Evidence, Ethics and Medication Management in Older People

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ABSTRACT

Prescribing in frail older people may be improved by application of the four tenets of medical ethics – beneficence, non-maleficence, autonomy, justice – rather than solely those of evidence-based medicine. Evidence-based medicine provides data primarily on the efficacy of interventions. In younger adults, this is often sufficient to make a decision to prescribe medications. In frail older people, there are additional issues that need to be considered, such as individualisation of efficacy data, increased risk of adverse drug reactions, patients' views on risk and benefit, difficulties in assessing capacity to understand risk and benefit, consent to treatment, and concerns about the cost-effectiveness of interventions in the very old. In such situations, evidence-based medicine can be useful in informing the prescriber about the ethical principle of beneficence. However, the decision to prescribe or withdraw medications is also influenced by the other three tenets of medical ethics: non-maleficence (adverse drug reactions, polypharmacy), autonomy (consent, competency) and justice (appropriate allocation of healthcare resources).

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INTRODUCTION

Older people are the greatest consumers of medications in society, yet there is widespread concern that their medication use is often inappropriate because of under-prescribing, over-prescribing, inappropriate choice of medications, polypharmacy, and significant harm from avoidable adverse drug reactions.[1-3] Evidence-based medicine was developed, in part, to solve the problem of inappropriate prescribing. Therefore, it is surprising that evidence-based medicine has not had a major impact on inappropriate prescribing in older people.[4] Although, evidence-based medicine uses all forms of evidence, the greatest weight is given to randomised clinical trials.[4] Typically, clinical trials focus on efficacy of medications in mostly homogeneous groups of subjects with a single disorder. In contrast, geriatricians are often concerned with avoiding adverse drug reactions in a heterogeneous group of patients with multiple comorbidities. This poses a dilemma for the application of evidence-based medicine to frail older people in clinical practice.

The typical older Australian has four or more comorbidities and consumes four or more different medications each day.[5-7] Polypharmacy, defined as the use of five or more medications, occurs in 20 to 40% of older people.[8] Although the benefits of appropriately prescribed and monitored medications are established, this must be balanced against the fact that the incidence of adverse drug reactions increases with age.[9,10] In older people, 20% of hospital admissions are medication-related, impaired cognitive and physical function are associated with drug burden, and adverse drug reactions and polypharmacy are associated with increased mortality.[7,11,12] Clearly, a better framework than evidence-based medicine is needed for prescribers and health professionals involved in improving the outcomes of older people who are prescribed medications. The field of medical ethics can provide such a framework.

MEDICAL ETHICS

Medical ethics is the science and philosophy of the moral dilemmas that occur in clinical practice.[13] The four tenets – beneficence, non-maleficence, autonomy, justice – form the main framework for ethical decision making in medicine.[14] These principles can and have been applied to prescribing medications in older people (Figure 1).[15,16]

Beneficence

Beneficence is the duty that all health professionals have to do good. Beneficence overlaps with efficacy that is defined by evidence-based medicine, i.e. how evidence-based medicine can inform beneficence in older people, especially frail older people.

Clinical Trials

Ideally, the most useful data would be sourced from clinical trials performed in or including old and frail subjects similar to real-life patients. In reality, all that is available for frail older people are data from clinical trials undertaken in other groups of subjects (Table 1). Unless the desired outcome in patients following prescription of a medication can be clinically monitored, there will always be uncertainty in assessing the efficacy of medications. Health professionals are often reliant on published reports of efficacy for medications obtained in clinical trials.[17] Such uncertainty is further magnified when it becomes necessary to extrapolate data from the clinical trial population to real-life frail older people. Unfortunately, the p values from clinical trials do not always reflect prescribability in terms of the benefit in frail older people

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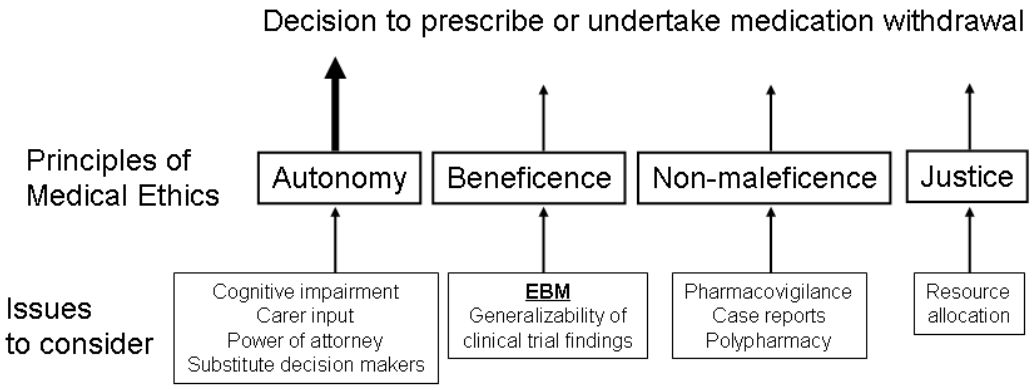

Figure 1. Relationship between evidence-based medicine and the four tenets of medical ethics. Although all the tenets are considered to have equal importance, autonomy takes precedence when interventions are planned. Evidence-based medicine is primarily useful in informing prescribers about beneficence and sometimes non-maleficence.

Table 1. Sources of clinical trial data and uncertainty about efficacy of medications in older people

Clinical trial evidence base for efficacy in older people	Sources of uncertainty when using the evidence to determine efficacy in old or frail patients
Any clinical trial	Early termination. Large number of dropouts. Analysis by last observation carried forward. Multiple and combined outcomes.
Clinical trials performed in older people	Differences between inclusion and exclusion criteria and/or patient characteristics in clinical trial and real-life older patients.
Analysis of a subgroup of older people recruited into clinical trials	Small numbers of subjects in each subgroup. Multiple subgroup analyses (false positive results). Age-interaction analysis (false negative results).
Extrapolation of clinical trial results performed in young adults	Although disease outcomes are usually worse in older people, it does not mean that the treatment will be more useful. Age-related differences in disease pathogenesis, drug metabolism and adverse drug reactions.

and does not provide perspective on possible harm the medications may cause.

Recruitment

As it is difficult to recruit older people into clinical trials, older people, particularly those who are frail or have multiple comorbidities are poorly represented in most clinical trials.[18,19] Clinical trials frequently have inclusion and exclusion criteria relating to level of functioning or comorbidities. These criteria may be justified by their influence on the primary outcome but lead to exclusion of many older people. For example, a recent Australian study found that the difference between the median age of patients with colorectal cancer or non-small cell lung cancer enrolled in clinical trials compared with the median age of Australians with these cancers had increased over the last two decades.[20] The authors concluded that international clinical trials for cancers are becoming unsuitable for application to Australians because of this age discrepancy.[20]

Interpretation

Even when clinical trials are performed in older people, it is important to carefully interrogate the results and conclusions. For example, many publications claim to study older people when they have recruited subjects over the age of 65 years. There is substantial difference between 65-year-old clinical trial subjects and real-life 85-year-old patients.

The Hypertension in the Very Elderly Trial (HYVET) investigated the treatment of hypertension in subjects over 80 years of age and concluded: 'results provide evidence that antihypertensive treatment with indapamide (sustained release) with or without perindopril in persons 80 years of age or older is beneficial'.[21] This trial clearly aimed to provide an evidence base to justify treating hypertension in older people, most of whom would have established vascular disease. However, the subjects had rates of stroke and death less than half of that seen in the same age groups in Australia, which makes generalisability of these results uncertain. The trial was stopped prematurely by the data monitoring committee for a positive effect on mortality which increases the risk of a false positive result, and the p value for the primary outcome of stroke did not reach statistical significance.[22]

Even when clinical trials are performed in older subjects it is important to examine the inclusion and exclusion criteria and the subject characteristics to see how they might compare to real-life patients. Clinical trials generate data on the efficacy of medications by carefully choosing subjects who might be administered the medication — clinical practice should be no different.

Subgroup Analysis

In the absence of clinical trials performed specifically in older patients, subgroup analysis is the next option available to provide an evidence base for efficacy. On one hand, there is a risk of both false positive and negative results when numerous subgroups are analysed *post hoc*. On the other hand, when age–interaction analysis is undertaken, then any differences in the responses of the oldest cohort of participants can be hidden by selective choice of the number and size of the other age cohorts. For example, although angiotensin converting enzyme inhibitors have had a major impact on the management of heart failure with systolic dysfunction, one meta-analysis of four major angiotensin

converting enzyme inhibitor trials reported that there was no statistically significant benefit for people over the age of 75 years for either death (OR 0.95; 95%CI 0.74–1.22) or the combined outcome of death, heart failure and myocardial infarction (OR 0.89; 95% CI 0.69–1.13).[23] Likewise, beta blockers have had a major impact on heart failure, yet the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) did not find any statistically significant benefit on the primary combined outcome of death and cardiovascular hospitalisation in subgroups of subjects over 75 years of age (HR 0.92; 95%CI 0.75–1.12) or over 85 years of age (HR 1.32; 95%CI 0.73–2.37).[24]

Comparison with Younger Cohort

Geriatricians may have to resort to extrapolating results from clinical trials performed in younger adults. It is often debated that beneficial effects seen in a younger cohort is likely to be greater in older people because disease and outcomes are more frequent in older people. This type of debate has been used widely to support the use of warfarin in older people. In clinical trials cited in the Cochrane review of warfarin use in atrial fibrillation, the average age in four of the five trials was 67 to 68 years with an overall average age of 69 years and subjects were at low risk of haemorrhage.[25] In this review, warfarin was found to substantially reduce the risk of subsequent stroke (OR 0.39).[25]

The majority of risk stratification scores for stroke in atrial fibrillation such as the $CHADS_2$ score (clinical scoring system quantifying a risk of stroke in patients with atrial fibrillation) included age 75 years or more as an indicator for warfarin therapy. In their review of antithrombotic use for stroke prevention in patients with atrial fibrillation, Lip et al.[26] concluded: 'anticoagulant therapy remains under used, particularly in the elderly, who probably have the most to gain from stroke prevention owing to their high absolute risk'. However, when quality adjusted life years are the primary outcome, anticoagulation has little if any effect or even harm in people over 65 years of age.[27,28] Moreover, the rate of serious and fatal haemorrhages among residents on warfarin who were recruited from 25 nursing homes were so high in one study that the authors concluded: 'the results of this study provide compelling evidence of serious safety concerns around the use of warfarin therapy in the nursing home setting'.[29] They estimated that there are 34 000 fatal or serious warfarin-related events per annum in nursing home residents.[29]

Although the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study has provided some reassurance, many of the enrolled subjects had previously been on warfarin, so there was selection bias to include subjects with lower risk of haemorrhage.[30] Australian data confirm that frail older hospital inpatients with atrial fibrillation are less likely to be prescribed antithrombotic therapy and are more vulnerable to the adverse outcomes.[31]

Evidence

Evidence gained from clinical trials provides prescribers with some data about the possible efficacy of medications in older subjects, however, many uncertainties remain. Applying conclusions from a clinical trial to individual patients is straightforward when the patients resemble the clinical trial subjects. However, in frail and/or older patients, prescribers often deal with considerable uncertainty as to the effectiveness of the medication and this uncertainty has to be balanced against the risk of adverse drug reactions and patient priorities.

For example, guidelines recommend the use of warfarin in the elderly with atrial fibrillation. A medical ethics approach would show that warfarin is appropriate in elderly patients with atrial fibrillation who do not have a history of haemorrhage, who are willing to comply with monitoring and consent to treatment after being made aware of the risks of haemorrhage. Elderly patients with cognitive impairment and regular falls who are unlikely to comply with monitoring and refuse to take medications would not be anticoagulated. Treatment decisions in older people need to be individualised and medical ethics provides a useful framework for such individualisation.

Non-Maleficence

Non-maleficence refers to the health professional's duty to prevent or do no harm to patients. Non-maleficence corresponds with the aim to avoid adverse drug reactions. Clinicians do not deliberately prescribe medications to cause harm, however, they may do so unknowingly, influenced by marketing, key opinion leaders and guidelines that advocate blanket prescribing for specific diseases, rather than individualisation of treatment.

Adverse Drug Reactions

The evidence base for adverse drug reactions is mostly sourced from pharmacovigilance studies, case reports and case-control studies because clinical trials are designed to focus primarily on efficacy rather than safety. Adverse drug reactions are more common, more severe, less likely to be reported and more likely to result in death in older people.[1,11,12] In a study of community-dwelling older people taking medications, the overall rate of adverse drug reactions was 50 per 1000 patient years, equivalent to a number-needed-to-harm of 20.[32] In subjects in nursing homes, the rate of adverse drug reactions was 227 per 1000 resident years equivalent to a number-needed-to-harm of 4.5.[33] It would seem reasonable that before making a decision to prescribe, the number-needed-to-harm be balanced against the number-needed-to-treat. In younger adults, prescribers can focus primarily on the efficacy of medications, because adverse drug reactions are less of a concern. In older people, adverse drug reactions are a concern, therefore, prescribers have an ethical duty to consider the risk of harm before deciding to prescribe.

Application of the results of clinical trial data obtained in younger adults to older people can cause them harm. Spironolactone was associated with reduced mortality in clinical trial subjects with heart failure aged around 60 years. When this finding was extrapolated to the general population where most people with heart failure are over 75 years of age, there was an increase in deaths from hyperkalaemia.[34] Cyclo-oxygenase-2 inhibitors were associated with reduced risk of gastrointestinal haemorrhages compared to non-selective non-steroidal anti-inflammatory drugs in clinical trial patients. Yet when cyclo-oxygenase-2 inhibitors were used in the general population where most people with arthritis are older, there was a 10% increase in hospital admissions for gastrointestinal haemorrhage.[35]

Inappropriate Prescribing

Inappropriate prescribing is a term frequently used in geriatric therapeutics.[3] The Beers criteria is a consensus list of medications deemed to be inappropriate in older people.[36] The prevalence of inappropriate prescribing defined by the Beers criteria is 10 to 66% in older people and is associated with increased rates of adverse drug reactions, death, nursing home admission and hospitalisation, and decreased quality of life.[3,8,37]

Polypharmacy

Polypharmacy increases the risk of adverse drug reactions.[38] In one study, the risk for adverse drug reactions was increased by 3.4–fold in older subjects taking four to six medications, 4.6–fold in those taking seven to nine medications and by 5.9–fold in those taking ten or more medications.[39] Polypharmacy is associated with the additive risk of an adverse drug reaction with each successive medication, the increased likelihood of drug interactions and prescribing errors.[40,41]

Non-maleficence reminds us that it may be unethical to extrapolate results from clinical trials performed in younger subjects to frail older patients, using medications deemed inappropriate by guidelines such as the Beers criteria and polypharmacy. At minimum, consideration should be given to the increased risk of harm caused by medications in older people, then attempts made to balance this against possible efficacy. Once medications are prescribed then it is important to have a monitoring plan to ensure they are discontinued as soon as adverse events occur.

Withdrawing Medication

Evidence is also needed that withdrawing medications complies with these ethical principles. Withdrawing medications or deprescribing has become a key aspect of the management of older people and is consistent with clinical trial methods.[42] All clinical trials require that subjects who develop significant adverse reactions have their medications ceased. The withdrawal rates can be high and it is only by withdrawing medications in subjects with adverse drug reactions are benefits accrued for the entire group of subjects.

In their systematic review, Iyer et al.[43] found that after withdrawal of antihypertensive therapy, many subjects (20 to 85%) aged 65 years and over remained normotensive or did not require reinstatement of therapy, and there was no increase in mortality. They also found that withdrawal of psychotropic medications was associated with a reduction in falls and improved cognition.[43] They concluded that there was evidence for the short-term effectiveness and/or lack of significant harm when antihypertensives, benzodiazepines and psychotropic medications are withdrawn with careful monitoring in older people.[43]

Autonomy

Autonomy refers to the health professional's duty to respect people and their rights of self-determination. Although all four tenets of medical ethics have equal standing, autonomy is the most important for interventions because of the power of veto. Thus, it is surprising that so few guidelines or surveys of 'rational' or 'appropriate' prescribing consider the issues of consent and autonomy.

Informed Consent

Informed consent is a particular problem in older people because of the high prevalence of cognitive impairment. Patients living with dementia are frequently covertly given medications without consent and often these are psychotropic medications.[44] Given the adverse effects of psychotropic medications in dementia and limited benefits, this practice would seem to contradict the tenets of beneficence, non-maleficence and autonomy.[45,46]

Consent and competency or capacity to consent, are complex. Decisions about competency are often based on sociopolitical factors rather than objective medical assessment of ability to understand and weigh up risks and benefits of treatment options.[47] Advance directives rarely if ever give detailed advice on the use of medications.[48]

Substitute Decision Makers

Apart from competency other factors also impact on autonomy. Filialism is a term used to describe the limiting of the freedom and autonomy of a older people by well-meaning sons and/or daughters who take over decision-making for their parents. In many situations, the family's wishes regarding health care and those of the older person are discordant.[49] In these situations, the role of substitute decision makers who are often carers and family members, can be complex. Although medical treatments can be approved by guardianship tribunals, this is rarely undertaken for routine pharmaceutical interventions.[50]

Justice

Justice refers to the health professional's duty to treat individuals fairly, free of bias and on the basis of medical need.[13] Justice is not dependent on arbitrary factors such as gender, race or age.[13] Any age-based allocation of health resources violates the principle of equality. The principle of justice would seem to require that older people be included in clinical trials so that high-quality evidence is available to guide their treatment.

Resource Allocation

Justice relates to the fair allocation of healthcare resources such as expensive medications. It has been debated that medical resources such as medications should be made less available for older people because they have lived a full life and it would be unfair to use resources to prolong older lives, thereby reducing resources for younger people. On the other hand, older people have not had access to modern healthcare resources in their lives and have made a longer contribution to society, sometimes in times of considerable hardship such as war. It could easily be asserted that older people should have priority in resource allocation.[48,51]

CONCLUSION

The four principles of medical ethics – beneficence, non-maleficence, autonomy, justice – provide a useful framework for individualising medication management in older people where the evidence base for efficacy is uncertain and concerns about adverse drug reactions are widespread. Although evidence-based medicine informs us about beneficence, care must be taken when extrapolating the efficacy results from clinical trials to frail older people.

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