Biases toward the null move the point estimate closer to unity regardless of whether it is above or below the null. Type 5 patients could create confounding that would likely bias results downward but would not create bias due to immortal time because this comparison does not involve metformin monotherapy users. Consistent with these expectations, Gamble and colleagues' results showed that misclassification moved the original point estimate (1.37) both monotonically downward and towards the null (to 1.34, 1.31, and 1.26 with increasing misclassification).

Under scenario 2, any bias due to type 3 patients, which would be towards the null, would be lessened because they would contribute fewer prescription time units to the sulfonylurea monotherapy group. Type 5 patients would again

cause downward bias due to confounding. However, Gamble et al. observed the bias in the opposite direction than would be expected. In their simulation study, the hazard ratio, which was 1.37 with no misclassification, increased with increasing misclassification. This is likely due to the fact that, rather than entering patients into the cohort at initiation of treatment, Gamble and colleagues looked into the future to determine which patients were always monotherapy users and which patients were ever combination therapy users. This can create both immortal time bias and bias due to confounding. By restricting the sulfonylurea group to those patients who never used metformin and sulfonylurea combination treatment, the authors created a relatively healthy comparison group of patients who did not intensify their treatment by adding metformin. Furthermore, for patients in the metformin and sulfonylurea combination therapy group who initiated sulfonylurea therapy and added metformin, their sulfonylurea-only exposed time is immortal because they could not have died before adding metformin. Both of these issues would, in expectation, result in upwards bias in Gamble and colleagues results, but should generally be avoided in drug safety studies by not defining exposure status by looking into the future.

3.3 Strategies to Mitigate Bias

Understanding the mechanisms by which restrictive reimbursement policies can cause bias in observational drug safety studies sheds light on appropriate strategies for mitigating the potential for bias. The use of an active comparator design, rather than one in which an investigator compares users of one drug to non-users of the drug, can mitigate bias due to exposure misclassification. In the metformin versus sulfonylureas comparison, initiators of metformin who were affected by a non-formulary policy fell out of the analysis without creating bias; however, a restrictive reimbursement policy that impedes access to a drug for a non-random sample of a population could create the opportunity for confounding. If a non-user comparator group were employed, these patients would have been misclassified as non-users, creating bias. Also, beginning follow-up for patients at treatment initiation, rather than looking into the future to determine exposure status, can mitigate bias from multiple sources.

Other strategies can be used to assess and correct for bias due to exposure misclassification. Bias modeling approaches, such as those described by Lash, Fox, and Fink [17], could be used for assessing the sensitivity of study findings to different degrees of exposure misclassification. Augmenting the primary claims database with data from other sources, such as electronic health record data, data from secondary or supplemental insurers, or surveys of patients or healthcare providers, might also provide some insight into the magnitude of potential under-capture of drugs in claims databases and may provide information that can be used to correct associated biases.

4 Discussion and Conclusion

Gamble and colleagues have shown that, at least in two Canadian provinces, administrative claims data can miss a substantial proportion of prescription fills for drugs affected by restrictive reimbursement policies. In some situations, this under-recording can create large biases in observational drug safety studies, while in others net bias may be negligible.

While the results of the simulation study by Gamble et al. show, under different degrees of misclassification, how much bias can occur in drug safety studies, it is generally not possible for the investigator to know how much misclassification a particular restrictive reimbursement policy might cause in a particular claims-based study. Nevertheless, it is possible to anticipate the presence, direction, and, to some extent, the magnitude of biases that the misclassification can create. The qualitative analysis above illustrates a framework for thinking through the potential impact of biases due to restrictive reimbursement policies and may be useful in future studies. Unfortunately, assessing the direction and magnitude of the net bias may be difficult without a simulation study. However, the framework above also sheds light on strategies that can be used to mitigate bias due to restrictive reimbursement in drug safety studies, including active comparator groups, not conditioning on future events, and sensitivity analyses.

The single most important strategy that investigators can use to assess whether the results of a claims-based drug safety study are affected by restrictive reimbursement policies is to know whether restrictive reimbursement policies are in place that might affect the capture of drugs of interest. Knowledge of restrictive reimbursement policies can usually be obtained by working closely with the data owner and by understanding the health systems that give rise to the data. While every observational study can produce valid results, whether or not they do often depends on how well the investigator knows the data.

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