CHANNELING BIAS IN THE INTERPRETATION OF DRUG EFFECTS

H. PETRI AND J. URQUHART
Department of Epidemiology, University of Limburg, 6200 MD Maastricht, The Netherlands

SUMMARY
Channeling is a form of allocation bias, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences. Claimed advantages of a new drug may channel it to patients with special pre-existing morbidity, with the consequence that disease states can be incorrectly attributed to use of the drug. For the study of adverse drug reactions, large databases supply information on co-medication and morbidity of patients. For diseases with a stepped-care approach, the drug history of patients, as available from some databases, can show channeling of drugs to patients with markers of relatively severe disease.

INTRODUCTION
When a new treatment is introduced it competes with pre-existing methods of treatment for the same conditions. Claimed advantages of the new treatment may be general superiority over pre-existing methods, but often narrowly defined advantages are all that can be claimed. Practitioners may adopt the new treatment method by displacing or supplementing pre-existing treatments or by prescribing selectively to new patients. If the promotion of the new product has succeeded in creating in physicians' minds a particular patient profile for the new product, then comparisons between observational data gathered on recipients of the new product versus recipients of the older products will be confounded by different morbidities in the two patient groups. Channeling is the term we have coined for this application of drugs in groups of patients who have a susceptibility to problems or who have special pre-existing morbidity.

Channeling can be considered as a special form of allocation bias, where interventions, self-selected or clinically assigned, are given to people with major prognostic differences. Drugs with similar actions that enter the market at different times, and thus in different competitive situations, may be channeled to different groups of patients. For example, a late-entry drug is more likely to be given to patients who have not responded satisfactorily to therapy with an established, early-entry drug. If competitive claims are made for a later-entry drug that differentiate it from earlier-entry products, the associated promotion may influence physicians to select different prognostic types of patients to receive the various products in a pharmacologic class.

Another factor that may be pertinent is patient and physician age. Since patients and physicians tend to grow old together, elderly patients may be more likely to use early-entry medicines, because they tend to be treated by longer-practising physicians, who tend to adopt later-entry medicines more slowly.

These varied reasons for such channeling by medical or prognostic status also tend to confound patient-related factors with drug-related factors. An often-used claim is less severe or fewer side-
effects for the new drug. This claim can lead to selective prescription of the drug to patients who experienced side-effect problems during treatment with an earlier-entry drug. Also, a claimed higher efficacy for the drug may channel it to patients where a prior treatment had failed. Thus, the later-entry product is also likely to end up in use by patients with different attributes.

An example of channeling appears to have occurred after the introduction of 'Osmosin', a controlled-release form of indomethacin, for which claims of fewer gastro-intestinal side-effects were vigorously promoted. When Inman studied this product using the prescription event monitoring method, he found a much higher prevalence of gastro-intestinal complaints among patients long after the end of use of the drug. This suggests that the product had been channeled to patients most likely to suffer from these disturbances. The product was withdrawn on the basis of reports suggesting an unexpectedly high occurrence of gastro-intestinal ulcerations, bleeding, or perforation. Inman pointed out, however, that because the drug was claimed to have fewer side-effects, it likely had been prescribed for patients who were most likely to develop these side-effects.

**POPULATION-BASED STUDIES**

Adverse drug reactions are often recognized only after market introduction of the new substance. The rarer reactions cannot be assessed in premarket clinical trials which include a limited number of patients. Also, more common but less obvious side-effects often are recognized only after a period of use in a larger and medically more diverse general population group than was studied in premarket trials.

Thus, the study of adverse drug reactions necessarily involves larger groups of patients than can be economically or logistically managed in randomized, controlled trials. However, studies are observational, rather than controlled, and thus are subject to various biases, including channeling bias. The occurrence of side-effects of drugs in one therapeutic class can be compared. A central issue in this situation is whether the groups of users are comparable in relevant characteristics: the treated disease, co-morbidity, age, sex, and other factors.

**CHOICE OF CONTROLS**

The effects of drugs – beneficial or unwanted – are often best studied in comparison to other drugs with similar therapeutic indications. For a new drug which is the first treatment for a condition, comparison to a placebo reference group is appropriate. In contrast, when other therapies exist, the comparison of the new drug should be to the existing therapies. A similar statement can be made for side-effects, especially as a new drug’s main benefit is often claimed to be fewer side-effects than old therapies.

In observational studies channeling will often make this type of comparison invalid. Generally, the analysis for such comparisons tries to correct for relevant patient baseline characteristics. Many can be collected in the data, but obviously some cannot, because the factors are not known or because the data cannot be gathered. This problem is ubiquitous in databases collected for one purpose and later used for other purposes.

Studies with existing databases are comparable in this respect to classical case-control or historical cohort studies where inevitably some relevant patient variables from the past will not be known. Even if a database was conceived for research purposes, later studies will be likely to suffer from a lack of relevant data, be it directly on medical aspects such as comorbidity or medication, or more indirectly on behavioural factors like smoking or occupational activities. These points are independent of whether the database is computerized or not.
CHANNELING BIAS IN THE INTERPRETATION OF DRUG EFFECTS

MEDICATION-USE DATABASE

The situation is quite different for coding medicine use than for coding other types of therapy or diagnoses. Owing to reimbursement requirements, pharmacy dispensing records are unequivocal about names of drugs, drug regimens, and amounts dispensed. Data are less specific for procedures like surgical operations which often have many variants. Diagnostic data tend to be the most difficult to classify, for diagnosis is a process with many uncertainties and many, often arbitrary, criteria.

While the nomenclature of medicines has few problems, other aspects of database use should not be ignored. The data on drugs may not be complete, or may not be identifiable on the individual patient level. Data on outpatient drug use can be collected from pharmacies or from health insurers. Pharmacies in most countries have no complete data on drug use at the individual patient level. An exception occurs in The Netherlands, where the national insurance scheme requires participating patients to designate one pharmacy from which they obtain all reimbursed drugs. In the U.S. a comparable situation prevails in some Medicaid data and in some managed care situations. Confidentiality regulations sometimes preclude the use of medication data for research purposes, as, for example, in the rather extreme Swedish case where privacy concerns preclude storing medication data in pharmacies for more than a day or two.

Having complete records on individual patients is essential, and the longer the duration spanned by the records, the better. A peculiarity of many administrative databases is they do not define a distinct start for the patient's record. Thus, even if the data are complete over a certain period it may be that only the first records of delivered care indicate coverage, leaving the preceding time ambiguous about actual coverage.

AN EXAMPLE: CHANNELING OF MEDICATION FOR ASTHMA

If a disease is treated in a stepped-care approach, the drugs given can be used as markers for disease severity. We studied the use of asthma medication for channeling of aerosol beta agonists, as recorded in a large pharmacy database. These aerosol beta agonists tend to be used as a first-line therapy for asthma, while inhalational steroids and other drugs are supplemented for the more severe disease. The three aerosol beta agonists available in The Netherlands differed considerably in concomitant use of inhalational steroids: 23.0 per cent of albuterol (salbutamol) recipients, 35.4 per cent of terbutaline recipients and 42.4 per cent of fenoterol recipients used inhalational steroids. These data support the notion that physicians channel fenoterol to patients with more severe asthma. This channeling of fenoterol may lead to a non-causal linkage of the drug to consequences of severe asthma.

NON-ETIOLOGICAL STUDIES

Databases are useful for other analyses than just drug intervention effects, for example, drug and facilities utilization studies. A rational use of health care facilities is promoted by knowledge of such aspects as the indication for prescription of drugs, multiple use of drugs, and markers of the health status of patients. Differences of delivered care in separate insurance schemes may reveal types of procedures or therapies that depend heavily on reimbursement. Between-physician and between-hospital differences in delivered care suggest inefficiencies or underuse or overuse of certain types of care. A strong variation in therapy use across physicians or regions can help identify the less useful therapies, though a final appraisal of efficacy can only come from a properly controlled trial.
CHANNELING IN SURGERY

Channeling is especially prominent in surgical therapy, not only because of surgeons' reluctance to operate on high-risk patients, but also when different procedures are perceived to entail different risks. An apparent example of this issue is recent controversy over a study of the effectiveness and long-term mortality of transurethral versus open prostatectomies for prostatic hyperplasia.

AN APPROACH TO AVOID CHANNELING BIAS

The choice of an appropriate control group is essential for any form of observational study. In studies of treatment effects, baseline characteristics pertaining to the outcome should be identified in advance. Stratification of the subjects into subgroups for these characteristics can correct for imbalances, though often not all relevant factors are known.

For some questions the selection of control patients can be obviated by comparing different periods of a person's medical history. This is analogous to the crossover design in experimental studies. An example is a recent study, in which we considered whether a widely-used anti-vertigo/anti-migraine drug, flunarizine, was responsible for causing mental depression. We studied drug dispensing records in a group of 155 patients who had, at some time during the period of data collection, received both flunarizine and an anti-depressant drug. We looked for a temporal clustering of prescriptions for anti-depressant drugs following the start of flunarizine.

Control data were taken not from other groups of patients, but from the patients themselves, in the periods before and long after their use of flunarizine. The within-patient comparisons revealed evidence of only a small risk of flunarizine-related depression because we avoided the confounding effect of what was a very sizeable channeling of flunarizine into use by depression-prone patients. The eventual recipients of flunarizine had a 3.5-fold higher background rate of anti-depressant drug prescribing than a reference group of recipients of any drug.

The actual within-patient comparison was done by comparing the incidence of initiation of anti-depressant therapy during the periods of flunarizine use (\(I_u\)) with the incidence during the rest of the time covered by the database, that is, the periods before and after use of flunarizine (\(I_{nu}\)). The incidence is defined as the number of first prescriptions per 1000 observation days. An incidence ratio was determined as \(I_u/I_{nu}\).

CONCLUSION

Channeling can be considered as a type of misclassification when not recognized in the analysis of observational studies. A consequence of the misclassification is that disease states can be incorrectly attributed to use of a drug. Alternatively, when there is knowledge about the differential use of a drug in different stages of a disease, or if a disease has a stepped-care treatment with medicines, the information about a patient's medication can be used to stratify for severity of condition. Within-patient control data can also help avoid channeling bias.

REFERENCES