



Frailty and Potentially Inappropriate Prescribing in Older People with Polypharmacy: A Bi-Directional Relationship?

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Abstract

Frail older adults commonly experience multiple co-morbid illnesses and other risk factors for potentially inappropriate prescribing. However, determination of frailty varies depending on the frailty instrument used. Older people's degree of frailty often influences their care and treatment priorities. Research investigating the association between frailty and potentially inappropriate prescribing is hindered by a wide variety of frailty definitions and measurement tools. We undertook a narrative review of selected articles of PubMed and Google Scholar databases. Articles were selected on the basis of relevance to the core themes of frailty and potentially inappropriate prescribing. We identified observational studies that clearly link potentially inappropriate prescribing, potential prescribing omissions, and adverse drug reactions with frailty in older adults. Equally, the literature illustrates that measured frailty in older adults predisposes to inappropriate polypharmacy and associated adverse drug reactions and events. In essence, there is a bi-directional relationship between frailty and potentially inappropriate prescribing, the underlying substrates being multimorbidity and inappropriate polypharmacy. We conclude that there is a need for consensus on rapid and accurate identification of frailty in older people using appropriate and user-friendly methods for routine clinical practice as a means of identifying older multimorbid patients at risk of potentially inappropriate prescribing. Detection of frailty should, we contend, lead to structured screening for inappropriate prescribing in this high-risk population. Of equal importance, detection of potentially inappropriate prescribing in older people should trigger screening for frailty. All clinicians undertaking a medication review of multimorbid patients with associated polypharmacy should take account of the important interaction between frailty and potentially inappropriate prescribing in the interest of minimizing patient harm.

1 Introduction

Medication management in older people experiencing multimorbidity is often challenging. As multimorbidity increases, the number of prescription medications increases in parallel, exposing patients to greater degrees of polypharmacy, thereby heightening the risk of potentially inappropriate prescribing (PIP) and adverse drug events (ADEs) [1].

Observational studies show that potentially inappropriate medications (PIMs), potential prescribing omissions (PPOs), and adverse drug reactions are highly prevalent in frail older adults [2–4]. Consequently, geriatricians recognize the importance of medication review and optimization as part of a routine comprehensive geriatric assessment. However, most multimorbid older adults managed in the community or undergoing unscheduled hospital attendance are not reviewed by specialist geriatricians. Furthermore, there are knowledge deficits about the factors that predispose some patients more than others to ADEs, which often cause geriatric syndromes such as falls, cognitive impairment, and incontinence. Although an international consensus on the operational definition of frailty is still lacking, it is generally recognized as an age-related state of decreased physiological reserve characterized by a weakened response to stressors and an increased risk of poor clinical outcome following acute illness [5, 6]. These characteristics predispose frail older adults to adverse outcomes from PIP compared with

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Key Points

Susceptibility to medication adverse effects is an intrinsic part of the frailty syndrome.

Potentially inappropriate prescribing and related adverse drug reactions may cause or exacerbate other features of frailty such as cognitive decline, falls, and incontinence and lead to a reduced physiological reserve.

Consensus around the measurement of frailty and how it may be linked to potentially inappropriate prescribing assessment tools is needed.

their age-matched non-frail counterparts. As age-related frailty is associated with adverse outcomes including functional decline, falls, hospitalization, and death in older people, it is essential for prescribers to identify frailty in order to optimize their care [6]. However, the prevalence of frailty varies widely depending on the frailty measurement instrument used [7, 8]. Additionally, the degree of patients' frailty often influences their care goals and treatment priorities [9–11].

In pre-frail and robust older people, certain medications may prevent the development or exacerbation of frailty syndromes. For severely frail older people with a short life expectancy, it is generally accepted that treatment choices should be focused on symptom management and quality of life rather than disease-based guidelines or long-term prevention. In their systematic review of unnecessary medication use and its avoidance in frail older adults, Tjia et al. concluded that the synthesis of overall effect sizes was difficult because of the heterogeneity of frailty measures, outcomes, and study designs, in line with more recent systematic reviews of frailty prevalence [12, 13].

In this narrative review, our aim was to explore the relationship between frailty and PIP and the various ways in which frailty may be exacerbated by PIP and may predispose older adults to PIP exposure. We also aimed to examine whether a practical and clinically applicable method of assessing frailty and PIP could be used to optimize prescribing decisions for older adults and correspondingly whether identification of PIP should act as a trigger for frailty assessment.

For this purpose, a literature search of PubMed and Google Scholar databases was undertaken. Search terms included: Frailty OR Measured Frailty, Frailty OR Measured Frailty AND Potentially Inappropriate Prescribing OR Potentially Inappropriate Medication Use OR Potential Prescribing Omissions OR Medication Underuse. We included

articles involving adults aged ≥ 65 years in all settings, i.e., community, hospital, and residential care. Studies with no access to the full-text article or English version of the article and studies exclusively describing patients aged < 65 years were excluded. We also performed reference searching for appropriate articles.

The following clinical vignette illustrates the need for a simple reliable definition of frailty that is related to clinical outcomes. It also shows how frailty detection should prompt an individualized medication assessment, using the individual components of the frailty syndrome or a cumulative deficit model as a guide to deprescribing, and why the presence of PIP should prompt an assessment of frailty.

Clinical Vignette

D.A. is an 81-year-old female who lives alone in her own home. Her past medical history includes hypertension, hyperlipidaemia, hypothyroidism and fragility fracture of her left wrist 3 years previously. She does not have any known cognitive impairment. Her current medications include ramipril, aspirin, levothyroxine, amlodipine and pantoprazole. She also takes paracetamol as required for episodic residual wrist pain. She is independent with her personal activities of daily living, though she receives assistance from her son for weekly shopping and pension collection. She was recently commenced on furosemide for dependant lower limb oedema. Subsequently, she has experienced nocturia and disturbed sleep. She attends her doctor about the sleep problem and is prescribed zopiclone. Within 2 weeks of starting zopiclone, she develops new onset nocturnal incontinence. With a presumptive diagnosis of overactive bladder, she is subsequently prescribed tolterodine. Unfortunately, her sleep problem does not improve and on follow-up with her doctor, she complains of feeling increasingly drowsy during the daytime. Her son notices she has become increasingly forgetful and disoriented and on one particular day finds her lying on the floor of her bedroom, confused and unable to move due to pain. She is admitted to hospital and is found to have a fractured neck of femur, delirium and acute renal failure. Her hospital admission is complicated by pneumonia and prolonged delirium. Following corrective hip surgery, she fails to regain her independent mobility and consequently is discharged to a nursing home for extended care.

Table 1 Selection of frailty assessment tools and a summary of their threshold scores for defining frailty and pre-frailty

Frailty instrument	Components	Classification	Pre-frailty	Medications assessed
(Physical/Fried) Frailty Phenotype [15]	Five items: weight loss, low physical activity, exhaustion, slowness, weakness	Frailty: ≥ 3 present, pre-frailty: 1–2 items, robust: 0	Yes	No
Cumulative Deficit Frailty Index [25, 26]	Minimum of 30 accumulated health deficits. Dichotomous yes/no. Index scores 0 (none present) to 1 (all present)	Frailty: > 0.25	No	If included in construction of index
Clinical Frailty Scale [17]	Nine graded pictures on visual or written chart. 1 = very fit to 9 = terminally ill	Frailty: ≥ 5	Yes	No
FRAIL Scale [51]	Self-rated scale, five items: fatigue, resistance, ambulation, illnesses, loss of weight (i.e., 1 point for each component; 0 = best to 5 = worst) and represent frail (3–5), pre-frail (1–2), and robust (0) health status	Frailty: ≥ 3 , pre-frailty: 1–2, robust: 0	Yes	No
Edmonton Frailty Scale [52]	Nine questions: cognition, general health, self-described health, functional independence, social support, medication use, nutrition, mood, continence, functional performance	Frailty: ≥ 7 , pre-frailty: 5–6, robust: ≤ 4	Yes	Yes
PRISMA-7 [53]	Seven self-reported items: age 85 years, male, social support, activities of daily living	Frailty score ≥ 3	No	No
FI-CGA [54]	Ten items: cognition, mood, communication, mobility, bowel function, balance, pADL/iADL, nutrition, social resources. Each domain scored 0 (no problem) to 2 (major problem)	Mild frailty = 0–7, moderate = 7–13, severe > 13	No	No
Groningen Frailty Indicator [55]	Fifteen self-reported items across four domains: physical, cognitive, social, psychological	Frailty score ≥ 4	No	No
Frail-VIG [56]	Twenty-five question frailty index assessing 22 domains: developed from CGA and designed for clinical use. No deficit = 0, deficit = 1	Frailty: > 0.25	No	Yes

CGA Comprehensive Geriatric Assessment, CHSA-92 Canadian Study of Healthy Aging in 1992, FI Frailty Index, iADL instrumental activities of daily living, pADL personal activities of daily living

2 Frailty

Frailty is a common clinical syndrome that becomes more prevalent with advancing age. Despite its high prevalence, there is no universally accepted method to confirm a diagnosis of frailty [5]. Frailty is defined as “a progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes” [14]. The terms frail, pre-frail and robust have emerged as descriptive categories with varying risks of adverse outcomes [15]. Although it is associated with multimorbidity, frailty is not in itself a surrogate for disease burden, i.e., a person may have multimorbidity and not be frail [16].

Over the last 20 years, various methods of accurately screening for and assessing frailty have been devised to identify those most at risk of adverse outcomes in the community, in healthcare settings and in hospital peri-operative situations [17–19]. The choice of frailty instruments may also be determined by the time available, location of assessment, space, and equipment required to carry out the assessment. A selection of commonly used frailty instruments is shown in Table 1, with a specific focus on their relationship with the assessment of medication use. This is not an exhaustive list; instruments were selected to demonstrate the numerous methods of quantifying frailty from identifying a phenotype to self-reported items.

In 2016, Buta et al. identified 67 frailty tools cited in the literature [17], of which nine had more than 200 citations. The most commonly cited were the Physical Frailty Phenotype and the Cumulative Deficit Frailty Index. A further systematic review in 2018 found that of the 51 instruments presented, 23 had the capacity to identify pre-frailty [20]. Most frailty assessment instruments can be broadly divided into frailty phenotype or frailty index/cumulative deficit categories. Both categories have been internationally validated for use in identifying older people at a high risk for adverse outcomes relating to frailty compared to other non-frail people of similar age.

The Frailty Phenotype was developed by Fried et al. in 2001 [15]. It includes five variables: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. People categorized as frail (three or more variables present) had higher rates of falls, impaired function, and death compared with people categorized as robust (0 variables) or pre-frail (one to two variables). Validated in the community, long-term care, and hospital in-patient settings [13, 21, 22], the Frailty Phenotype is the most commonly cited frailty measurement in the literature. However, it has some limitations [23], including the substantial time required to translate the five variables

into clinical practice, the narrow focus on physical characteristics, the requirement for measurement equipment, and the variable effect of acute illness on the frailty variables. These limitations are potential obstacles to its routine clinical application [24].

Mitnitski et al. utilized a cumulative deficit model to create the frailty assessment tool. Using a holistic and multi-dimensional construct of frailty, they proposed that frailty is caused by the lifelong accumulation of deficits such as falls, cognitive impairment, co-morbidities, and abnormal laboratory variables. The greater number of deficits present results in greater levels of frailty [25]. A published standard procedure for the development of a frailty index using a minimum of 30 deficits allows the cumulative deficit model to be applied to different sets of data and has led to the development of further indices such as the Electronic Frailty Index based on primary care electronic health record data. The use of a graded frailty index also discriminates moderate frailty from severe frailty and although it does not identify pre-frailty, it has been validated across multiple clinical settings [21, 26].

Following from the Frailty Index, Rockwood et al. later developed a 7-point Clinical Frailty Scale (CFS) The outcomes of institutionalization and mortality were highly correlated with a 7-point CFS range ($r = 0.80$) and with the original Frailty Index. Each category increment of the CFS significantly increased the medium-term risks of death (21.2%, 95% confidence interval [CI] 12.5–30.6) and institutionalization (23.9%, 95% CI 8.8–41.2) in multivariable models that adjusted for age, sex, and education [17]. The CFS is highly dependent on the clinical judgment of the user, nevertheless, it is quick and easy to use and has been validated in primary care, hospital, and long-term care settings. The second version of the CFS includes nine grades in which the category of ‘vulnerable’ was replaced with ‘living with very mild frailty’ [27]. The creators of the CFS have expressed caution regarding the use of this judgment-dependent instrument by those inexperienced in frailty evaluations [27].

A meta-analysis of studies has shown an average pooled frailty prevalence of 18% across all clinical settings, with the highest prevalence encountered in the hospital in-patient and nursing home settings (54.1–54.2% and 62.1–68.8%) [22]. Based on a systematic review and meta-analysis of data involving over 61,500 patients, Collard et al. found that, on average, 10.7% of community-dwelling older persons are overtly frail and 41.6% are pre-frail. However, the reported prevalence differed substantially within the included studies, with a range from 4.0 to 59.1%, reflecting the different instruments used to measure frailty [28]. A large multinational meta-analysis confirms this variance, producing a pooled estimate of 12% (11–13%) for physical frailty and 24% (22–26%) for the deficit accumulation model [13].

In nursing home residents, frailty prevalence ranged from 36.4% (95% CI 23.8–51.1) using the Fried Phenotype to 71.8% (95% CI 62.8–79.5) using the CFS [29].

This variability in reported prevalence in frailty according to the measurement tool and setting is readily reflected in practice if one applies the different frailty tools to our clinical vignette. For example, using the CFS, Mrs DA would be considered to have mild frailty (CFS <5), she would not be classified as frail on the Edmonton Frail Scale or Frail-Vig Index, and the Frailty Phenotype would require further examinations of grip strength that may not be practical or accurate in the emergency department but would be feasible in the primary care setting. The Frailty Phenotype would be affected the most by her intercurrent acute illness while collateral histories would be required to complete the Frailty Indices.

3 Potentially Inappropriate Prescribing

Potentially inappropriate prescribing occurs where there is a lack of evidence or indication for a medication, where there is avoidable adverse drug–disease or drug–drug interaction exposure, where the risks of medications outweigh their benefits, or where the time to benefit from treatment exceeds individual life expectancy. Potentially inappropriate prescribing also encompasses omission of potentially beneficial medications that are clinically indicated for the treatment or prevention of a disease, mis-prescribing, and prescribing cascades [30–32]. We refer to the term PIP to include the prescription of PIM, potential prescribing omissions, or both.

Potentially inappropriate prescribing is associated with reduced health-related quality of life, excess adverse drug events, increased hospitalization, re-hospitalization, and increased mortality [33]. To minimize exposure of frail older adults to PIP, a structured medication review with appropriate deprescribing is a logical approach. Several tools have been developed to help identify PIP. A recent systematic review that included 42 prescribing assessment tools found that only 13 had been externally validated, with hospitalization being the most commonly measured patient-related outcome [34]. Deprescribing tools are classified as explicit, implicit, or a combination of both. Explicit criteria tools such as Beers criteria, LaRoche criteria, EU-7 criteria, and STOPP/START criteria typically contain lists of drugs or drug classes that are known to expose older adults to potential harms that outweigh their benefits [35–38]. In the STOPP/START criteria, there is also a list of ‘potential prescribing omissions’, i.e., drugs that probably should be prescribed in older people but are not for various inappropriate reasons, including perceived high-level frailty. Implicit PIP assessment tools such as the Medication Appropriateness

Index require knowledge of individual treatment goals and comorbidities in the context of each prescribed drug [39]. While the Medication Appropriateness Index is patient centred, it is time consuming to apply to older adults with polypharmacy and hyper-polypharmacy and requires comprehensive knowledge of the prescribed drugs.

Given the number and range of methods for measuring PIP, it is unsurprising that PIP prevalence, like frailty, varies greatly depending on which assessment tool is used and the patient population studied. A wide range of PIP prevalence (22–79%) has been reported in studies with the wide variance attributed to the different patient populations being assessed and the PIP assessment tool used [40, 41]. Returning to Mrs. DA’s medications, one can discern several instances of PIP using both explicit tools and implicit tools. Applying STOPP/START criteria, her initial medications of aspirin with no clear indication for primary cardiovascular prevention and a proton pump inhibitor to minimize gastrointestinal side effects of aspirin are potentially inappropriate. Subsequent addition of a loop diuretic for lower limb edema in the absence of heart failure and a further inappropriate addition of a bladder antimuscarinic and a hypnotic may have caused her confusion and injurious fall. This would likely be reflected in a high Medication Appropriateness Index score. Beers criteria would have identified zopiclone as a drug to avoid in this case with previous falls and aspirin as a drug to use with caution for primary prevention; the high anticholinergic burden of tolterodine would also be detected. There are also multiple avoidable prescribing cascades representing another form of PIP in Mrs DA’s medications, such as amlodipine causing the misdiagnosed drug-induced lower limb edema and subsequent inappropriate introduction of a diuretic. Prescribing cascades represent an important, often under-recognized, element of problematic polypharmacy. Cascades occur when an ADE is misinterpreted as a new medical condition, with the subsequent prescription of another, potentially inappropriate drug [42]. With Mrs DA, she is subsequently prescribed a sedative and anticholinergic medicine to treat unrecognized adverse events of the diuretic.

4 Frailty and Potentially Inappropriate Prescribing

There is growing interest in the relationship between PIP and frailty. Physiological systems associated with susceptibility to impaired homeostasis in the context of frailty include the central nervous system, the sympathetic nervous system, the endocrine system (particularly pituitary and adrenal glands), and the immune system [43]. With attenuated physiological reserve in other systems including the cardiovascular, respiratory, and renal systems, an overtly frail individual with

Table 2 Selection of studies exploring the association between potentially inappropriate prescribing and frailty

Study (year)	Type of study	Population characteristics	Frailty criteria	Medication appropriateness measurement	Main findings
Cullinan et al. (2016) [46]	Retrospective analysis of randomized controlled trial database	<i>n</i> = 711 Sex = not reported Age = not reported Acute hospital inpatients	Novel 34-item FI developed using variables available in the database	STOPP/START	The mean FI score above which patients experienced at least one instance of PIP was 0.16. Patients above this threshold were twice as likely to experience PIP [OR = 2.6 (2.0–3.6); <i>p</i> < 0.0001] and to develop an ADR [OR = 2.1, <i>p</i> < 0.0001]. Patients taking more than six medications were three times more likely to experience PIP
Dalleur et al. (2012) [57]	Cross-sectional study	<i>n</i> = 302 Female = 62.6% (189) Median age [P25–P75] = 84 years [81–88 years] Acute hospital inpatients	Identification of Seniors At Risk	STOPP/START	PIMs were found in 144 of the 302 frail older adults (prevalence 47.7%), with the following distribution: 1 PIM (29%), 2 PIMs (16%), and ≥ 3 PIMs (3%). The prevalence of PPOs was 62.9% (190/302), with the following distribution: 1 PPO (29%), 2 PPOs (19%), and 3 PPOs (15%)
Hanlon et al. (2004) [58]	Cross-sectional, secondary analysis of data from a randomized controlled trial	<i>n</i> = 397 Female = 2.8% (11) Age ≥ 75 years = 184 (46.4%), 65–74 years = 213 (53.6%) Acute hospital inpatients ^a	> 2 of 10 frailty criteria	MAI	365 (91.9%) patients had ≥ 1 medications with ≥ 1 MAI criteria rated as inappropriate
Récoché et al. (2017) [4]	Cross-sectional study	<i>n</i> = 229 Female = 156 (68.1%) Age (SD) = 82.14 (6.22) years Day hospital patients	Gerontopole Frailty Screening Tool Fried Phenotype	Criteria based on Larochette list and STOPP/START	Among the 229 frail patients included, 163 (71.2%) had ≥ 1 instance of PIP
Muhlack et al. (2020) [3]	Longitudinal cohort study	<i>n</i> = 2865 Female = 1480 (51.7%) Age (SD) = 70.2 (5.9) years Community-dwelling older adults	Fried Phenotype	2015 Beers criteria 2015 Beers dementia sub-list PRISCUS EU(7)-PIM list	At baseline, 32.1% (919) participants were classified as robust, 58.8% (1685) were pre-frail, and 9.1% (261) were frail. The baseline PIM prevalence varied between 9.2% (Beers dementia PIM) and 37.5% (EU(7) PIM). 21% of participants became frail during the follow-up. All PIM criteria were significantly associated with incident frailty in the unadjusted and in the age-adjusted and sex-adjusted analyses; however, not significant after adjustment for a number of medicines and propensity scores
Gutiérrez-Valencia et al. (2018) [2]	Cross-sectional analysis from a concurrent cohort study	<i>n</i> = 110 Female = 79 (71.8%) Age (SD) = 86.3 (7.3) years Nursing home residents	Fried Phenotype, Imputed Fried Frailty Criteria, Rockwood Frailty Scale, and FRAIL in nursing home scales	STOPP/START	Prevalence of frailty was 71.8%, 42.7%, and 36.4% according to the Rockwood CFS, FRAIL-NH, and FRIED Index, respectively. (Fried Phenotype was only assessed in 40% of participants). Under-prescription was more prevalent in frail participants but only reached significance when Fried criteria were used
MacLagan et al. (2017) [47]	Retrospective cohort study	<i>n</i> = 41,351 Female = 26,748 (64.7%) Age range: 65–74 years = 3691 (8.9%), 75–84 years = 15,130 (36.6%), ≥ 85 years = 22,530 (54.5%) Newly admitted to nursing homes with a history of cognitive impairment or dementia	72-Item FI	Beers criteria 2015	44% of patients were frail at admission, 36.9% were pre-frail, and 19.1% were non-frail 44.3% of the cohort had at least one PIM. PIMs were most prevalent among frail residents across the age cohorts, i.e., 48.1% vs 42.7% vs 38.7% (<i>p</i> ≤ 0.001). After adjustment for potential confounders, frail residents were also significantly more likely to be newly prescribed PIMs

Table 2 (continued)

Study (year)	Type of study	Population characteristics	Frailty criteria	Medication appropriateness measurement	Main findings
Bolina et al. (2019) [49]	Cross-sectional study as part of a longitudinal study	n = 1607 Female = 1036, (64.5%) Age range: 60–70 years = 611 (38.0%), 70–80 years = 707 (44.0%), 80 years or more = 289 (18.0%) Community-dwelling older adults ^b	Fried Frailty Phenotype components	Beers criteria 2012	Prevalence of frailty was 13.6% and pre-frailty was 51.1%. PIM use was 51.1% for the frail group, 33.2% for the pre-frail group, and 17.0% in the non-frail group

ADR adverse drug reaction, FI Frailty Index, MAI Medication Appropriateness Index, OR odds ratio, PIM potentially inappropriate medication, PIP potentially inappropriate prescribing, PPO potential prescribing omission, SD standard deviation, START Screening Tool to Alert doctors to Right Treatments, STOPP Screening Tool of Older Persons' potentially inappropriate Prescriptions

^aPatients were excluded if they were admitted from a nursing home, were already receiving care at an outpatient clinic for geriatric evaluation and management, had previously been hospitalized in an inpatient unit for geriatric evaluation and management, were currently enrolled in another clinical trial, had a severe disabling disease or terminal condition, or severe dementia

^bThose with cognitive decline and unable to undergo a physical assessment were excluded

compromised reserve in one or more systems is more susceptible than non-frail or pre-frail persons to physiological stress arising from adverse medications. Medications may also play a role in worsening measured variables that characterize frailty. Delirium, falls, anorexia, functional impairment, cognitive impairment, renal impairment, and impaired balance are recognized commonly occurring ADEs that may be attributed incorrectly to irreversible aspects of age-related frailty. In our vignette patient, as a consequence of inappropriate prescribing, she experiences incontinence, new-onset cognitive decline, and falls. Several studies have examined the relationship between frailty and PIP in hospital, community, and institutional settings. Table 2 summarizes a selection of these studies and briefly summarizes the variable methods of assessment.

5 Frailty and the Associated Risk of Potentially Inappropriate Prescribing

Frail older adults are exposed to higher levels of polypharmacy and hyper-polypharmacy, established independent risk factors for PIP [41]. Frail older people are more likely to experience increased clinical complexity, extreme vulnerability to stressors, and reduced physiological reserve. Frail older people are also commonly excluded from drug trials [42]. With increased multimorbidity, a related increase in the number of physician consultations often follows, resulting in a higher risk of drug–drug and drug–disease interactions [44]. The association between frailty and polypharmacy has been established, though a meta-analysis in this area has also been hampered by a lack of homogeneity in the definition of frailty [45]. Cullinan et al. applied a novel frailty index as a means of investigating the association between frailty and PIP defined by STOPP/START criteria in older hospitalized patients with multimorbidity and polypharmacy. Though limited by the database variables available, a significant correlation between frailty, adverse drug reaction, and STOPP/START criteria breaches was found [46]. Gutiérrez-Valencia et al. have reported that frail institutionalized older people had a significantly higher average number of START criteria PPOs compared with non-frail institutionalized age-matched control subjects, independent of polypharmacy (1.9 vs 1.0, $p = 0.017$) [2]. Another study designed to estimate the prevalence of PIMs among older adults with cognitive impairment and dementia in long-term care found that after adjustment for potential confounders, frail residents were more likely to be prescribed benzodiazepines, antipsychotics, and anticholinergics [47]. Using a 72-item frailty index and 2015 Beers criteria, Maclagan et al. found PIMs were most prevalent among frail residents across the age cohorts, i.e., 48.1% versus 42.7% versus 38.7% ($p \leq 0.001$) in frail, pre-frail, and robust adults, respectively [47]. In a sample

of ambulatory patients, Récoché et al., assessing for frailty using the Gerontopole Frailty Screening tool and Fried's Phenotype, demonstrated a prevalence of 71.2% of participants with at least one identified STOPP/START or Laroche list-defined PIP [4]. Frailer older adults experience a greater sedative medication load compared with non-frail age-matched counterparts, which increased in proportion to greater levels of frailty [48]. This predisposes to impaired psychomotor function, falls, and cognitive impairment in frail older people.

6 Potentially Inappropriate Prescribing Increasing the Risk of Frailty/Associations

While there are fewer studies investigating the association between PIP and the risk of frailty, a study of community-dwelling older people by Bolina et al. found that PIP (Beers criteria) was associated with a higher incidence of frailty and pre-frailty (Fried's Phenotype) [49]. Similarly, Muhlack et al. [3] demonstrated that PIMs (Beers criteria) were significantly associated with incident frailty (Fried's Phenotype) in both the unadjusted and age-adjusted and sex-adjusted analyses, though not significantly associated after adjustment for the number of daily drugs, concluding that incident frailty was restricted to drugs that could induce frailty syndromes. Pazan et al., examining the effects of medication optimization and pharmacological interventions for frailty, concluded that evidence for a direct causal relationship between medications and frailty was inconclusive and emphasized the need for further research using an internationally consistent and reproducible measure of frailty.

7 Challenges in Measuring and Reducing the Risks of Potentially Inappropriate Prescribing

There is notable heterogeneity both in the frailty measurement tools and also in the criteria utilized to assess medication appropriateness, leading to some difficulty with applying research study findings to a clinical case such as Mrs. DA. This patient could be classified as frail or robust depending on the frailty assessment tool used and its time of application. Current research on the effects of medication optimization is limited to studies on the effect of a single drug adjustment accompanied by multi-component interventions for frailty, and there are no studies assessing the negative effects of drugs on frailty. In their recent systematic review, Pazan et al. concluded that there is a clear need for randomized controlled trials to examine the impact of medication optimization or pharmacological interventions

on frailty or aspects of frailty based on a comprehensive and reproducible concept of frailty assessment [50].

8 Conclusions

Pharmacotherapy in frail older people requires an understanding not only of age-related physiological, pharmacokinetic, and pharmacodynamic changes but also frailty-related physiological changes, which predispose to adverse medication-related outcomes. Many studies investigating PIP in older adults focus on age alone as a prompt for medication review. We propose measured frailty as the more important prompt for a structured medication review to guide individual treatment goals. Not only should the presence of frailty prompt a structured medication review but patients who are identified as pre-frail may benefit from judicious prescribing to avoid PIP. Changes in frailty status or the accumulation of new deficits may be attributable to medication use and should trigger a further analysis of medications including long-term medications that may no longer be appropriate. Overall, different frailty measurement tools may be appropriate for different settings and different groups of patients, and having a baseline assessment and identifying changes in vulnerability may assist the clinician in preventing medication-related morbidity. We conclude that different frailty assessment tools may have been more appropriate for Mrs. DA at different stages in her protracted illness. The physical phenotype model may have been suitable to identify vulnerability when she was not experiencing any disability in the community setting but she possibly had underlying pre-frailty. When she was admitted to hospital, a collateral history and frailty index might have identified the forthcoming rapid decline in physical and cognitive function.

Measured frailty should be an important factor when considering new medication choices and when reviewing existing medications as well, as when considering deprescribing decisions in older adults with limited life expectancy. There is a need for further research on the role of inappropriate prescribing in those at risk of developing frailty syndromes such as falls, incontinence, cognitive decline, weight loss, and lethargy. Use of established PIP assessment tools such as STOPP/START criteria, STOPPfrail criteria, or Beers criteria may assist in deprescribing once the degree of frailty has been identified.

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