Understanding Frailty in the Geriatric Population

Clinicians who work with the frail elderly know what frailty looks like, but until recently, they have had no science-based definition of this condition. Frailty is classified as a medical syndrome, and Fried et al. were among the first to standardize the definition of frailty as a distinct syndrome with biologic underpinnings. Their definition describes a clinical phenotype of decreased reserve and resistance to stressors, with clinical manifestations of a mutually exacerbating cycle of negative energy balance, sarcopenia, diminished strength, and exertion intolerance. Age is no longer considered a defining characteristic, although frailty is still considered primarily a geriatric problem. Approximately two-thirds of affected individuals enter frailty in a slow, progressive way, while one-third become frail cataclysmically. Weakness is a common early sign, and exhaustion and weight loss are often late manifestations. Observing early behavioral changes before frailty develops could provide insight into its development and suggest early interventions. Since frailty is clearly associated with adverse outcomes, a healthy, active lifestyle is the cornerstone of prevention, and many researchers suggest that resistance training can reverse some muscle loss and improve functioning. When the health care team proposes any change in care, including a new medication, it should be prepared to describe how the intervention may affect cognition, memory, energy, or function.

KEY WORDS: Frail elderly, Frailty, Grip strength, Unintentional weight loss, Weakness.

ABBREVIATIONS: ADL = Activity of daily living, BMI = Body mass index, CHS = Cardiovascular Health Study, WHAS = Women’s Health and Aging Studies.

The beginning of my association with The Consultant Pharmacist 15 years ago, was, like the start of any worker’s first days at a new job, instructive. In peer review process, the reviewers frequently would ask, in one way or another, for me to “Speak more to the frail long-term care resident,” or “How does this disease (or side effect or morbidity) manifest in frailty?” Normally I would head for a dictionary when I think—but am not sure—how to define a word. Looking for a definition of frailty in the mid-1990s was almost futile; it hadn’t yet been developed. Regardless, clinicians who worked with the frail elderly knew what frailty looked like when they saw it and how it could undermine a diagnosis, a treatment plan, and, sadly, a life.

About 10 years ago, several researchers began a quest to define frailty and look for its signs, symptoms, and, possibly, its causes. By 2004, a common criterion indicated a patient might be considered frail if he or she was older than 85 years of age, dependent in more than one activity of daily living (ADL), had three or more comorbid conditions, and had one or more geriatric syndrome (incontinence, dementia, delirium, falls, neglect/abuse, osteoporosis). This was a good start.
Fried et al. were among the first to standardize the definition of frailty as a distinct syndrome with biologic underpinnings. They described a clinical phenotype of frailty so precise and suggestive of the typical long-term care resident's decreased reserve and resistance to stressors, it resonated with clinicians. The clinical manifestations they described—a mutually exacerbating cycle of negative energy balance, sarcopenia, diminished strength, and exertion intolerance—elucidated a problem long-term care providers had struggled with daily. By finding that name for this chronic state of vulnerability and identifying its characteristics, we have started to understand how we may someday defeat this foe.

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Defining Frailty

Central to what is now called Fried’s definition of frailty is the requirement that patients have three of five phenotypic criteria—low grip strength, low energy, and slowed walking. Other researchers also use a 30- to 70-item frailty index (FI) that predicts adverse health outcomes more sensitively—it counts the patient’s deficits accumulated over time, including disability, diseases, physical and cognitive impairments, psychosocial risk factors, and geriatric syndromes such as falls, delirium, and urinary incontinence. The comprehensive nature of the FI, including its length and complexity, preclude the use of this instrument routinely in clinical settings. In addition, these researchers designate a “prefrail condition,” in which the patient meets one or two criteria. Patients considered prefrail are at high risk of progression to frailty. Age is no longer considered a defining characteristic, although frailty is still considered primarily a geriatric problem. Although people who are considered frail tend to be elderly, younger people can be frail as well.

Currently, frailty is classified as a medical syndrome. Medical syndromes:
- Are groups of signs and symptoms that aggregate in a hierarchical order
- May trigger a cascade of alterations across other systems
- Characterize a particular abnormality

Current definitions of frailty are based in large part on findings from the U.S. Cardiovascular Health Study (CHS) and the Women’s Health and Aging Study (WHAS) II (Table 1). Fried used the CHS data, but excellent information came from WHAS II, a 7.5-year longitudinal study with 420 participants that describes the typical onset of frailty over time. Although women who became frail over the course of observation noted a variety of manifestations when their decline began, weakness was the most common first manifestation. Further, weakness, slowness, and low physical activity preceded exhaustion and weight loss in 76% of the women who were not frail at baseline, but became frail. This may be related to the now recognized decline in muscle strength beginning in midlife or with sarcopenia. It is unclear why sarcopenia occurs over time, but age-related declines in alpha-motor neurons, growth-hormone

Pharmacists, recognizing that certain comorbidities are likely to occur, can address frailty using careful drug regimen review.
production, sex steroid levels, and physical activity seem to contribute. Fat gain, increased catabolic cytokine production, and reduced dietary energy and protein may also be causes.9

Elders accumulate frailty criteria in different ways, and probably do so as the result of different causative pathways. They progress at different rates, with around two-thirds of affected individuals entering frailty in a slow, progressive way, and one-third becoming frail cataclysmically. Individuals may reach the terminal point of their frailty with organ-specific symptoms or systemic physiologic dysregulation.7,10 The points at which patients progress from nonfrail to prefrail to frail are called transitions. Approximately 80% of transitions to frailty involve adding exhaustion or weight loss to other criteria; weakness is a common early sign, and exhaustion and weight loss are often late manifestations. If exhaustion or weight loss are early manifestations, however, frailty is more likely to occur, and progression may be faster than in others.5,7

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The Frail Few
Using frailty criteria developed in CHS, researchers looked at community-dwelling adults 65 years of age or older who were not disabled at baseline in four essential ADLs (bathing, dressing, walking inside the home, and transferring from a chair). They found the overall prevalence of frailty ranged from 7% to 12%. Its prevalence was lowest in the group 65 to 74 years of age (3.9%) and increased to 25% in participants older than 85 years of age, with a slightly higher prevalence in women.2

As individuals become overtly frail, they tend to adapt behaviorally as they realize their physiologic reserve and capacity to meet environmental challenges is declining. Observing early behavioral changes in the period before frailty develops could provide insight into its development and suggest early interventions.11 Decreasing life space—the size of the area people purposely move through in their daily life and the frequency of travel in a specific time frame—is an example of a parameter that could be observed as a behavioral precursor to frailty. Life space measures spatial mobility as well; put more simply, life space is range, independence, and frequency of movement.12,13 In a study that looked at life space among women (N = 599) 65 years of age and older enrolled in the WHAS, women who left their neighborhood fewer than four times per week were 1.7 times more likely to become frail than those who left more often. Those who never left their homes experienced a three-fold increase in death before the onset of frailty. This study also found that for many patients, declining mobility, instrumental ADLs, and ADLs alone did not necessarily reduce life space; a subset of participants adapted. This suggests strongly that a slightly constricted life space may increase risk for frailty and may be a useful screening tool or intervention target.14

Frailty isn’t a unidirectional syndrome, however, as a study in New Haven, Connecticut, demonstrated. Following 754 subjects age 70 and older, the Precipitating Events Project used the five frailty criteria discussed above. After 54 months, 57.6% of study subjects made at least one transition. From baseline to 36 months, 19% worsened from prefrail to frail. Remarkably, 16.5% also moved from prefrail to nonfrail during the observation period. This study was observational, so no interventions were identified to promote improvement. It does highlight the possibility for prevention and reversal of frailty.15

Associating Frailty with Adverse Outcomes
Frailty is clearly associated with adverse outcomes. The most obvious—increasing dependence and the need for increased and increasing personal care—leads to greater use of health care services and higher mortality.6,16 Elders who have a greater number of frailty criteria generally have longer hospital stays, more postoperative complication, and greater likelihood of discharge institutionalization if they require surgery.5 Frailty is also associated with other comorbidities and conditions.
### Table 1. Comparison of Two Frailty-Defining Criteria

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cardiovascular Health Study</th>
<th>Women’s Health and Aging Studies</th>
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<tbody>
<tr>
<td>Weight loss</td>
<td>Unintentional weight loss of 10 pounds (4.5 kg) or more in one year</td>
<td>Weight loss of &gt; 10% of weight after age 60 follow-up: BMI &lt; 18.5 kg/m² or an unintentional weight loss &gt; 5% of baseline in a year</td>
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<td>Exhaustion</td>
<td>Self-report of either: • “Everything I did in the last week was an effort,” or • “I could not get going in the last week”</td>
<td>Self-report of: • Energy level lower than usual or • Feeling unusually tired in the last month or • Feeling unusually weak in the last month</td>
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<td>Low energy expenditure</td>
<td>Based on an 18-item activity scale: • Women used &lt; 90 kcal • Men used &lt; 128 kcal</td>
<td>Based on an 18-item activity scale: • Women used &lt; 270 kcal • Men used &lt; 383 kcal</td>
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<tr>
<td>Slowness</td>
<td>When asked to walk 15 feet (4.57 m) at usual pace: • Women: Time ≥ 7 s for height ≤ 159 cm Time ≥ 6 s for height &gt; 159 cm • Men: Time ≥ 7 s for height ≤ 173 cm Time ≥ 6 s for height &gt; 173 cm</td>
<td>When asked to walk 13 feet (4 m) at usual pace: • Women: Speed ≤ 4.57 m in 7 seconds for height ≤ 159 cm Speed ≤ 4.57 m in 6 seconds for height &gt; 159 cm • Men: Speed ≤ 4.57 m in 7 seconds for height ≤ 173 cm Speed ≤ 4.57 m in 6 seconds for height &gt; 173 cm</td>
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<td>Weakness</td>
<td>Grip strength • Women: ≤ 17 kg for BMI ≤ 23 ≤ 17.3 kg for BMI 23.1-26 ≤ 18 kg for BMI 26.1-29 ≤ 21 kg for BMI &gt; 29 • Men: ≤ 29 kg for BMI ≤ 24 ≤ 30 kg for BMI 24.1-26 ≤ 30 kg for BMI 26.1-28 ≤ 32 kg for BMI &gt; 28</td>
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**Note:** Criteria for men in the Women’s Health and Aging Studies column extrapolated.

**Abbreviations:** BMI = Body mass index, m = meters.

**Source:** References 2, 7.
DALIRESP® (roflumilast) tablets Rx Only
Brief Summary of Full Prescribing Information
Initial U.S. Approval: 2011

INDICATIONS AND USE DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Limitations of Use DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS The use of DALIRESP is contraindicated in the following conditions: Moderate to severe liver impairment (Child-Pugh B or C) [see Clinical Pharmacology (12.3) and Use in Special Populations (8.6)].

WARNINGS AND PRECAUTIONS Treatment of Acute Bronchospasm DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm. Psychiatric Events Including Suicidality Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.4%) for DALIRESP versus 1.0%, 0.9%, and 0.0% for placebo, respectively [see Adverse Reactions (6.1)]. Incidences of suicidal ideation and behavior, including completed suicide, have been observed in depressed patients. These patients experienced psychiatric adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who took placebo.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare providers. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

Weight Decrease Weight loss is a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [see Adverse Reactions (6.1)]. In addition to being reported as adverse reactions, weight loss was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as >5% body weight loss) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo lost >10% body weight (defined as severe weight loss). During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored closely. Unexplained or clinically significant weight loss, weight loss which occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

Drug Interactions A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP4A and CYP1A2 [see Clinical Pharmacology (12.3)]. Drugs That Induce Cytochrome P450 (CYP) Enzymes Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 450 inducers (e.g., rifampin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended. [see Drugs That Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)]. Drugs That Inhibit Cytochrome P450 (CYP) Enzymes The co-administration of DALIRESP (500 mcg) with CYP4A inducers or dual inhibitors that inhibit CYP4A and CYP1A2 simultaneously (e.g., erthyromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. [see Clinical Pharmacology (12.3)]. Oral Contraceptives Containing Gestodene and Ethinyl Estradiol The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase systemic exposure to gestodene and ethinyl estradiol. Oral contraceptives containing gestodene and ethinyl estradiol may reduce the systemic exposure to roflumilast N-oxide and roflumilast. Use of oral contraceptives containing gestodene and ethinyl estradiol provides a reliable contraceptive method.[see Clinical Pharmacology (12.3)]. USE IN SPECIFIC POPULATIONS Pregnancy Teratogenic effects: Pregnancy Category C. There are no adequate and well-controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in rabbits, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. DALIRESP induced decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m^2 basis at maternal doses of ≥ 1 mg/kg/day and 5 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m^2 basis at maternal doses ≥ 0.6 mg/kg/day). No treatment-related effects on offspring were observed in mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m^2 basis at maternal doses of 1.5, 0.2, and 0.6 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP-decreased pup survival at approximately 49 times the MRHD (on a mg/mg2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased pup body weight and delayed pinna detachment in mouse pups at approximately 57 times the MRHD (on a mg/mg2 basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

Labor and Delivery DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/mg2 basis at a maternal dose of 2 mg/kg/day).

Nursing Mothers Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use Of the 4438 patients with COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were > 65 years of age and 471 were > 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted. [see Clinical Pharmacology (12.3)].

Hepatic Impairment Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age- and weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 43%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) [see Contraindications (4) and Clinical Pharmacology (12.3)].

Renal Impairment In twelve subjects with severe renal impairment administered a single 500 mcg dose of DALIRESP, the elimination half-life of roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 18% and 12%, respectively. No dosage adjustment is necessary in patients with renal impairment [see Clinical Pharmacology (12.3)].

OVERDOSAGE Human experience No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP the following symptoms were observed at an increased rate after a single oral dose of 2500 mg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

Management of Overdose In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialysable by peritoneal dialysis.
Interventions

Some researchers think that frailty can be prevented or even reversed. To do this, we need to know more about frailty’s individual components—low grip strength, low energy, slowed walking speed, low physical activity, and unintentional weight loss—and what causes them. Since frailty occurs on a continuum, addressing it means assessing the individual patient and matching interventions to the patient’s physical, psychological, social, and environmental needs.\textsuperscript{20} Intuitively, we can see that a healthy, active lifestyle is the cornerstone of preventing frailty. Many researchers propose resistance exercise that can reverse some muscle loss and improve functioning. The results of clinical trials are difficult to interpret and inconsistent, since the “dose” of exercise is difficult to define, and many patients have trouble adhering to regular exercise routines. Additionally, a “dose” of exercise that is too high could be harmful.\textsuperscript{21-24}

Recognizing frailty as a complicating factor can help clinicians work with elders and their families. If surgery is necessary, for example, clinicians should be realistic about the elevated risk and potential discharge to a long-term care facility (if the patient is community-dwelling).\textsuperscript{16} In fact, when the health care team proposes any change in care, including a new medication, they should be prepared to discuss whether the frail patient may react differently than others to the proposed intervention. They should also describe how the intervention may affect cognition, memory, energy, or function directly and honestly.\textsuperscript{25}

In the case of medication, many clinicians believe the frail elderly are more vulnerable to adverse drug reactions. A recent study of 377 patients 65 years of age or older found no association between degree of frailty and a patient’s risk of adverse drug reactions. It also found that the greatest risk factor for an adverse drug reaction was the number of new medications recently added to a patient’s medication regimen.\textsuperscript{26}

Pharmacists, recognizing that certain comorbidities are likely to occur, can address frailty using careful drug regimen reviewing, with an eye toward reducing unnecessary polypharmacy.\textsuperscript{17} In the frail elderly, it is prudent to studiously avoid unnecessary drugs. The Beers criteria, which list drugs inappropriate for use in elders 65 years of age or older, can provide a beginning framework for eliminating unnecessary drugs. But these criteria do not include additional drugs that are not appropriate for significantly older or more frail persons.\textsuperscript{27,28} In particular, pharmacists should be wary of drugs that cause fatigue as a side effect. Additionally, they should recognize that many frail elders will have osteoarthritis and need analgesics, but pain is also independently associated with frailty.\textsuperscript{18} Using the basic precepts of pain management is critical.

Early findings in community-dwelling older women suggest that mildly low and low-normal hemoglobin levels increase frailty risk, and comorbid cardiovascular disease also increases this risk. This identifies another potentially modifiable risk factor for frailty that pharmacists can address with the health care team.\textsuperscript{29}

<table>
<thead>
<tr>
<th>Table 2. Comorbidities and Conditions Associated with Frailty</th>
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<td>Polypharmacy</td>
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<tr>
<td>Osteoarthritis</td>
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<td>Analgesic use</td>
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<td>Heart failure and cardiovascular disease</td>
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<td>Risk of falling</td>
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<td>Depressive symptoms</td>
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<td>Cognitive dysfunction</td>
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Sorted by strength of association, i.e., polypharmacy strongest, cognitive function weakest

Source: Adapted from References 2, 17-19.
End Note

Frailty can take on a poetic persona; “human frailty” is used to explain mistakes and excuse indiscretions. For residents of long-term care facilities, however, frailty is an energy-robbing presence that signifies life is coming to an end. Finding ways to prevent and reverse frailty could empty many long-term care beds.

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Consult Pharm 2011;26:634-45.
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References