Biases Related to Prescribing Decisions in Retrospective Database Research in Diabetes

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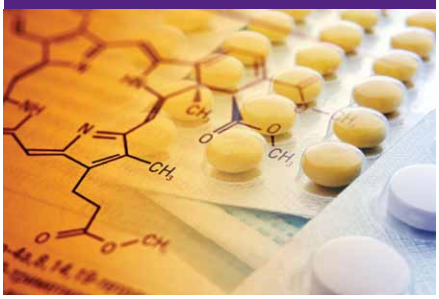
KEY POINTS . . .

There are four types of biases that are related to prescribing decisions in database research: detection; protopathic; channeling; and disease severity biases.

These biases are likely to be introduced in database research involving therapeutic areas with stepwise drug treatment, e.g. diabetes.

Resources in the area of real-world evidence can be mobilized to distinguish between, and control these biases to aid the interpretation and application of study findings.



Introduction

During the past decade, the arsenal of drug treatments for most chronic conditions, including diabetes, has expanded beyond within-class growth to include new pharmacological classes, and additional agents with novel pharmacological actions are expected to enter diabetes therapeutic arena within the next few years. Additionally, treatment of diabetes involves an ongoing process of risk-benefit assessment by prescribers, which include frequent medication switching within and across pharmacological classes. Generally, prescribers consider many factors to initiate and switch medications within therapeutic area, including drug's effectiveness; tolerability and safety; patient's affordability; and disease severity.

As recommended in disease management guidelines, stepwise drug therapy is standard-of-care in most chronic diseases, such as diabetes, asthma, and rheumatoid arthritis. When patients do not respond to or tolerate first-line therapy, they might require the addition of another medication or switch to a different class of medications as second-line therapy to manage their disease. Those who do not respond well to first-line therapy usually have more severe disease states and prescribers tend to conduct thorough clinical, biochemical, or histological investigations before stepping up therapy regimens. During this process, the likelihood of detecting new diseases or manifestations of ongoing subclinical diseases is higher in those patients than in others with less severe disease states. Moreover, most of the underlying diseases for which the medications are indicated, e.g. diabetes, are risk factors for other conditions, e.g. cancer. Studying the association between exposure to chronic medications and such outcomes in retrospective analysis of health databases has many methodological challenges that lead to biases, especially those related to prescribing decisions in terms of initiation and switching between medications, including detection bias; protopathic bias; and confounding by indication in forms of channeling bias and disease severity bias. Using diabetes treatment as a motivating example, the following is a description of these biases and how to account for them in pharmacoepidemiologic and outcomes research.

Detection Bias

Detection (or surveillance) bias is introduced when the knowledge of exposure status influences the diagnosis of the outcome, where the exposure to the drug elicits the search for the outcome. It can be a form of selection bias when the study population does not represent the target population (especially in case-control designs) or measurement bias when systematic errors are introduced in outcome measurement. There are three main types of detection bias: diagnostic suspicion bias; unmasking bias; and mimicry bias. Prescriber's knowledge about the risk profile of a drug or a class could influence more thorough investigation to look for the outcome, which could be stimulated by risk communications, e.g. health care provider letters sent by pharmaceutical industry. In diagnostic suspicion bias, exposure to the drug of interest serves as another diagnostic measure for the disease (outcome of interest), and individuals who are exposed to the drug undergo detailed examinations and might have earlier diagnosis of the outcome of interest, e.g. the association between pioglitazone and urinary bladder cancer, as a consequence of prescriber's awareness of this potential risk.

Unmasking bias is introduced when exposure to the drug produces signs and symptoms that support the diagnosis of the outcome, e.g. the association between sodium-glucose co-transporter 2 inhibitors and urinary bladder cancer, as these medications increase urinary tract infections with bladder signs and symptoms that are easily confused with those of urinary bladder cancer. On the other hand, when the drug produces a symptomatic benign condition that is clinically close to the outcome, mimicry bias takes place, e.g. the association between glucagon-like peptide-1 (GLP-1) receptor agonists and pancreatic cancer, as pancreatitis is a known risk with these drugs and shares similar clinical presentation with pancreatic malignancy (Fig. A).

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In retrospective database research, investigators should consider the hierarchy of drug therapy in chronic conditions and compare initiators of drugs that are equivalent with regard to the severity of the underlying disease for which the drug is prescribed. Additionally, the distribution of diagnostic tests and procedures between exposure groups should be compared at baseline and index date (exposure initiation). Uneven distribution of these characteristics between exposure groups denotes detection bias. Moreover, the addition of an exposure group for which the outcome of interest is not an established risk, i.e. a negative control, is recommended; e.g. benzodiazepines and pancreatic cancer. Likewise, the addition of a negative outcome can also be used to aid interpretation of study findings, e.g. the association between GLP-1 agonists and glaucoma.

Protopathic Bias

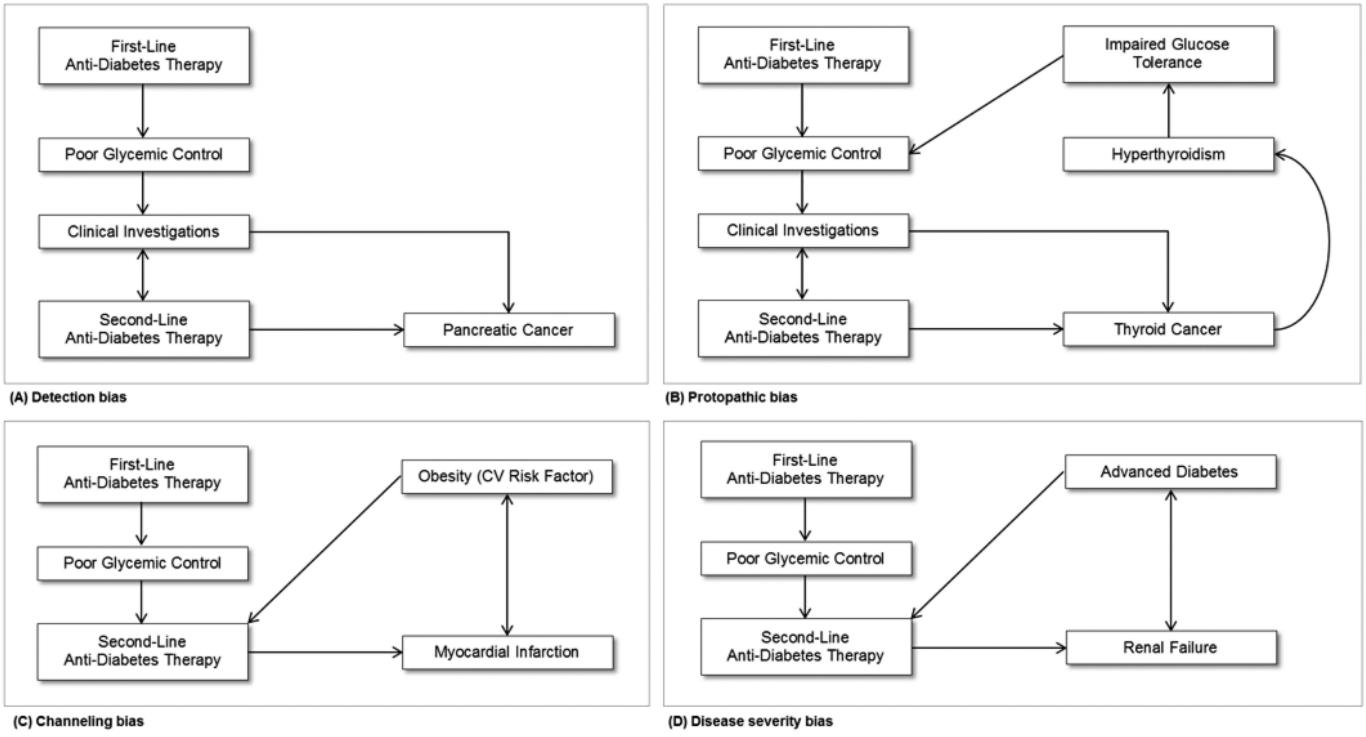
Protopathic bias is introduced when subclinical stages of the disease influence the exposure to the drug, especially when the drug is prescribed to treat a condition that is a manifestation of the already developed disease (outcome of interest). It is a form of measurement bias, and sometimes mistaken for confounding by indication. There are two types of protopathic bias: reverse causality and sick quitter bias. When the drug is prescribed to treat early manifestations of an outcome that has not been yet diagnosed, reverse causality is introduced, e.g. the association between GLP-1 agonists and thyroid carcinoma, as the cancer-related thyroid malfunction contributes to poor glucose control in patients with diabetes, which might necessitates, switching therapy to GLP-1 agonists (Fig. B).

Sick quitter bias occurs when chronic users of a drug of interest stop treatment due to the early manifestations of an outcome. When studying the relationship between the drug and that outcome, current users can be misclassified as unexposed at the time of exposure-quitting (or switching), e.g. the association between rosiglitazone and heart failure, as chronic users of the drug who develop fluid retention are switched to other anti-diabetes therapy, and the relationship between rosiglitazone and heart failure is under-estimated if this prevalent-user approach is used.

Data sources and expertise in design and analysis methods in the area of real-world evidence can be mobilized beyond traditional confounding control and exposure/outcome measurement.

Investigators should compare the incidence rates of the outcome of interest over multiple periods in the follow up; when rates are higher at earlier periods following exposure to the drug of interest and dissipates in subsequent periods, protopathic bias could occur. Also, both detection and protopathic bias are likely if the distribution of the stages of the outcome (if the outcome permits pathological progression staging, e.g. malignancies) varies between exposure groups by follow up periods, e.g. earlier stages at the earlier periods in the exposure of interest group and stages increase over time, e.g. thyroid cancer stages I and II in earlier period vs. stages III and IV in subsequent period following exposure.

Figures A-D. Illustration of biases related to prescribing decisions in retrospective database research.



Confounding by Indication

Confounding by indication is mainly divided into two types: channeling bias and confounding by disease severity (or disease severity bias). In channeling bias, the association between the exposure and the outcome is distorted when a drug, or a class of drugs, is preferentially prescribed to individuals with preexisting comorbidity at baseline. Failure to account for the comorbidity will confound the findings, e.g. the association between GLP-1 agonists and myocardial infarction, since for the GLP-1 agonists' weight reduction properties, these agents are more likely to be prescribed to obese or overweight individuals (Fig. C).

Disease severity bias occurs when the drug of interest is preferentially prescribed to individuals with different severity stages of the disease for which the drug is used. Thus, the drug effect could be mixed with the uncontrolled disease state, e.g. the association between dipeptidyl peptidase-4 inhibitors and renal failure, as these drugs are prescribed to patients who have advanced diabetes with poor glycemic control when treated with first-line therapy and exhibit diabetes complications such as early stages of nephropathy (Fig. D).

These types of confounding by indication are common in chronic diseases that are treated in a stepwise approach where patients switch between medications, and decisions for stepping up therapy (or sometimes stepping down such as in asthma) are influenced by multiple factors as mentioned earlier, such as drug effectiveness (objective and subjective benefits), safety (risk tolerability and adverse event experience), or patient adherence. Therefore, investigators should account for all indices of disease severity and comorbidities, as well as factors that affect prescribing decisions including contra-indications.

Conclusions

Exposure propensity scoring approaches are efficient as long as such indices are carefully selected and accurately reflect the severity of the underlying disease and comorbid conditions. Equally, variables that reflect health care utilization and duration of the disease should be included in the propensity score models to minimize detection bias and protopathic bias. The extent of control for such factors depends on the richness of the used healthcare database in terms of important variables, including treatments; diagnoses; procedures; laboratory tests; and other factors. Even the most comprehensive database, however, does not include all such indices; e.g. diabetes duration, which reflects disease severity, is increasingly difficult to estimate in database research. Therefore, failure to include all the important variables to account for these biases will introduce residual confounding, which refers to the presence of confounding despite adjustment, as well as selection bias in terms of not having similar exposure groups with regard to disease severity, e.g. comparing oral anti-glycemic medications with insulin therapy in terms of cardiovascular and cancer risks.

It is common to have inconclusive findings in pharmacoepidem–iologic and outcomes research and it is common to ascribe such findings to unmeasured confounding or chance, but the potential for biases related to prescribing decisions can contribute to these findings, and knowing how to illustrate, distinguish, and account for these types of biases aids in the interpretation and application of study findings. Nevertheless, data sources and expertise in design and analysis methods in the area of real-world evidence can be mobilized beyond traditional confounding control and exposure/outcome measurement. ■

Additional information:

To read the previously published "A Checklist for Medication Compliance and Persistence Studies Using Retrospective Databases" from the ISPOR Medication Adherence & Persistence Special Interest Group, go to: http://www.ispor.org/workpaper/MedComplianceChecklist.asp, or refer to "A Checklist for Retroactive Database Studies – Report of the ISPOR Task Force on Retrospective Databases," at: http://www.ispor.org/workpaper/healthscience/ret_dbTFR0203.asp

You may also be interested in the new ISPOR Digest of Databases Special Interest Group. Information on this new ISPOR SIG can be found at: http://www.ispor.org/sigs/retrospective_db.asp

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