

Pharmacoepidemiology, Adverse and Beneficial Effects

Pharmacoepidemiology has been defined as “the study of the distribution and determinants of drug-related events in populations and the application of this study to efficacious drug treatment” [26]. Similar definitions have been given by several authors [37, 53]. The term “drug” in the definition is generally understood to include biologics, such as vaccines, and the populations are understood to be human. The emphasis is on studies of the safety and effectiveness of drugs used for medical purposes. Both randomized (*see* **Clinical Trials, Overview**) and non-randomized (**observational**) designs are used, with the latter being more common, especially for the study of adverse effects. Pharmacoepidemiology may be regarded as a subdiscipline of both **clinical epidemiology** and clinical pharmacology [53]. However, clinical pharmacologists typically use small, carefully controlled studies to examine drug **pharmacokinetics** (absorption, distribution, metabolism, and excretion) and pharmacodynamics (the relationship between the drug level and drug effects), while pharmacoepidemiologists typically examine drug effects in larger populations under conditions more representative of clinical practice. Pharmacoepidemiology is an essential component of risk management of pharmaceutical products. Risk Management “encompasses processes for identifying and assessing the risks of specific health hazards, implementing activities to eliminate or minimize those risks, communicating risk information, and monitoring and evaluating the results of the interventions and communications” [56].

Current US federal regulations require evidence of both safety and effectiveness of drugs prior to approval for marketing (*see* **Drug Approval and Regulation**). However, such evidence is limited by the extent, duration, and patient characteristics of preapproval clinical trials. In addition, unexpected potentially beneficial effects are sometimes found after marketed use and questions may arise about

the effectiveness of various drugs under conditions of use and in patient populations not included in premarketing clinical trials. A well-known international guideline on the extent of patient exposure to assess the clinical safety of drugs intended for chronic use in the treatment of non-life-threatening conditions summarized limitations of preapproval information on safety by noting, first, that it is expected that short-term adverse events with a cumulative 3-month incidence of about 1% or more should be well characterized prior to approval; secondly, that events where the rate of occurrence changes over a longer period of time may need to be characterized depending on their severity and importance to the risk–benefit assessment of the drug; and thirdly, that adverse events occurring in less than one in 1000 patients treated are not expected to be characterized prior to market approval [22]. Thus, it is often necessary to conduct pharmacoepidemiologic studies of risks and benefits of drugs and vaccines under conditions of marketed use (*see* **Postmarketing Surveillance of New Drugs and Assessment of Risk**).

To design and interpret such studies it is essential to understand the clinical pharmacology of the drug and the pathophysiology and natural history of the diseases which the drug is used to treat or prevent. It is also essential to understand basic principles of epidemiologic study design (*see* **Pharmacoepidemiology, Study Designs**) and to identify and avoid potential sources of **bias**.

Some Common Sources of Bias in Pharmacoepidemiologic Studies

In the epidemiologic literature *bias* refers to an error which causes an estimate of a parameter to differ in a systematic way from the true value [26] in the source population, also known as the *study base*, whose person-time experience (*see* **Person-Years at Risk**) the study is designed to sample [31, 57]. Numerous authors have provided methodologic approaches by which sources of bias in epidemiologic studies may be categorized [41, 43, 51] (*see* **Bias in Case-Control Studies; Bias in Cohort Studies; Bias in Observational Studies; Bias, Overview**). We will briefly discuss some of the more common sources of bias in epidemiologic studies of drug effects.

Selection bias refers to errors arising because the estimated exposure effect among subjects included in

the study differs from that which would have been obtained from including the entire study base [41]. For example, selection bias may occur when the cases included in a study represent a nonrandomly selected subset of all of those arising from the study base [45]. Selection bias may also occur in **hospital-based case-control studies** if the drug exposure is related either positively or negatively to the diagnoses used to select **controls** or the drug exposure in the catchment population of the diagnoses used to identify cases differs from that in the catchment population of the diagnoses used to identify controls [57]. Differences in catchment populations are a particular problem with hospital-based studies because in many teaching hospitals patients may be drawn from hundreds of miles away for treatment of certain illnesses requiring particular skill in management and from only the immediate surrounding few miles for treatment of common disorders that are often used to select controls (*see Hospital Market Area*). Selection bias can produce serious distortions in estimates of disease natural history or treatment outcomes of patients drawn from referral centers [1, 28].

Confounding in epidemiologic studies occurs when exposure groups differ with respect to an extraneous factor related to the outcome. Estimates of exposure effects that fail to account appropriately for the imbalance are subject to bias. A full discussion of the assessment and control of confounding is beyond the scope of the present article and may be found in standard textbooks and in the current literature [41, 58, 60]. However, it is useful to mention *confounding by indication*, a particularly problematic form of confounding in studies of medical interventions when an indication for the intervention is itself a risk factor for the outcome under study [44, 59]. Studies in which confounding by indication has been an important consideration include mortality among asthma patients using long-acting inhaled beta agonists [7], myocardial infarction among hypertensive patients prescribed calcium channel blockers [38], and renal cell carcinoma in association with the use of diuretics [19]. A common way to avoid some obvious confounding by indication is to compare adverse outcomes of two drugs used for the same indication [7, 38]. However, even when the nominal indication is the same for two drugs, there may be subtle differences in patient characteristics and clinical judgments which lead to the choice of one drug over the other,

are not documented in medical records, and yet which may be risk factors for the outcome.

A form of bias, which is closely related to but conceptually distinct from confounding by indication is *protopathic bias* [12, 44]. This occurs when early symptoms of a disease which is present but not yet recognized lead a patient to take a drug, which then appears to be the cause of the disease when it is eventually diagnosed. A classic example of this form of bias was seen in early studies of the antiulcer drug cimetidine, where a higher than expected incidence of gastric carcinoma was found among users than among nonusers. It is likely that many of the cancers were present but undiagnosed at the time the cimetidine was started. Subsequent studies with this class of drug have shown that elevations in gastric cancer risk diminish with duration of follow-up, returning to baseline with long-term use [23]. Not only protopathic bias but also confounding by indication was likely present in the association between cimetidine and gastric carcinoma. Peptic ulcer is both an indication for cimetidine and a risk factor for gastric carcinoma, with *Helicobacter pylori* being causally related to both peptic ulcer disease and gastric carcinoma.

Information bias arises from inaccuracies in the information collected on subjects in the study, resulting in **misclassification** of exposure, outcomes, or **covariates**. For example, patient recall of previous drug exposures has been shown to be subject to error, with the extent of inaccuracy differing by medication type, duration of therapy, recall interval and patient age [25, 61] (*see Recall Bias*). The misclassification of outcome is said to be *differential (nondifferential)* with respect to exposure if the misclassification probability differs (does not differ) depending on exposure. **Differential** and **nondifferential** misclassification of exposure with respect to outcome are defined similarly (*see Bias, Nondifferential*). In a simple cross-classification of exposure and outcome, nondifferential misclassification creates a **bias toward the null** [41]. However, even slight deviations from completely nondifferential misclassification can produce large biases away from the null [3].

When both exposure and outcome are misclassified and the misclassifications are **correlated**, the bias may be in either direction even when the misclassifications are nondifferential [4]. With more than two exposure levels, nondifferential misclassification will bias the most extreme category to the null but can bias

intermediate levels of exposure in either direction [2]. Bias due to misclassification of **confounders** results in loss of ability to control confounding and cannot be adequately dealt with by methods used to control confounding [13]. One practical conclusion from all of these findings is that it is *not* correct to conclude that risks of adverse drug effects estimated from inaccurate information are likely to represent underestimates simply because the misclassification may be presumed to be nondifferential.

Misclassification is a particular problem in epidemiologic studies using hospital discharge diagnosis codes to define outcomes and confounders, because the codes often do not correctly reflect diagnoses recorded in the medical records [20]. This may occur through miscoding, use of nonspecific codes, omissions of codes in complicated patients with many different diagnoses, or failure to modify a code for an admission to “rule out” a condition when the condition was ruled out. For example, in a sample of about 1000 hospitalizations with the discharge diagnosis of acute myocardial infarction (AMI), medical record review found that 26% did not meet clinical criteria for AMI. Most were hospitalizations to rule out AMI in which the code remained even though AMI had been ruled out [20]. One approach which avoids some of problems with information bias is to use computer-based discharge diagnosis codes to identify potential cases and to confirm these by medical record review [40].

Adverse Drug Effects

Pharmacologic Classification

To help guide evaluation of adverse drug effects, clinical pharmacologists have classified them into two types, designated A and B, depending on their relationship to known pharmacological properties of the drug [39]. Type A (“augmented”) effects are caused by exaggerated pharmacological actions of a drug. Such effects are also sometimes called “mechanism-based” adverse effects. They are somewhat predictable on the basis of the pharmacology of the drug and are typically dose-dependent. Examples include hypotension with anti-hypertensive drugs and gastrointestinal hemorrhage with nonsteroidal anti-inflammatory drugs [14]. Most type A effects are likely to have been at least identified before market approval. However, the predisposing factors,

dose–response relationships, warning signs, spectrum of severity and long-term consequences may not have been adequately characterized at the time of initial marketing. Subsequent studies may reveal an increased risk in some patients with impaired metabolic clearance, concomitant use of drugs with competing metabolism, or increased target-organ sensitivity. Pharmacoepidemiologic studies of type A effects should be aimed not only at quantifying risks but also at finding ways to anticipate and reduce the risk through identification of predisposing factors and improved dosing guidelines [8].

Type B (“bizarre”) effects are those that are not expected from the known pharmacologic properties of a drug given in usual doses to patients who metabolize the drug in a normal way [39]. Such effects include idiosyncratic, immunologic, allergic, pseudo-allergic, teratogenic, or carcinogenic reactions for which mechanisms are often unknown. Type B effects are typically rare, serious, unpredictable, not dose-dependent, and unlikely to have been adequately characterized or even recognized before market approval. The liver, blood, and skin are among the most common sites of type B reactions to drugs, while some vaccines have been associated with type B reactions of the nervous system [16, 21, 24, 36, 42, 55, 64]. Both drugs and biologics have been associated with rare allergic and pseudo-allergic type B reactions [9]. Pharmacologic studies of type B effects are typically constrained by the rarity of the events, but should attempt to identify patient subgroups at increased risk whenever this can be done.

Perhaps the most comprehensive example of using epidemiologic information to identify risks and benefits in different patient subgroups and providing this information to patients and physicians is given by the US prescribing information for oral contraceptives [34]. A more limited example is given by studies of agranulocytosis in association with the angiotensin-converting enzyme inhibitor captopril; it was found that the risk was extremely low except in well-defined subgroups in whom use of the drug could generally be avoided [5].

Timing of Adverse Effects in Relation to Duration of Therapy

One of the most important aspects to consider in both the clinical and epidemiologic evaluation of adverse drug effects is the timing in relation to duration

of therapy [15, 17, 52, 54, 62]. Some effects, such as angioedema with angiotensin-converting enzyme inhibitors, are more common early in therapy [50]. Others, such as tardive dyskinesia with phenothiazines, are typically seen only after prolonged exposure to the drug. For some effects there may be a time window of highest risk. For example, onset of Guillain–Barré syndrome following the so-called “swine flu” vaccine was highest 17 days after vaccination and declined thereafter [46]. Serum-sickness-like reactions to drugs typically occur from 7 to 21 days after starting therapy [9]. Depletion of susceptibles may also affect the hazard function for adverse events in relation to duration of therapy [62]. Accounting for timing of adverse effects in relation to duration of therapy requires collecting information on timing of the event not only in relation to last exposure to the drug but also in relation to duration of therapy. Failure to account properly for timing may result in over- or underestimation of risks and can create artifactual treatment-by-subgroup **interactions** when comparing patient groups with different temporal patterns of usage [15].

Beneficial Effects

Intended Beneficial Effects: Efficacy, Effectiveness and Outcomes Research

Efficacy refers to the benefits of an intervention as measured under ideal circumstances in a randomized, controlled clinical trial conducted in a homogeneous set of patients with careful attention to the protocol. Clinical trials conducted to provide demonstrations of drug efficacy needed for drug approval are typically conducted under conditions which maximize internal validity of the trial itself at the possible expense of external validity – generalizability to usual clinical practice [48] (*see Validity and Generalizability in Epidemiologic Studies*). *Effectiveness* refers to the benefits of the intervention as measured under conditions intended to resemble closely the settings and patient populations where the intervention will be used in clinical practice. Effectiveness depends not only on efficacy but also on ease of administration, acceptability to patients and prescribers, compliance, and impact on use of health care resources. Consequently, effectiveness of an intervention depends not only on the intervention, but also on the setting in which it is delivered.

Recently there has been an increased emphasis on judging the results of health interventions in terms of their ability to improve *health outcomes*, i.e. changes in health status noticeable by patients, rather than exclusively in terms of their ability to improve laboratory tests or physiological parameters [10, 11, 48]. The field of **outcomes research** seeks to evaluate the overall effects of different interventions on health outcomes in clinical practice [10, 11, 27].

Because of the difficulty and expense of conducting randomized clinical trials in a clinical practice setting, observational studies are often used for the comparison of treatment outcomes [11, 27]. Observational studies of drug effectiveness are subject to selection bias, which may be impossible to control because the factors which lead to the choice of one therapy over another may not be fully reflected in any data source [6, 12, 28–30, 32, 59]. Selection bias in the study of intended effects of drugs may be more difficult to overcome than in the study of unintended effects [30]. Confounding by the indication for therapy must be considered in all pharmacoepidemiologic studies, and is particularly difficult to control in observational studies of intended drug effects [30, 59, 63]. Because most differences in effectiveness between active agents are likely to be moderate, observational studies are especially prone to distortion caused by bias and confounding [30, 32, 63]. This cautionary note also applies to observational studies of vaccine effectiveness, though to a lesser extent, because the effect sizes are typically much larger than for effectiveness studies of drugs [33, 47] (*see Vaccine Studies*). As an alternative to observational studies of drug effectiveness in clinical practice, randomized effectiveness trials have been conducted [35, 49]. Such studies have the potential for producing more valid estimates of effectiveness than can be obtained from observational studies.

Unintended Beneficial Effects

Some current indications for drug treatment began with the serendipitous finding of an unexpected **association** between drug exposure and a beneficial effect. The initial hypothesis of a beneficial drug effect usually arises from **case series** or laboratory observations, followed by formal epidemiologic studies. As useful as such studies have been in providing quantitative estimates of benefit, randomized clinical trials

are essential for **hypothesis testing**. For example, data from randomized clinical trials of beta-carotene in the prevention of lung cancer have not confirmed findings of earlier observational studies which had suggested a protective effect [18].

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(See also **Drug Utilization Patterns**)

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