ARTICLE

Prescribing for frail older people

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SUMMARY

Frailty is associated with greater exposure to polypharmacy and medicines with anticholinergic and sedative effects, which may increase the risk of adverse outcomes including falls.

People who are frail experience a higher incidence and severity of adverse drug events because of their medicine use and potential changes in pharmacokinetics and pharmacodynamics.

Prescribing for these patients requires constant vigilance and review, considering the impact of every medicine, as well as overall drug load, comorbidities, function and goals of care.

Introduction

Frailty is a multifactorial syndrome associated with functional impairment and increased susceptibility to disease, disability and mortality and can occur at any age. The clinical definition describes frailty as 'a state of vulnerability to poor resolution of homeostasis following a stress and is a consequence of cumulative decline in multiple physiological systems over a lifespan'.[1]

Although at present, there is no universal way to identify patients with frailty in clinical practice, the two most common approaches used in research are:[1]

- the phenotype model – frailty defined as the presence of at least three criteria including exhaustion, weakness, unintentional weight loss, slow walking, low physical activity
- frailty indices – accumulation of medical, functional or social deficits.

The prevalence of frailty defined using the phenotype criteria is 9.9% across studies conducted in community-dwelling older adults. Frailty increases with age – 15.7% of adults aged 80–84 years were identified as frail compared with 26.1% of those aged 85 years and over.[2] Frailty is very common in Australian acute geriatric medicine inpatients (approximately 90%)[3] and in residents of aged-care facilities (approximately 40%, depending on country studied and scale used).[4] Frailty is a dynamic state and people can move in and out of it.

Medicine use in frail people

There is a lack of guidelines to inform appropriate prescribing for frail older adults. They tend to receive more drugs than robust older adults. In community-dwelling older men, polypharmacy (≥5 drugs) was reported in 64.7% of frail men compared with 27.2% of robust men.[5] Using the Drug Burden Index, which is associated with functional impairment in older people, exposure to anticholinergic and sedative medicines was reported in 45.5% of frail men compared with 20.1% of robust men. Preventative drugs such as statins are used less often by frail men than by robust men (7.6% vs 10.4%).[6]

In acute care, frail patients use significantly more medicines overall compared with other patients (frail 9.8 ± 4.3 vs robust 4.4 ± 3.3), and more medicines that increase the risk of falls (frail 3.4 ± 2.2 vs robust 1.6 ± 1.5).[7] This was also observed in a national sample of inpatients, with higher frailty indices seen in patients with polypharmacy and hyperpolypharmacy (≥10 drugs).[8]

Impact of frailty on pharmacokinetics and pharmacodynamics

Evidence of the impact of frailty on drug disposition and effects is very limited. Animal models of frailty are only just starting to emerge, which may shed some light on the impact of frailty on pharmacokinetics and pharmacodynamics.[9]

Applying the limited evidence on the clinical pharmacology of frailty is challenged by different definitions of frailty in trials. For example, many studies use living in a nursing home as a frailty surrogate, although not all nursing home residents are frail when measured by objective measures. Also, studies are often underpowered because of the difficulty recruiting and sampling from frail older people and because this population has increased inter-individual variability.

The physiological changes of frailty are likely to impact on pharmacokinetics and pharmacodynamics. These are outlined in Table 1, along with any evidence available.[7,10-17]

Table 1 **Impact of frailty on pharmacokinetics and pharmacodynamics**

Pharmacology	Physiological changes with frailty	Hypothesised impact of frailty	Data comparing frail and robust older people
Absorption	Slowed gastric motility and reduced hepatic metabolism	Delayed absorption and reduced bioavailability of drugs administered orally	–
Distribution	Sarcopenia and relative adiposity	Reduced volume of distribution of water-soluble drugs and increased volume of distribution of fat-soluble drugs	Volume of distribution of gentamicin not significantly reduced in frailty* [10]
	Reduced plasma albumin	Decreased protein binding of acidic drugs	
Metabolism	Reduced hepatic volume and blood flow	No consistent effects on phase I clearance	No independent effect of frailty on erythromycin breath test (measures CYP3A4 and P-glycoprotein)* [11]
		Reduced phase II clearance	Aspirin esterase activity reduced in plasma [12] but not in liver in frailty [13]
			Reduced paracetamol clearance in frailty [14]
Excretion	Glomerular filtration rate reduced	Reduced renal drug clearance	Reduced gentamicin clearance in frailty* [10,15]
Pharmacodynamics	Reduced resilience to external stressors	Exaggerated or reduced drug effects	Increased sedation with metoclopramide [16]
	May be some reduced receptor function in presence of chronic inflammation		Increased susceptibility to falls with drugs acting on the CNS and cardiovascular system* [7]
			May be reduced response of platelet aggregation to aspirin in frailty* [17]

* Study used an objective measure of frailty. CYP cytochrome P450 CNS central nervous system

Increased risk of adverse effects

People who are frail are more likely to experience adverse drug events because of their patterns of drug use and, potentially, changes in pharmacokinetics and pharmacodynamics. Also they are more susceptible to the effects of adverse drug reactions because of reduced resilience. Patients with a higher frailty index score are twice as likely to have at least one potentially inappropriate medicine prescribed. They are also more likely to experience an adverse drug reaction compared to those below the frailty threshold.[18]

Recent evidence suggests that increasing medication load is associated with transitioning from the pre-frail to frail status and subsequent death. Each additional drug was associated with a 22% greater risk of death in men who were initially defined as robust.[19] Pharmacoepidemiological studies on the effects of specific drug classes, such as ACE inhibitors[20] or statins,[21] on incident frailty have not found significant associations.

Results from clinical trials

Trial results observed in the general population cannot necessarily be extrapolated to the frail population. Studies of the impact of frailty on the effects of medicines show varying results (see Table 2).[6-8,22-25] The observational studies highlight the effects of polypharmacy, the use of drugs that increase the risk of falls, and drugs recommended by guidelines for secondary prevention of cardiovascular disease. They suggest that frail older people are more susceptible than non-frail to adverse outcomes, such as falls, institutionalisation and death with drug use.

There are also secondary analyses of randomised controlled trials that examine the impact of frailty on different treatment outcomes. These suggest that with antihypertensive treatment, frail participants may get similar reductions in cardiovascular outcomes and mortality compared to non-frail participants.

Recent debate has focused on whether frailty should be considered when prescribing antihypertensives to older adults. The Hypertension in the Very Elderly Trial (HYVET) suggests benefit with antihypertensive therapy irrespective of frailty status.[25] In the Systolic Blood Pressure Intervention Trial (SPRINT) of adults aged 75 years or older, treating to a systolic blood pressure target of less than 120 mmHg compared with a target of less than 140 mmHg resulted in significantly lower rates of fatal and nonfatal major cardiovascular events and all-cause mortality.[24] Frailty did not appear to modify this relationship, although the trial was not powered to assess this.

Table 2 **Medication outcomes in older people stratified by frailty status**

Study	Participants (number, mean age)	Frailty definition	Outcomes
Peeters et al. 2016* [22]	Community-dwelling women with ischaemic heart disease and using at least one guideline-recommended drug (n=885, 82.7 years)	'Frail scale' i.e. at least 3 of • >5% weight loss over 3 years • feeling fatigued • difficulty climbing stairs • difficulty walking 100 m • having ≥5 chronic conditions	Adherence to optimal therapy associated with increased risk of falls with no significant gain in cardiovascular health
Gnjidic et al. 2015* [23]	Community-dwelling men with ischaemic heart disease (n=462, 78 years)	Presence of geriatric syndromes including frailty (defined using modified frailty phenotype)	Optimal therapy associated with lower risk of institutionalisation and mortality, stratified according to presence of geriatric syndromes including frailty
Gnjidic et al. 2013* [6]	Community-dwelling men (n=1665, 76.9 years)	Modified frailty phenotype	Frail men more likely to be institutionalised or die than robust men, regardless of their statin use
Poudel et al. 2016* [8]	Inpatients (n=1418, 81 years)	Frailty index	Risk of composite adverse outcome higher in frail patients with polypharmacy compared to robust patients with polypharmacy
Bennett et al. 2014* [7]	Inpatients admitted with falls (n=204, 80.5 years)	Reported Edmonton frail scale	Risk of recurrent falls increased in frail patients taking 1.5 FRIDs and in robust patients taking 2.5 FRIDs
Williamson et al. 2016 (SPRINT trial)† [24]	Community-dwelling adults with hypertension and without diabetes (n=2510, 79.9 years)	Frailty index	Effects of intensive vs standard blood pressure treatment not significantly modified by frailty status
Warwick et al. 2015 (HYVET trial)† [25]	Community-dwelling adults with hypertension (n=2656, indapamide ± perindopril group: 83.6 ± 3.2 years, placebo group: 83.4 years)	Frailty index	Antihypertensive treatment reduced risk of stroke, all-cause mortality or cardiovascular events in both frail and robust patients

* observational study
† clinical trial
FRIDs falls-risk increasing drugs, refers to all drugs acting on the central nervous system or cardiovascular system (e.g. sleeping pills)
SPRINT Systolic Blood Pressure Intervention Trial
HYVET Hypertension in the Very Elderly Trial

Drug interactions

The prevalence of clinically relevant drug–drug interactions is higher in frail compared to robust inpatients. Our studies in a tertiary referral hospital identified more potential interactions in frail patients compared to robust patients (35% vs 5%).[7] Clinically relevant statin interactions were found in 9.5% of frail versus 6.8% of robust older inpatients.[26]

Deprescribing

Deprescribing is defined as withdrawing an inappropriate medicine, supervised by a healthcare professional, with the goal of managing polypharmacy and improving outcomes.[27,28]

In view of the limited evidence of benefit for medicines in frail older people and strong observational evidence of the increased risk of and from adverse drug events, trials of deprescribing have recently been conducted in frail older people. In a Western Australian study of people living in residential aged-care facilities, individualised medication reviews significantly reduced the number of regular medications by 2.0 ± 0.9 (95% confidence interval 0.08–3.8, p=0.04) compared to the control group, with no significant change in clinical outcomes.[29]

Irish consensus criteria on drugs that are potentially inappropriate in frail older patients with limited life expectancy have recently been published.[30]

Known as 'STOPPFrail' (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy), they suggest deprescribing any medicine without a clear clinical indication or where compliance is poor, and include specific recommendations for 25 drug classes and indications.

Tailoring therapy for frail older people

When prescribing for older people, frailty status should be considered when applying the six steps in the World Health Organization's Guide to Good Prescribing.[31] Medicines prescribed for chronic conditions need to be reviewed frequently to assess whether they are providing net benefit or net harm. Goals of care change frequently in frail people, and changes should prompt and inform re-evaluation of the patient's prescriptions. Opportunities to re-evaluate goals and treatment with patients and their families include acute admission to hospital, admission to a residential aged-care facility, and functional decline or a terminal illness such as the terminal phase of dementia.

Step 1: Define the patient's problem

Diagnoses can be difficult in frail older people as they often present with non-specific multifactorial geriatric syndromes such as falls, cognitive impairment and incontinence. Their presentation may also be affected by a reduced response to external stressors, for example they may not develop a fever or increased white cell count in response to an infection. Frailty may also impact on clinical decisions to conduct investigations. It is important to consider whether the patient's presentation is attributable to an adverse drug event as these are the most reversible causes of the geriatric syndromes. Also failure to recognise an adverse drug event could inadvertently result in a prescribing cascade.[32]

Step 2: Specify the therapeutic objective

The therapeutic objective refers to the desired pharmacodynamic effect of the drug. Frail older people are rarely represented in clinical trials, so there is limited evidence to support the efficacy and safety of most treatments for these patients. Often observational data or secondary analysis of clinical trial data can be used to inform therapeutic decisions (see Table 2). For example, in secondary prevention of cardiovascular disease, observational data suggest that optimal medical therapy (aspirin, ACE inhibitor, beta blocker and statin) reduce the risks of institutionalisation and mortality to a similar extent in older men with and without geriatric syndromes including frailty.[23] There is also increasing evidence from subgroup analyses on the impact of polypharmacy on the safety and efficacy of drugs for specific disease states.[33]

Step 3: Verify whether the treatment is suitable for the patient

In people with multiple morbidities and disability, the benefit of the drug must be considered in view of the patient's other conditions, other medicines (and potential drug interactions) and global therapeutic objectives (goals of care). A full medication review is essential before starting a new medicine. For example, subgroup analysis of controlled trial data suggests that in frail older people intensive blood pressure control may reduce the risk of cardiovascular events, stroke and mortality.[25] However, these outcomes may not be as high a priority for some frail older patients as reducing the risk of falls, which may increase with antihypertensives.

Step 4: Start the treatment

Discuss the therapeutic decision with the patient and their carers. Adjust the dose to account for the pharmacokinetic and pharmacodynamic changes of frailty (see Table 1). Use formulations that make administration simple. For example, use once-daily slow-release formulations if the patient can swallow them.

Step 5: Provide information, instructions and warnings

It is important to give clear information verbally and in written form to the patient, their carers and other healthcare providers, including any specialists. An updated medication list is also important. Follow-up is important to ensure that the patient's plan has been communicated and is being implemented. Warnings should include adverse events seen commonly in frail older people that may not be prominent on standard consumer medicine information, such as the risks of falls, confusion, incontinence and polypharmacy.

Step 6: Monitor (stop) the treatment

Treatment can be stopped when the problem has been solved. In frail older people, 'solving' acute problems with medicines may involve completing a course of antimicrobials for an infection or analgesics for acute pain. If treatment for an acute or chronic problem is not effective, safe or convenient, it needs to be reviewed using the six steps again.

If a decision is made to stop a medicine, it is important to check whether it can be stopped suddenly or needs to be weaned gradually.[34] It is important to monitor the outcomes of stopping treatment. These may include adverse drug withdrawal events, but more often than not there is no change or any adverse effects resolve quickly.

Conclusion

Frail older people are major users of medicines, despite a paucity of evidence on pharmacokinetics and pharmacodynamics and decreased resilience to adverse drug events in this population. When prescribing it is essential to consider the patient's goals of care, function, comorbidities and overall medication load. Frequently review all medicines for frail older patients to ensure that they are receiving net benefit. Clinical trials (including deprescribing trials) and observational studies are starting to include objective measures of participants' frailty. This will help prescribers assess how the findings apply to frail and robust older patients in clinical practice. ≺

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