The Effects of Polypharmacy in Older Adults

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An assessment of the safety and efficacy of multiple medications in older adults requires clinically relevant objective outcomes and pharmacological measures of medication exposure. Important outcomes include geriatric syndromes and objective measures of physical function. Measurements of medication exposure have evolved from merely counting the drugs to a consideration of pharmacologic principles such as drug class, dose response, and maximal effect. Emerging evidence regarding the effects of cumulative medication exposure on functions critical for independence may provide guidance for prescribers.

There is very little high-quality evidence to guide prescribing for older people, particularly those with multiple medical conditions for which multiple medications may be indicated and for those with disabilities.¹ Evidence-based prescribing guidelines rely predominantly on the results of clinical trials that exclude older people with multiple comorbidities.² The application of published guidelines to older patients with multiple comorbidities results in polypharmacy, with high risks of drug interactions and adverse reactions.³ Polypharmacy is commonly defined as the use of multiple medications or the use of a medication that is not indicated.⁴ Measures of the “appropriateness” of prescribing are often based on expert consensus statements, such as the updated Beers criteria,⁵ but the Beers criteria do not provide guidance on combinations of medicines. Most of the evidence on the effects of medicines in frail older people is from observational studies; there is very little evidence from randomized controlled trials (Supplementary Tables S1–S3 online). The tables present important relevant studies relating to the effects of different measures of medication exposure on older people in hospitals, the community, and residential facilities for the care of the aged, identified using PubMed. Although observational studies describe the effects of medications beyond the stringent inclusion and exclusion criteria and monitoring procedures of randomized trials, they are limited by confounding and bias. Current best practice in prescribing for geriatric medicine patients relies on regular evaluation of the safety and efficacy of each medication and of the combination of medications for each patient.¹

OUTCOMES OF MEDICATION EXPOSURE

Over the past 50 years, there has been significant progress in defining clinically relevant objective outcomes of medication exposure in older people. In addition to traditional measures of efficacy and safety, such as effects on disease and adverse drug reactions (ADRs), the effects of medications on geriatric syndromes, cognition, and physical function have recently been investigated.

ADRs are an important measure of the risks of medication exposure. A disproportionately high proportion of serious adverse drug events occur in older people, even after adjusting for increased drug use in old age.⁶ Hospital admissions related to ADRs have increased over the past 20 years, particularly among patients above the age of 80 years.⁷ Hospitalization is a critical clinical outcome of medication use in older people, as it is frequently associated with adverse events and functional decline.⁸ In Sweden, fatal ADRs account for ~3% of all deaths and occur in men and women with median ages 83 and 81 years, respectively.⁹ While it is important to minimize iatrogenic deaths, with increasing age and proximity to the maximal human life span, death is more likely regardless of therapy, and the focus of care switches from life extension to compression of morbidity.¹⁰

In frail older people, ADRs may present as geriatric syndromes such as falls and delirium, which are not formally monitored in most clinical trials.¹¹ Falls and delirium independently predict nursing home placement in older people¹¹,¹² and may be important ADRs to monitor when selecting an outcome that is meaningful to the individual patient.

Functional independence is a key goal in the care of older people, and functional measures may be important outcomes of medication exposure. Functional and cognitive impairment are strong independent predictors of nursing home placement in older people.¹³ Self-report measures of disability, which are susceptible to reporting bias and are influenced by environmental factors, have been included as outcomes in some clinical trials.¹⁴ Objective measures of lower-extremity function, such as the Short Physical Performance Battery and gait speed measurement, may be useful functional outcomes of clinical trials in older people.¹⁵ The battery has excellent reliability and is sensitive to clinically important changes. It has been shown to

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Objective measures of physical function, such as the Short Physical Performance Battery, may be useful for assessing outcomes in prospective clinical trials for drugs developed to prevent or treat sarcopenia and frailty or to treat specific diseases or disease risk factors. They could also be used to measure the effects of combinations of drugs or changes in drug regimen for older people. No drug has been consistently shown to prevent functional decline in humans. However, animal studies suggest that supplementation with resveretrol is associated with improved functional performance in old age. Recent trials have investigated the effects of specific drugs and groups of drugs on self-reported and objective measures of physical function in older people (examples in Supplementary Tables S1–S3 online). In the frail elderly who have multiple comorbidities and minimal functional reserve, and on whom there is very limited evidence concerning the effects of medications on outcomes to guide prescribing, the impact of a change in medication regimen on physical function may be a clinically useful marker of drug response.

MEASURES OF MEDICATION EXPOSURE

Measures of medication exposure used in studies to assess the effects of medications in older people have progressed from simple counts of the number of drugs taken to a consideration of pharmacokinetic and pharmacodynamic principles, such as drug class, half-life, dose response, and maximal effect.

Examples of the effects of the use of multiple medications in older people, including ADRs, mortality, hospitalization, falls, fractures, and functional outcomes, are shown in Supplementary Table S1 online. While it may be a useful “red flag” for a high risk of medication-related problems, a finding of multiple medication use does not guide the prescriber with respect to which of the drugs should be continued and which should be reduced or stopped. There is some evidence that even the apparently strong association between multiple medication use and the incidence of falls in the elderly (Supplementary Table S1 online) may not be significant when indications for the medicines and the types of drugs that are prescribed are considered.

The effects of specific drug classes on outcomes such as falls, fractures, cognitive and physical function, and mortality have been described in the elderly. Examples of some of the best-studied drug classes are provided in Supplementary Table S2 online. The associations between exposure to medications and these outcomes appear to be stronger in studies of community-dwelling elderly persons than in those living in nursing homes. This may reflect the higher prevalence of geriatric syndromes, functional decline, and mortality in nursing home residents from myriad causes. As shown in Supplementary Table S2 online, for most drug classes, a majority of the studies on association with functional outcomes are observational. Randomized trials have been performed with antihypertensives and with testosterone, neither of which appears to have a consistent significant effect on cognitive or physical function.

The most common pharmacokinetic factors included in measures of medication exposure in older people are half-life and dose response. The associations between measures of benzodiazepine exposure (including pharmacokinetic factors) and the incidence of falls and fractures have been studied extensively. There is good evidence of a dose–response relationship, with less consistent results with regard to the role of half-life in determining these associations (Supplementary Table S2 online).

Drug–drug interactions also influence medication exposure. They are common and are strongly associated with the number of dispensed medications. Drug–drug interactions have been associated with ADRs in older people. However, the impact of pharmacokinetic drug interactions has not been systematically included in models of drug exposure that have been associated with clinical outcomes in older people. Pharmacodynamic interactions, such as the cumulative effects of medications that act on similar receptors or end organs, have been estimated in recent measures of drug exposure in older adults, particularly with respect to medications that act on the central nervous system and anticholinergic medications. Supplementary Table S3 online summarizes the studies (all observational) on the associations between increasing exposure to medications that act on the central nervous system or medications with anticholinergic effects and the incidence of falls, fractures, ADRs, and impairment of physical and cognitive functions.

MEDICATION EXPOSURE AND FUNCTIONAL OUTCOMES IN OLDER PEOPLE

A measure of medication exposure that is associated with functional outcomes may be a clinically useful prescribing tool. Exposure to increasing numbers of medications was not independently associated with performance measures in observational studies of two epidemiologic study populations of older adults in the United States. These findings are supported by a randomized trial of interdisciplinary medication review that reduced polypharmacy but did not affect function. However, an increase in exposure to “high-risk” medications (which are variably defined) has been associated with impaired physical function in older people. In longitudinal observational studies, exposure to benzodiazepines has been associated with functional decline and disability (Supplementary Table S2 online). In observational studies, an increase in exposure to medications with anticholinergic effects (variously defined by different investigators) has been consistently associated with impaired physical function (Supplementary Table S3 online). A cross-sectional study of older people found that exposure to “inappropriate” drugs, as defined by the Beers criteria, was associated with impaired physical performance. Although “fall-risk-increasing drugs” were defined based on evidence of an association between each of these drugs and an increased risk of falls, they include many medication classes that have been associated with impaired function in the elderly, and withdrawal of fall-risk-increasing drugs has been associated with improvement in mobility measures.

The drug burden index is an integrated model of exposure to the medications that have been most consistently associated with functional impairment: those with anticholinergic and sedative effects (Supplementary Tables S2 and S3 online). The drug burden index is essentially a linear additive model.
of pharmacological effect. It incorporates principles of pharmacokinetics (dose) and pharmacodynamics (dose response, maximal effect) to measure cumulative exposure to anticholinergic and sedative medications. In objective measures of physical performance and cognition in two populations of older adults, drug burden index has been independently associated with impairment.24,25 The addition of the total number of medications, excluding anticholinergics and sedatives, to the model did not improve correlations with physical performance or cognition in older populations. This simple evidence-based model may be a clinically useful tool for measuring the impact of medication exposure on functioning in an elderly patient. The index may be incorporated into comprehensive risk-assessment tools that are used for screening elderly patients for risk of functional impairment. Such tools currently rely on multiple-medication exposure in order to detect medication-associated risk.30 Randomized interventional clinical trials are required to assess whether pharmacologically calculated measures of medication exposure can guide prescribing to optimize function in older adults who are on multiple medications.

Functional outcomes have now been recognized as important therapeutic goals in older adults. While polypharmacy may be a useful cue for medication review, it is not an independent predictor of the functions essential for independence in older people. Measures of medication exposure have been developed that incorporate pharmacologic principles such as the classes and doses of medications. However, more accurate measures will require a better understanding of the pharmacokinetic and pharmacodynamic changes associated with old age, particularly in the presence of multiple medications and comorbidities. The available evidence is limited primarily to observational studies on the risks of medication exposure, with little evidence from studies in humans of any medications that can improve function in older people. Therefore, such models can measure only the risk of functional impairment associated with medication exposure in older adults. More information on the efficacy of medicines in frail older people is needed to allow clinicians to estimate the risk-benefit ratio when prescribing for older patients.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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CONFLICT OF INTEREST

S.N.H. has applied for an international patent for the drug burden index with D. Abernethy and D. Mager. D.G. declared no conflict of interest.

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