Pharmacoepidemiology in older people: Purposes and future directions

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Pharmacoepidemiology in older people

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Summary

Knowledge of the benefit/risk ratio of drugs in older adults is essential to optimise medication use. While randomised controlled trials are fundamental to the process of drug development and bringing new drugs to the market, they often exclude older adults, especially those suffering from frailty, multimorbidity and/or receiving polypharmacy. Therefore, it is generally unknown whether the benefits and harms of drugs established through pre-marketing clinical trials are translatable to the real-word population of older adults. Pharmacoepidemiology can provide real-world data on drug utilisation and drug effects in older people with multiple comorbidities and polypharmacy and can greatly contribute towards the goal of high quality use of drugs and well-being in older adults. A wide variety of pharmacoepidemiology studies can be used and exciting progress is being made with the use of novel and advanced statistical methods to improve the robustness of data. Coordinated and strategic initiatives are required internationally in order for this field to reach its full potential of optimising drug use in older adults so as to improve health care outcomes.

KEYWORDS

Pharmacoepidemiology; Aged,80 and over; Pharmacovigilance; Drug utilization; Polypharmacy

Abbreviations

ACB: anticholinergic cognitive burden scale

ADS: anticholinergic drug scale

ARS: anticholinergic risk scale

CASP-19: control-autonomy-satisfaction-pleasure – 19 items

DBI: drug burden index

DUR: drug utilization research

EMA: European Medicines Agency

EUGMS: European Union Geriatric Medicine Society

IPTW: inverse-probability-of-treatment-weighting

OPPEN: optimizing geriatric pharmacotherapy through pharmacoepidemiology network

OPQUOL: older people's QoL questionnaire

PIMs: potentially inappropriate medications

RCTs: randomized clinical trials

SPB: systolic blood pressure

SPRINT: systolic blood pressure intervention trial

SSA: sequence symmetry analysis

TZDs: thiazolidinediones

WHOQOL-OLD: World Health Organization quality of life questionnaire – version for older people

Background

Older people make up the fastest growing population group. From 2000 to 2030, the worldwide population aged 65 years and older is projected to increase from approximately 550 million to 973 million (15.5% to 24.3% of population in Europe, 6% to 12% in Asia, 12.4% to 19.6% in the USA) [1].

Ageing is characterized by a gradual decline of body functions, marked by a considerable inter-individual variability in the onset, the rate and the severity of decline in both functional and cognitive functions. Ageing is also strongly associated with an increased occurrence of chronic conditions, which accumulate over time [2-3]. Multimorbidity often requires the prescription of several concomitant medications. In high-income countries, polypharmacy (usually defined as 5 or more regular medications) is encountered in 40% to 50% of older adults [4-6]. Polypharmacy is associated with adverse health outcomes, such as adverse drug reactions, hospitalisations, frailty, disability, cognitive impairment and even mortality [7-8].

Randomised clinical trials, such as those used to establish benefits and risks of medications in pre-marketing studies, are insufficient to inform evidence-based care of older adults due notably to limitations in their generalisability. There is an under-representation of older adults, particularly those with multimorbidity and polypharmacy, in clinical trials compared to actual conditions of medicine use in real-world practice [9]. For example, the systolic blood pressure intervention trial (SPRINT) found a reduction in cardiovascular events and mortality among older community-dwelling individuals (aged 75 years or older) with intensive therapy (targeting a systolic blood pressure [SBP] of less than 120 mm Hg compared to standard therapy [SBP target of less than 140 mm Hg]) [10]. However, only 21.5% of real world patients aged 75 years and more would have been eligible for inclusion in SPRINT [11]. In other terms, the SPRINT results can be applied to about one-fifth of people aged 75 years. This demonstrates that the evidence drawn from randomised clinical trials applies to a selected group of individuals and that their generalisability to the older population is unlikely. In addition, clinical trials are limited in duration while older adults suffer from chronic diseases that need protracted treatments. Traditionally, primary outcomes in these studies are based on surrogate markers (i.e. risk factors for diseases), absence of chronic diseases, event rates and mortality. However, these outcomes are not always in line with the priorities of older people [12]. Older adults report that they want preservation of their physical and cognitive functions, autonomy and social activities, even if this means not achieving the longest possible survival [12]. Moreover, the effects of drugs should be put in perspective with the goals of care and with the remaining life expectancy [13-14]. Some medications are effective at achieving their clinical outcome only after a period of several months, sometimes years – a timeframe that is hardly meaningful for older patients with severe illness and at most a few months to live [15]. Older people also frequently have visual and hearing impairment, grasping disorder, difficulty swallowing, cognitive impairment that could lead to a poor adherence. The pill burden, i.e. the number of swallowing tablets or capsules that a patient takes on a regular basis per day, can also represent a reason of nonadherence. Therefore, it is generally unknown whether the benefits and harms of medicines established through pre-marketing clinical trials are translatable to the real-word population of older adults.

Pharmacoepidemiology can provide real-world data on drug utilisation and drug effects in older people with multiple comorbidities and polypharmacy. A wide variety of pharmacoepidemiology studies can be used and exciting progress is being made with the use of novel and advanced statistical methods to improve the robustness of pharmacoepidemiology data. The aim of this paper is to discuss the purposes and future directions of pharmacoepidemiology to enhance safe and effective use of medicines in older people.

Purposes of pharmacoepidemiology studies in older population

Describing the patterns of drug use among older adults: drug utilisation research

Drug utilisation research (DUR) studies aim to estimate the patterns of medication use in large populations: the number of patients exposed to a defined set of drugs (prevalence, incidence), within a given time period and/or within a given place (community, nursing home, hospital, region, country) and their trends over time; the profiles of drug users such as multimorbidity, concurrent medications (polypharmacy), doses, drug-drug or drug-disease interactions, timing in the life-course (e.g. the last part of life). Drug utilisation studies are also useful to describe the prescribers' characteristics (such as specialty, factors influencing therapeutic decisions) and to estimate adherence to prescribing guidelines for a condition in a population [16]. Large surveys of older adults and caregivers to determine experiences, attitudes and beliefs about medicines may be considered under pharmacoepidemiology methods.

DUR can also be used to estimate adherence to prescribed medicines. Adherence to medications is frequently poor among older patients, reducing the potential benefit of drugs and increasing the risk of adverse events and costs [17]. Medication adherence is a complex process without real consensus on the taxonomy. Moreover, potential barriers to adherence can be categorized as patient-level factors, system-level factors, and medication-specific factors. Currently, there is an important methodologic challenge to assess medication adherence across a population and to determine associations between medication adherence and clinical outcomes [18].

Quality of drug use is a major issue in the older population, including both underuse of appropriate therapies and use of potentially inappropriate medications (PIMs). Inappropriate drug use is a significant health problem in older people and is associated with morbidity, increased health service use and mortality [19]. The prevalence of PIM use ranges from 20% to 75% in acutely ill older patients admitted to hospital, from 7% to 88% in hospital older inpatients with and without cognitive impairment, from 0% to 98% in the community setting, and from 5.4% to 95.0% in nursing homes [20-23]. PIMs can be identified with implicit criteria, involving clinical judgment (e.g. Medication Appropriateness Index) and explicit criteria, based on lists of drugs established by expert consensus (e.g. Beers criteria, STOPP/START criteria) [24-26]. A recent review identified 36 articles on PIMs based on explicit criteria published from 1991 to 2017 [25]. A total of 907 different medications/ medication classes, 536 different drug-disease interactions involving 84 diseases/conditions, and 159 drug–drug interactions were listed among the various PIM lists. Benzodiazepines, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants and first-generation antihistamines were the most commonly included medication classes on these PIM lists for older people. Surprisingly, there exists only a limited overlap between the different PIMs lists. In a study comparing five different sets of criteria developed in five different countries, the overall exposure to potentially inappropriate drug use was similar, in particular for the criteria developed in Europe, even though these sets of criteria overlap very little both in content and in the population they cover [27]. For public health policy makers and stakeholders, PIM indicators are useful as they can quantify concerns and highlight the most commonly used PIMs. However, for health professionals, the applicability in daily practice can pose a problem, especially if no consensually therapeutic alternatives are proposed.

Other quality indicators measure the risk pharmacological exposure entails, for instance scales summarizing the anticholinergic and/or sedative load of medications. The most often used tools are the anticholinergic risk scale (ARS), the anticholinergic cognitive burden scale (ACB), the anticholinergic drug scale (ADS), the drug burden index (DBI) and the sedative load [28-29]. Currently, there is a lack of international consensus on anticholinergic scales in terms of which drugs should be included; however, regardless of approach used to measure exposure, anticholinergic burden seems to be associated with falls, impairment of cognitive function and mortality in older people [29-31].

Observational studies contribute also to the understanding of prescribing cascades that amplify the polypharmacy phenomenon. Prescribing cascades happen when a new drug is prescribed to treat symptoms of an unrecognized adverse drug reaction (ADR) related to a pre-existing drug, with this new drug itself increasing the risk for developing additional ADRs. Older adults with chronic diseases and multiple drugs are at risk for prescribing cascades. For example, antiparkinsonian medications have been initiated for the treatment of symptoms arising from the use of drugs such as antipsychotics or metoclopramide. The antiparkinsonian drugs then could induce new ADRs, including orthostatic hypotension and delirium that would require a new treatment if not identified as other ADRs [32-33].

Therefore, DUR can contribute to draw the attention on the need both for clinical management and for further interventions (such as educational interventions) to optimise medicine use in older adults.

Safety of drug use in older adults

The risk of ADRs increases in older patients due to changes in pharmacokinetics and pharmacodynamics, frailty, multiple concurrent comorbidities and medicines [2]. The evaluation of medication risks combines two fields of expertise: pharmacovigilance and pharmacoepidemiology [34].

Pharmacovigilance is essentially based on the study of spontaneous reports and has been the first drug assessment method in real-life set up to provide data on the safety of drugs. Reporting analysis can detect rare ADRs, which can be especially valuable in groups that are particularly excluded from clinical trials. In the 1980s, one-year after the introduction of bepridil for the treatment of angina on the French market, about 110 cases of torsades de pointes, some fatal, occurred in patients aged 70 years and more [35]. Modifications in the recommendations for the use of bepridil – avoiding use with other antiarrhythmics and cautious use with diuretics - resulted in an immediate and dramatic decrease in the incidence of arrhythmias. More and more often, a safety issue detected by spontaneous reporting data could be confirmed by pharmacoepidemiology studies. For example, case reports of acute renal failure with the concurrent use of diuretics, drugs blocking the renin-angiotensin system (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) and nonsteroidal anti-inflammatory drugs were particularly observed in older patients in pharmacovigilance [36-37]. A nested case-control study in a large primary care database containing longitudinal data on patients' medical history, smoking, alcohol use, body mass index and indication for use of antihypertensive drugs, confirmed the risk of acute kidney injury with triple therapy, particularly during the first 30 days of use [38]. In another example, deaths occurring in older adults with dementia using antipsychotics were reported in pharmacovigilance; the increased risk of mortality was confirmed by meta-analyses of randomised controlled trials and observational studies [39-41]. This detection and confirmation of safety concerns contributes to drug safety through black box warnings, changes in drug labelling and even withdrawal from the market.

Although spontaneous reporting provides valuable information in drug safety, it presents inherent limitations, including under-reporting, difficulty in identifying low risks, and the frequent unfeasibility of quantifying risk. Several methods are therefore proposed for safety signal detection in healthcare databases such as disproportionality analysis, traditional pharmacoepidemiology designs (e.g. self-controlled designs), sequence symmetry analysis (SSA), sequential statistical testing, temporal association rules, supervised machine learning and the tree-based scan statistic [42]. For example, SSA is a method applied on computerized claims data for detecting adverse drug events based on the concept of prescribing cascade. SSA analyses the sequences of medications; if one medication (drug B) is more often initiated after another medication (drug A) than before, it may be an indication of an adverse effect of drug A [43]. Founded on a simple principle, SSA has the ability to provide a risk estimate that may be useful to characterise the signal detection in administrative database and support decisions [42].

Effectiveness of medicines and quality of life for older people

Randomised clinical trials (RCTs) are considered the gold standard to estimate the efficacy of drug therapy. However, they are conducted under ideal conditions, and their external validity is limited. In comparison, observational studies can evaluate the effectiveness of drug therapy in older people in real conditions, but their nature makes them prone to suffer from potential biases (Table 1). Many biases are of concern with observational studies, such as for example (i) confounding (stemming from covariate imbalance and clinical indication, for example); (ii) immortal time bias due to an unclear definition of time zero and to a biased reassignment of people who deviate from the treatment strategy that they were assigned to; (iii) protopathic bias which occurs when a drug is initiated in response to the first symptoms of the disease which is, at this point, undiagnosed [34, 44]. However, recent advances in pharmacoepidemiology studies fill the gap left by RCTs, when conducted under rigorous methodological standards [45]. Pragmatic trials, case-control or cohort studies conducted with healthcare databases have been specially adapted to the constraints of drug assessment in real-life. New approaches have been developed to control for confounding in observational studies such as marginal propensity scores and structural models [46]. Mixed-effect modelling or time-dependent Cox models are likely to produce biased estimates in the presence of time varying confounders affected by prior exposure (e.g. by a change in drug exposure over time). G estimation, inverse-probability-of-treatment-weighting (IPTW) and parametric G-formula methods are better alternatives [46]. Network analysis is a novel methodology for analysing effectiveness of drugs and may offer interesting perspectives [47].

Observational studies are also useful to estimate quality of life in real-life conditions [48]. The influence of medications on well-being is probably more important to assess than the effect on mortality according to values and preferences of older adults. Several validated tools have been developed as self-reported quality-of-life surveys in older adults, such as older people's QoL questionnaire (OPQOL), control-autonomy-satisfaction-pleasure - 19 items (CASP-19) and World

Health Organization quality of life questionnaire - version for older people (WHOQOL-OLD) [49]. They provide feedback on the patients’ physical and mental performance, can indicate a change in health status and may be useful in predicting future adverse events [48].

Optimal therapy in the care of older adults: what level of evidence?

According to the research question, the methodological approach and the level of evidence require careful thoughts. The classical hierarchies of studies (e.g. Oxford centre for evidence based medicine, Bradford Hill’s guideline, GRADE) in order to categorize the level of evidence does not necessarily apply to all types of situations encountered in pharmacoepidemiology studies [50]. However, while the GRADE process (which is used in the development of clinical guidelines) allocates RCTs as high quality and non-RCTs as low quality as a starting point, it does allow for increasing the quality of evidence rating of observational studies where they have been robustly conducted and decreasing the quality rating of RCTs where issues of bias, inconsistency, indirectness, or imprecision have been identified [51]. Meta-analysis is considered as the higher level of evidence. However, meta-analyses are often based on the synthesis of data issued from one type of study. Wald and Morris propose an underused approach, called teleoanalysis, to obtain a quantitative general summary of (a) the relation between the cause of a disease and the risk of the disease and (b) the extent to which the disease can be prevented [52]. Teleoanalysis combines data from different study designs (case reports or case series, cohort or case-control studies, randomised clinical trials, meta-analyses...) across all grades of evidence rather than from one type of study. For instance, it was recommended to use with caution thiazolidinediones (TZDs) in the management of type 2 diabetes because these drugs may increase the risk of heart failure (50). Singh et al conducted a teleoanalysis to 1) estimate the magnitude of the risk of heart failure with TZDs using data from observational studies and randomized controlled trials and 2) classify this adverse effect under the novel dose-time-susceptibility system using data from published case reports and spontaneous reports from the Canadian drug reaction monitoring program [53]. The results confirmed the increased magnitude of heart failure risk with TZDs. Teleoanalysis could be especially useful when certain categories of patients are excluded from randomised clinical trials, such as older people, in order to increase the level of evidence. Overall, further advances in the methodology and utilisation of pharmacoepidemiology studies in the older population are required to ensure that all evidence can be incorporated into evidence-based practice (such as informing clinical practice guidelines) [54].

Costs associated with drug therapy in older people

Expenditures on medicines are significantly higher among those aged 65 years and over than among younger people. In the USA, the mean expenditure on prescribed medications is three times higher among older adults compared to non-elderly adults ($US 324 vs $US 102) [55]. In Canada, while it is estimated that older adults comprise 13.6% of the population, they are responsible for 39% of the pharmaceutical expenditure [56]. The cost of pharmacological care associated with the older population can be expected to increase with the predicted increase in number of older adults. The total costs associated with drug therapy encompass both the costs for medication acquisition, administration and monitoring (for example therapeutic drug monitoring) as well as costs that may arise due to adverse drug events such as primary care visits, hospitalisations, laboratory tests and procedures, and transportation to medical care facilities. Pharmacoepidemiology studies are ideal to assist in rationalising the costs of medication in the older population and ensuring adequate allocation of resources [57].

Future directions

There are several initiatives occurring internationally with the aim of finding ways to improve the development, the evaluation and the safety monitoring of medicines for older patients.

Since 2011, the European Medicines Agency (EMA) has proposed specific guidelines for drug development across the complete span of drug lifecycle as well as information meant for older patients

[58-59]. The EMA has also set up a geriatric expert group on issues related to the older adults to provide advice on both the designs of clinical trials and the baseline characteristics of the older populations to be included (e.g. frailty, comorbidities, comedications). Improving product information to enhance the clarity of geriatric-specific issues in summaries of product characteristics and package leaflets is also an important challenge for the EMA. A pilot study is currently under way to decide on the inclusion of adapted updates in the standard templates [56]. Regarding pharmacovigilance, the EMA considers that benefit-risk assessment, medication errors and monitoring of specific side effects occurring in older patients should be included in the risk management plan or as post-authorisation measures. And lastly, a specific module of the guideline on good pharmacovigilance practices addressing the specific needs of the geriatric population is being developed by the EMA.

The involvement of organisations representing the interests of older adults in Europe (e.g. AGE platform Europe, European Union Geriatric Medicine Society [EUGMS]) in the above described initiatives is essential. Stakeholder and consumer groups should also be involved with governments to ensure that initiatives are relevant, feasible and can be implemented in a sustainable way. For instance, EUGMS is a European clinician network whose goal is to improve the use of drugs in older subjects, to promote the inclusion of older people in clinical trials, to promote appropriate drug prescription in older people, and to develop pharmacogenetics research in older patients [56-61].

Recently, the International Society of Pharmacoepidemiology, considering that pharmacoepidemiology is central to the understanding of drug safety in older adults, has created a geriatric pharmacoepidemiology special interest group [62]. Its aims are to facilitate a collaborative forum to discuss the challenges and endeavours of geriatric pharmacoepidemiology, to develop and to improve the methods used with high-quality standards for geriatric pharmacoepidemiology research, and to promote the geriatric perspective by outreach, collaboration and educational activity applications. For example, the optimizing geriatric pharmacotherapy through pharmacoepidemiology network (OPPEN) workshop defined 8 research priorities for optimizing geriatric pharmacotherapy: 1) quality of medication use; 2) vulnerable patient groups; 3) polypharmacy and multimorbidity; 4) person-centred practice and research; 5) deprescribing; 6) methodological development; 7) variability in medication use; and 8) national and international comparative research [63].

Conclusion

Given the international ageing population and the costs associated with caring for older adults, it is imperative to ensure that medicines are being used appropriately and efficiently in this population. More importantly, use of inappropriate medications can lead to harms in older adults and reduce their quality of life. The field of pharmacoepidemiology can greatly contribute towards improving the quality use of medicines in older adults. Through drug utilisation research, patterns of medicine use (including inappropriate medicine use) can be assessed and used to inform interventions and changes in policy and practice. Comparative effectiveness research and pharmacovigilance contribute to the knowledge of the benefits and harms of medicine use in the real-world population, informing evidence-based practice. However, there are challenges to the field of pharmacoepidemiology and coordinated and strategic initiatives are required internationally in order for this field to reach its full potential of optimising medicine use in older adults to improve health care outcomes.

Disclosure of interest

The authors declare that they have no competing interest.

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Table 1. Characteristics of randomised clinical trials (RCTs) and observational studies

Randomised clinical trials	**Observational studies**
Usually limited sample size	Usually large numbers of patients
Selective population	Real life conditions
Short-term follow-up	Potential for long-term follow-up
High internal validity	Low internal validity
Low external validity	High external validity
Reduced confounding	High risk of confounding
Expensive	Low cost or relatively inexpensive