Role of Postmarketing Assessment

At the time of marketing of most new drugs, there is very limited information available on their effects in older people. Older people are typically excluded from first in man studies due to the higher risks of unanticipated toxicity and for similar reasons are often also excluded from Phase II studies. International guidelines suggest that Phase III studies include older adults, defined as those aged 65 years and older, do not unnecessarily exclude patients with concomitant illness, and include patients who are representative of the population that will be treated if the drug is licensed (1). However, this guideline is not a requirement for licensing and is often very minimally applied (2). Phase I to III trials, termed as postmarketing studies do not provide adequate information on postmarketing drug response (3). Participants may not reflect the real-life patients in whom the drugs will be used, study participants may receive better care than real-life patients, and small numbers of participants make it unlikely that less common adverse reactions will be detected (4). Premarketing studies are often limited in duration and only rarely provide information on comparative effectiveness (5).

Therefore, Phase IV or postmarketing trials are essential to evaluate the safety or efficacy of drugs in real-world settings, particularly for older people with multiple comorbidities and comedications. Postmarketing trials can include any study type such as randomized clinical trials, drug–drug interaction studies, special population studies, or observational pharmacoepidemiology studies. Pharmacoepidemiology is a discipline that applies epidemiological methodologies to the study of the utilization and effects (beneficial or adverse) of medications in large populations. Compared with studies performed before marketing, Phase IV studies are more likely to include a broader range of patients, managed under “real-life” conditions and to include a broader range of clinical end points. Pharmacovigilance is the process that incorporates the detection, assessment, understanding, and effective prevention of adverse effects (6). Pharmacovigilance studies are essential building blocks in the development of our evidence base on the safety and efficacy of drugs in older people. Incentives to perform pharmacovigilance include quest for knowledge to inform and optimize clinical care, regulatory requirements, and financial incentives by avoiding postmarketing risk and potential drug withdrawal. These studies make important contributions to drug safety through changes in drug labeling, new black box warnings, and in some cases, withdrawal from the market (4).
Pharmacovigilance includes many methodologies, such as spontaneous adverse event reporting, observational studies, and randomized controlled trials (Table 1). Postmarketing randomized trials have a potential role in establishing the effects of drugs in older adults but are limited by high costs. Furthermore, participation of older people in clinical trials is limited by factors that include trial design (eg, exclusion criteria, participant requirements), ethical issues around informed consent, and willingness of older people to participate (15). Most countries currently rely on spontaneous reporting of adverse events. This is limited by underreporting and poor quality of data. In older people, spontaneous reporting is particularly problematic as many adverse drug effects are nonspecific geriatric syndromes and multifactorial (16). The value of proactive case detection of medicines ceased due to lack of efficacy or adverse events from sources such as primary care databases has recently been demonstrated (17).

Pharmacoepidemiology provides important insights into the effects of drugs in older people in a real-world setting. Recent advances in defining the population studied, the medication exposure, and relevant outcomes for older people have improved the validity of pharmacoepidemiologic studies. Pharmacoepidemiologic methods have been used to evaluate new tools that measure medication risk in older people. To date, more progress has been made using pharmacoepidemiology to define risk than to define benefit of drugs in older people (18). In the future, pharmacoepidemiologic methods can be focused by using a systems approach to risk prediction based on the pharmacology of the drug and the characteristics of the patients taking it. This review will provide an overview on the role of pharmacoepidemiologic studies in determining the safety and efficacy of medicines in older people. We searched PubMed to review relevant studies on postmarketing assessment, pharmacoepidemiology, and geriatric pharmacology.

**Pharmacoepidemiology to Evaluate Drugs in Older People**

**Real-Life Conditions**

Under real-life conditions, adherence is likely to be significantly lower than in more closely regulated early phase trials. Interestingly, poor adherence itself is a risk factor for adverse events. For example, noncompliant participants in the placebo arms of trials of patients with heart failure had higher mortality (19,20) and older people with poor medication adherence have an increased rate of falls (21). Poor adherence has been demonstrated in postmarketing studies, even when a potential barrier, such as the cost of medicines, is addressed (22). Although old age itself is not a risk factor for poor adherence, older people frequently have risk factors for poor adherence that must be managed, such as visual and hearing impairment, poor hand function, difficulty swallowing, and cognitive impairment (23,24).

Under real-life conditions, older people frequently take multiple drugs for multiple medical conditions. The current evidence base from randomized trials and disease-based clinical guidelines do not provide adequate guidance for these patients (25). There is potential to consider this com-

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**Table 1. The Advantages and Disadvantages of Conducting Different Observational Studies (13,14)**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Purpose</th>
<th>Sensitivity</th>
<th>Complexity</th>
<th>Limitations</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous case reports and case series (passive surveillance)</td>
<td>Initial signal</td>
<td>+/-</td>
<td>+</td>
<td>Incomplete reporting</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Signal confirmation</td>
<td>–</td>
<td></td>
<td>Biased reporting</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>More common events</td>
<td>–</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Rare events</td>
<td>+/-</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Cross-sectional studies (active surveillance)</td>
<td>Initial signal</td>
<td>+</td>
<td>++</td>
<td>Methods in development</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Signal confirmation</td>
<td>++</td>
<td></td>
<td>Confounding</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>More common events</td>
<td>+</td>
<td></td>
<td>Selection bias</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Rare events</td>
<td>+/-</td>
<td></td>
<td>Recall bias</td>
<td>+</td>
</tr>
<tr>
<td>Case–control studies</td>
<td>Initial signal</td>
<td>–</td>
<td>+++</td>
<td>Confounding</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Signal confirmation</td>
<td>++</td>
<td></td>
<td>Selection bias</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>More common events</td>
<td>++</td>
<td></td>
<td>Recall bias</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Rare events</td>
<td>–</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Prospective cohort/randomized studies</td>
<td>Initial signal</td>
<td>–</td>
<td>+++</td>
<td>Cost</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Signal confirmation</td>
<td>+++</td>
<td></td>
<td>Loss to follow-up</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>More common events</td>
<td>+++</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Rare events</td>
<td>–</td>
<td></td>
<td></td>
<td>–</td>
</tr>
</tbody>
</table>

*Note: Symbols +/- indicate the level of suitability.*
Anticholinergic scales, with details of any internal or external validity studies that have been published. A gold standard for such studies (27). However, many pharmacoepidemiologic studies are limited to databases that may contain less valid information, such as prescribed medicines, dispensed medicines, or self-reports of medicines (28).

There have also been attempts to measure cumulative drug exposure, with a range of definitions emerging, such as anticholinergic burden, sedative burden, drug burden index, and central nervous system–acting drugs (29–33). However, there is still a lack of consensus on how to define the drugs or exposures in many of these measures. For example, the range of anticholinergic scales available (29,34–36) makes it difficult to compare findings between studies. Table 2 shows the components of several commonly used anticholinergic scales, with details of any internal or external validity studies that have been published. A gold standard for defining anticholinergic burden is required to achieve internal as well as external validity. Pharmacoepidemiologic studies of these tools are described in more detail in the section on evaluation of risk assessment tools.

Internal Validity

One of the challenges of pharmacoepidemiologic studies in older people is achieving internal validity. Internal validity, the extent to which the results accurately represent the study population, can be achieved through accurate measurements using an increasing range of objective tools in older people. Methods have been developed to optimize collection of accurate information on the population studied, medication exposure, outcomes, and potential confounders.

Recent efforts have been made to define the population of older people studied in terms of not only age and sex but also comorbidity, pharmacogenetics, functional state, place of residence, and frailty. Detailed description of the study population not only ensures that the findings reflect the population studied but is also important for assessment of external validity and is discussed in more detail in that section below.

Collection of accurate information on medication exposure is essential for valid pharmacoepidemiologic studies. Observed medication histories taken by a trained investigator from a patient with their medicines have been well established as a gold standard for such studies (27). However, many pharmacoepidemiologic studies are limited to databases that may contain less valid information, such as prescribed medicines, dispensed medicines, or self-reports of medicines (28).

There have also been attempts to measure cumulative drug exposure, with a range of definitions emerging, such as anticholinergic burden, sedative burden, drug burden index, and central nervous system–acting drugs (29–33). However, there is still a lack of consensus on how to define the drugs or exposures in many of these measures. For example, the range of anticholinergic scales available (29,34–36) makes it difficult to compare findings between studies. Table 2 shows the components of several commonly used anticholinergic scales, with details of any internal or external validity studies that have been published. A gold standard for defining anticholinergic burden is required to achieve internal as well as external validity. Pharmacoepidemiologic studies of these tools are described in more detail in the section on evaluation of risk assessment tools.

Evaluation of the effects of drugs in older people has recently been improved by development of validated tools with which to measure relevant outcomes in older people. Many premarketing studies and randomized trials are limited to surrogate outcomes, which may not be meaningful in older people. For example, lowering cholesterol by 1.0 mM with an HMG co-A reductase inhibitor is associated with a greater reduction in ischemic heart disease in younger than in older patients (46). Health outcomes, such as disease,
hospitalization, and death, are important for older people and can be more easily assessed in observational pharmacoepidemiologic studies. This is also true for other key outcomes for older people, especially the geriatric syndromes, such as falls, delirium, incontinence, quality of life, functional decline, and frailty (47,48). These end points are rarely measured until long after drugs are licensed. For example, the first benzodiazepine, chlordiazepoxide, was licensed in 1960. Over 20 years later, pharmacoepidemiologic studies in older people were published that demonstrated the association of benzodiazepine exposure with increased risk of falls (49) and hip fracture (50). Subsequently, these findings have been confirmed in randomized trials of withdrawal of psychotropic drugs in older patients (51), which demonstrated significant falls reduction with psychotropic withdrawal. Valid measurements of falls have been refined over this time, with the use of falls diaries, improving the internal validity of such studies (52). Objective measures of functional impairment are now included in many longitudinal studies of older people, as well as routine assessments of health care, and thus are available for pharmacoepidemiologic analyses. One of the most commonly used measures of functional impairment is the Short Physical Performance Battery, which predicts clinically meaningful outcomes such as disability, nursing home admission, and death (53).

Collection of accurate information on potential confounders is also critical for the internal validity of pharmacoepidemiologic studies. The quality of information available on critical confounders, such as disease and disease severity, is often limited in the large databases used for these studies. Surrogate markers, such as medication use to indicate disease, are often substituted, with emerging data on their accuracy (54). Recent advances in the development and use of statistical methodologies to improve data quality have been recognized for their potential in aging research (55). Establishment of electronic medical records and databases that include the necessary information for pharmacoepidemiologic evaluations will be essential for ensuring both internal and external validity.

External Validity

External validity, or generalizability to other populations of older people, is much more difficult to achieve. Some progress has been made through efforts to define the population studied, as indicated above under internal validity. Pharmacoepidemiologic studies in people of all ages are influenced by the study population’s age, sex, socioeconomic status, and their country or region’s system of health care. There is substantial variability between populations of older people beyond these factors. Very little of this variability can be captured by considering chronologic age and sex. Biological age, a measure of cumulative deficits (56), describes the risk of mortality much better than chronologic age and may be a useful tool to evaluate the generalizability of findings of pharmacoepidemiologic studies. Place of residence (independent or residential aged care) of the population studied may also provide information on the applicability of the findings. However, significant differences in both residents and prescribing between residential aged care facilities mean that pharmacoepidemiologic findings also differ between populations living in residential aged care facilities. For example, in postmarketing pharmacoepidemiologic studies, proton pump inhibitors appear to be associated with mortality in older people in high-level residential aged care in Finland but not in community-dwelling older people (57). However, proton pump inhibitors are not associated with mortality in older people in residential aged care in Australia (58). Similarly, the drug burden index, a measure of a person’s total exposure to drugs with anticholinergic and sedative effects, is associated with impaired physical function in community-dwelling older people in the United States (31,59,60), Australia (61), and Finland (62) but not in older people from Australian residential aged care facilities (63). Frailty, a condition of increased vulnerability, has been shown to affect drug use (64), pharmacokinetics (65–67), and pharmacodynamics (65,68). With the development of objective validated measures (69), frailty may be useful to stratify older people in clinical pharmacology studies, before and after marketing. The comparative frailty of populations studied may help determine the generalizability of pharmacoepidemiologic findings.

External validity may also be improved by pharmacogenetic studies to stratify populations within pharmacoepidemiologic studies. Pharmacogenetics have been very useful in defining those at risk of “idiosyncratic” adverse drug reactions, such as drug-induced liver injury (70) and antiepileptic-induced skin reactions. They can also define those people likely to respond to treatment, for example, Apo E allele status is associated with outcomes of treatment with acetylcholinesterase inhibitors in patients with mild cognitive impairment (71). There is no known survival advantage with the relevant variants and therefore no reason why these associations should change with increasing age. However, pharmacogenetics may be less relevant with increasing age and with increasing prevalence of other causes of variability in drug response, such as impaired hepatic and renal function, intercurrent disease (72).

Bias

Another challenge of any pharmacoepidemiologic study is bias, which can be considered in terms of selection bias, information bias, and confounding. Many efforts have been made to overcome selection bias in population studies of older people. Traditional study designs tended to limit the population involved either directly by age or comorbidity profile or indirectly through protocols that a person with physical or cognitive impairment could not comply with (15). Techniques such as in-home assessments, validated data collection by telephone, and from caregivers have overcome some of these limitations (73,74).
Information or misclassification bias has also been a problem in studies of older people, particularly those with cognitive impairment. In many cases, this can be a nondifferential misclassification, making it more difficult to detect an association between the exposure and the disease. For example, in the evaluation of the risk of falls with exposure to cardiovascular medications, cognitive impairment will result in inaccurate measurement of exposure and outcomes. However, in some cases, cognitive impairment may be an outcome of or indication for exposure to the drug, resulting in differential misclassification. For example, observational studies investigating the association between benzodiazepines and cognitive impairment may be biased by limited recollection by the patients of their exposure to benzodiazepines or by poor self-report of memory problems, which both result in a bias toward the null hypothesis. These issues can be minimized by seeking objective information, such as observed measures of medication exposure (prescribing, dispensing, or administration records), falls (falls diaries), and cognitive function (Mini-Mental State Examination and psychometric tests).

Confounding is a major limitation of pharmacoepidemiologic studies, particularly confounding by indication. Although it may be possible to control for the presence of a disease that is likely to be the indication for the drug of interest, in population studies, data on disease severity are rarely adequate to completely control for the confounder. Many outcomes in older people, such as functional impairment, geriatric syndromes, hospitalization, nursing home placement, and mortality, are multifactorial, and it is very difficult to capture all of the biopsychosocial factors that are potential confounders in a multivariate model. For example, cohort studies of the association between use of antipsychotic medicines in patients with dementia and mortality have yielded conflicting results. This may be due to different controlling for confounders in different studies (Table 3), as well as differences between the populations studied as described in the section on External Validity. Recently, the dementia antipsychotic withdrawal randomized trial demonstrated an increased risk of mortality in people who take antipsychotics (81). Efforts have been made to capture multiple confounders using propensity scores, and this technique may be useful in pharmacoepidemiologic studies in older people (82).

### Risk Assessment Tools

Pharmacoepidemiologic studies in older people have recently focused on risk assessment tools. Studies of these tools have defined high-risk medicines in older people, through pharmacologic evidence and/or expert consensus, described the exposure of various populations to such tools, and assessed any adverse outcomes associated with exposure. Such tools aim to inform prescribers of the risk to older patients when prescribing particular drugs or combinations of drugs.

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Measured confounders</th>
<th>Services Use</th>
<th>Comorbidities</th>
<th>Demographics</th>
<th>Percentage Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older adults living in British Columbia, United States</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Older adults living in British Columbia, United States</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Older adults living in British Columbia, United States</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Older adults living in Canada</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Older adults living in Finland</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Older adults living in Italy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Note: Table is sorted by the country.
Many risk assessment tools consider individual drugs or doses, such as the modified Beers’ criteria (83) or the Screening Tool of Older Person’s Prescriptions criteria (84). Others consider combinations of drugs, such as the drug burden index (31), several measures of anticholinergic burden (29,35,85), central nervous system–active drugs (33), falls risk–increasing drugs (86), and polypharmacy (87). Different indices have been associated with different risks across different populations of older people, with very little data validating these measures in frail older people (88).

Observational pharmacoepidemiologic studies of risk assessment tools should be followed by randomized trials to assess the role of these tools in clinical practice. For example, although a higher drug burden index is associated with a number of measures of functional impairment in several populations of community-dwelling older people from different health systems (31,59,61,62), a pilot randomized controlled trial of providing information on drug burden index to prescribers found that this resulted in a reduction of drug burden index in only 32% of patients in the intervention group (89). Randomized trials of well-designed interventions are required that are powered to investigate changes in medication exposure and clinical outcomes before these risk assessment tools are used in clinical practice.

Assessment of Effectiveness

Pharmacoepidemiologic studies have not had a large role in assessment of drug effectiveness in older people. Effectiveness refers to the benefits of the intervention where and how it will be used in clinical practice. Observational studies on drug effectiveness are limited by the challenges of validity and bias described above and can only be considered hypothesis generating for further evaluation in randomized clinical trials.

FUTURE DIRECTIONS AND CONCLUSIONS

Initiatives have been suggested to address limitations of the current system used for studying drug safety. A model of conditional approval of new drugs in the United States was recently proposed (90). This included a shortened Phase III, followed by conditional approval with required postmarketing studies. Cumulative information on safety and efficacy of new drugs would be reevaluated within 5 years of licensing. This model could be applied to older people, such that if the new drugs were likely to be used by older patients, then required postmarketing studies could include pharmacoepidemiologic studies and clinical trials in older populations with different characteristics.

Pharmacoepidemiologic studies are much more likely to make real findings (as opposed to Type I errors) if they are based on theoretical hypotheses. Targeted screening for adverse events with new drugs may be informed by the chemical or pharmacological properties of the drug (91). Most adverse drug reactions are Type A or predictable from a drug’s pharmacology (92). Many Type B or idiosyncratic reactions can also be predicted from the chemical properties of the drug and/or the pharmacogenetics of the patient. Large population–based databases held by regulatory and other bodies may be used to generate this information. This knowledge could focus proactive pharmacovigilance studies.

Pharmacoepidemiologic studies have become increasingly important in assessing the risks of medicines in older people. Many methods have been developed to improve the internal and external validity of pharmacoepidemiologic studies in older people. However, further advances in the methodology of pharmacoepidemiologic studies are required to validly and reliably assess the effects of medicines on outcomes in populations of older people. Finally, findings of pharmacoepidemiologic studies need to be confirmed with intervention randomized trials in populations of older people.

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CONFLICT OF INTEREST

S.N.H. and D.R.A. hold an international patent for the Drug Burden Index with Dr. D. E. Mager.


