Frailty in Older People – How Pharmacists Can Intervene

Tracy L Brooks, PharmD, BCPS, BCNSP, CPE
Assistant Professor, Pharmacy Practice
Department at Manchester College of Pharmacy
Palliative Care Pharmacist at Parkview Regional Medical Center, Fort Wayne, IN
Webinar Description:

With our aging population, it is common to encounter an elderly patient with frailty. Frailty is a “faster than typical decline” in physiological reserve with aging. We are going to explore three interesting topics where pharmacists can potentially improve outcomes: weight loss, polypharmacy and resultant adverse drug reactions, and pain management.
Objectives:

• Summarize the pathophysiology of frailty
• Interpret the current literature looking at pharmacologic therapy to reverse weight loss
• Construct evidence-based strategies for addressing polypharmacy
• Formulate an analgesic plan in a frail elderly patient
There is no gold standard to detecting frailty in older adults. Old age itself does not define frailty. Frailty is a syndrome of physiological decline in late life, characterized by marked vulnerability to adverse health outcomes. They are less able to adapt to stressors such as acute illness or trauma.
Meet Judy

• 66 yof admitted from home. Lives independently, able to do self-care, gets assistance with grocery shopping, errands, etc.
• Admitted with nausea, vomiting and diarrhea due to partial bowel obstruction, now resolving.
Problem list:

- DM II (average Hgb A1C 9%)
- Depression
- Fibromyalgia
- HTN
- ↑ Lipids
- Osteoarthritis
- Anemia
Frailty: **Faster** than typical decline for their chronological age.

Frailty in elderly people
Clegg, Andrew et al.
The Lancet, Volume 381, Issue 9868, 752 - 762

Diagram:
- Minor illness (eg, urinary tract infection)
- Functional abilities
  - Independent
  - Dependent
Identified frailty = CSHA Frailty Scale Level 4 or above
Concept of Frailty

“FRAIL”

F atigue (“Are you fatigued?”)
R esistance (“Can’t climb one flight of stairs?”)
A mbulation (“Can’t walk one block?”)
I llnesses (greater than 5)
L oss of weight (greater than 5%)

“Yes” to three or more questions indicates frailty. “Yes” to one or two questions indicates pre-frailty.
SOCIAL & BEHAVIORAL FACTORS
- smoking, dietary quality, exercise, obesity etc.

ANTIOXIDANTS
- carotenoids, ascorbate, plant polyphenols, selenium, antioxidant enzymes, uric acid, etc.

DISEASE
- (Subclinical or Clinical)

REACTIVE OXYGEN SPECIES
- *OH, H₂O₂, NO, O₂⁻, etc.

INFLAMMATORY SIGNALS
- cytokines, bacterial products, virus, stress, etc.

AGING

OXIDATIVE DAMAGE SKELETAL MUSCLE
- protein carbonyls, lipid peroxidation, oxidative DNA damage

INFLAMMATORY PATHWAY
- NF-κB, AP-1 transcription factors

INFLAMMATION
- IL-6, IL-1β, CRP, etc.

↓ MyoD

Direct Muscle Damage

Catabolic Effect

↓ Anabolic Effect (Muscle)

SARCOPENIA

DECLINE IN PHYSICAL PERFORMANCE
- muscle strength, walking speed
Sarcopenia

- Age-related Chronic Inflammation

Muscle Atrophy
- Loss of Muscle Mass
- Disability
- Diminished Quality of Life
- Mortality

Cachexia

- Inflammatory-Related Diseases (e.g. Cancer, AIDS, Sepsis, etc.)
CHANGES IN STRENGTH WITH AGE

- age related loss of muscle strength is as a result of substantial loss of muscle mass
- which accompanies aging and decreased physical activity

- there is evidence that older people who continue anaerobic (power) exercises
- maintain strength up to the level of an untrained person of 20 years of age
Anorexia of aging
Malnutrition

Low protein intake

Anabolic resistance
Physical inactivity

Muscle protein
dyshomeostasis

Diseases
Inflammation

Unmet higher
protein requirements

Loss of lean body mass
Declining physical performance

Negative outcomes
Disability
Higher morbidity and mortality
Objectives:

- √ Summarize the pathophysiology of frailty
- Interpret the current literature looking at pharmacologic therapy to reverse weight loss
- Construct evidence-based strategies for addressing polypharmacy
- Formulate an analgesic plan in a frail elderly patient
Effects of megestrol acetate (MA) on appetite

Published meta-analyses:
1. Appetite improvement (NNT 3-4)
2. Weight gain (NNT 8)
3. The influence of MA on survival rate in advanced cancer patients has not been demonstrated
4. In the majority of patients, weight loss progresses independently of treatment (weight gain is short term)
Review Article

Describes general use of MA in cachectic elderly, cancer and HIV patients:

- Improved appetite occurs by 6 weeks; weight gain seen after 12 weeks
- Trend for the weight gained in the form of fat. A non-significantly higher percentage of patients had > 5% weight gain.
- Old formulation Megace OS is best given 480-800 mg with meals
- Newer MA nanocrystal suspension (Megace ES) 625 mg (5ml) in fed or unfed state (increased absorption)

Focus on MA in elderly

• Included predominantly male patients (median age 76 years) residents of VA Home in NY with weight loss $\geq 5\%$ in previous 3 months or body weight 20% below their IBW

• Karnofsky status 55%

• Excluded: life expectancy $\leq 24$ months, poorly controlled HTN, CHF, systemic infections, serious intercurrent illness, depression

• 12-week, randomized, double-blind, placebo-controlled trial with 13-week follow-up period.
• Placebo versus megestrol acetate 800 mg/day (Megace OS)
• Primary outcomes: weight, appetite, and survival (4 years)
• Results:

<table>
<thead>
<tr>
<th>Gain ≥ 4 lbs</th>
<th>Placebo (n=25)</th>
<th>MA Tx (%) (n=26)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>28%</td>
<td>34.6%</td>
<td>&gt; 0.2</td>
</tr>
<tr>
<td>16 weeks</td>
<td>25%</td>
<td>33.3%</td>
<td>0.2</td>
</tr>
<tr>
<td>25 weeks</td>
<td>21.7%</td>
<td>61.9%</td>
<td>0.043</td>
</tr>
</tbody>
</table>
• MA improved appetite
• Kaplan-Meier Curve showed no significant difference in survival at 4 years between the groups (p=0.72)
• Adverse events were similar between the groups
Overall summary of the literature

• MA improves appetite
• MA may cause weight gain in the form of fat
• No clear benefit to quality of life, nor has any study shown a survival benefit
• Place in therapy – earlier rather than later in patients with good performance status, in patients that physical exercise can be implemented.
• Conversation about goals/Risks (thrombosis and edema)
CIC Pathogenesis (CPR > 10 mg/L)

Tumor cells causing increased production of interleukins, interferon γ and tumor necrosis factor α

Increased hepatic protein synthesis

Increased lipolysis

Increased muscle proteolysis

Amino acid substrate

Muscle cell
CHRONIC ILLNESS
  e.g. Chronic heart failure
  Chronic obstructive pulmonary disease,
  Chronic kidney disease,
  Chronic infection & Sepsis,
  Cancer

Anorexia

Inflammation

Insulin resistance

Hypogonadism

Anemia

FAT LOSS

MUSCLE WASTING

Weight loss

Weakness & Fatigue
  reduced muscle strength, VO_{2}max,
  And physical activity

CACHEXIA DIAGNOSIS

Weight loss of at least 5%
In 12 months or less
(or BMI < 20 kg/m^2)

Decreased muscle strength
Fatigue
Anorexia
Low fat-free mass index
Abnormal biochemistry:
  Increased inflammatory
  markers (CRP, IL-6)
  Anemia (Hb < 12 g/dL)
  Low serum albumin ( < 3.2 g/dL)

3 of 5
Mediators of inflammation

**CELL-DERIVED**
- Preformed mediators in secretory granules
- Newly synthesized

**MEDIATORS**
- Histamine
- Serotonin
- Prostaglandins
- Leukotrienes
- Platelet-activating factor
- Reactive oxygen species
- Nitric oxide
- Cytokines
- Neuropeptides

**SOURCE**
- Mast cells, basophils, platelets
- Platelets
- All leukocytes, mast cells
- All leukocytes
- All leukocytes, EC
- Macrophages, EC
- Macrophages, lymphocytes, EC, mast cells
- Leukocytes, nerve fibers

**PLASMA PROTEIN-DERIVED**

**PLASMA**
- Complement activation
  - C3a
  - C5a
  - C3b
  - C5b-9 (membrane attack complex)

**LIVER**
- Major source

**Factor XII (Hageman factor) activation**

**Kinin system (bradykinin)**

**Coagulation / fibrinolysis system**
Acute / Chronic Inflammation

Pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha)

Liver

C-Reactive Protein
Objectives:

• √ Summarize the pathophysiology of frailty
• √ Interpret the current literature looking at pharmacologic therapy to reverse weight loss
• Construct evidence-based strategies for addressing polypharmacy
• Formulate an analgesic plan in a frail elderly patient
Drug Pharmacokinetics and pharmacodynamics changes in frail old people

- Absorption – reduced gastric acid, delayed gastric emptying, dysphagia
- Distribution – Increased body fat, low serum albumin
- Renal elimination – GFR estimated from plasma creatinine may overestimate the true CrCl for frail patients
- Metabolism – Liver mass and hepatic blood flow decrease by 20-30% and 20-50% respectively, however, activities of CYP450 enzymes remains well preserved in older people
- Pharmacodynamic changes – increased sensitivity to anticoagulants, cardiovascular drugs and psychotropic drugs
ADR-related hospitalization

- Polypharmacy and inappropriate medication use (IMUP) are an under-recognized cause of readmissions to hospital.
- Based on a retrospective cohort study in a veteran population (median age 81), the overall proportion of potentially preventable medication-related hospitalizations was 20.3% over a 5-year period.

Feasibility Study of a Systematic Approach for Discontinuation of Multiple Medications in Older Adults Addressing Polypharmacy  D Garfinkel

- Prospective cohort study included elderly patients (mean 82.8 years) referred by PCP (75 patients)
- Excluded patients with advanced disease (life-expectancy < 4 months)
- Outcome – stop as many “non-life saving drugs” as possible for at least 3 months
Improving drug therapy in elderly patients—the Good Palliative–Geriatric Practice algorithm. Revised from Garfinkel et al with permission from the Israel Medical Association Journal.

Figure Legend:
• “Intervention failure” was defined as recurrence of clinical signs and symptoms or worsening lab test results
• Whenever discontinuation failed, the drug was resumed
• Follow up every 3-6 months
An evidence-based consensus exists for using the drug for the indication given in its current dosing rate in this patient’s age group and disability level, and the benefit outweighs all possible known adverse effects.
Considering both diseases and syndromes, 94% of the patients had 3 or more and 51% had more than 6.
### 70 patients total; Mean follow up 19 months

<table>
<thead>
<tr>
<th></th>
<th>Number of medications Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of medications at the start of the study</td>
<td>7.7 (3.7)</td>
</tr>
<tr>
<td>Discontinuation <strong>recommended</strong> in 64 patients (311 medications total)</td>
<td>4.4 (2.5)</td>
</tr>
<tr>
<td>Percent drug therapies restarted</td>
<td>2%</td>
</tr>
<tr>
<td>Overall successful discontinuation (considering nonconsent and failures)</td>
<td>81% = 3.5 (2)</td>
</tr>
</tbody>
</table>

Mean follow up of 13 months; No significant adverse events or deaths were attributable to discontinuation; 88% of patients reported global improvement in health.
Objectives:

- √ Summarize the pathophysiology of frailty
- √ Interpret the current literature looking at pharmacologic therapy to reverse weight loss
- √ Construct evidence-based strategies for addressing polypharmacy
- Formulate an analgesic plan in a frail elderly patient
Pain

• Highly prevalent in older people and has significant detrimental effects on function and quality of life

• Relatively limited clinical evidence to inform the safe and effective use of these medications in the older population

• Older people have the highest rate of surgical procedures and are more likely to suffer from musculoskeletal pain

Main Point:

While it is understood that frail older people have an increased susceptibility to the adverse effects of analgesics, analgesic medicines can still be used safely and effectively in this patient population.

A study investigating the development of delirium in hip fracture surgery found severe pain and the use of low doses of opioids to be correlated significantly with the progression to delirium. There was no significant association found between the use of higher doses of opioids.

Main Points

• AGS 2002 panel recommends ATC pain control versus “prn”
• Use acetaminophen (avoid NSAID)
• Avoid tramadol and codeine
• Start opioids at lower doses – 25-50% of the dose given to younger patients
• Avoidance of polypharmacy – use ONE opiate and titrate to effect
• Dose escalation depends on half-life of the agent (typically 25-50%)

• Do not routinely use anti-emetics, especially phenothiazines
• Never use “IM” opioids
• The degree of respiratory depression depends upon the serum level of the opioids; tolerance develops rapidly
• When opioid therapy is initiated, sedation is common until tolerance develops.
• Initiative laxative simultaneously to prevent OIC
• Tend to avoid morphine in patients with renal insufficiency (CrCl < 30 ml/min)
• Do not use fentanyl patches in opioid naïve patients
• Closer monitoring; small, frequent adjustments

Objectives:

- √ Summarize the pathophysiology of frailty
- √ Interpret the current literature looking at pharmacologic therapy to reverse weight loss
- √ Construct evidence-based strategies for addressing polypharmacy
- √ Formulate an analgesic plan in a frail elderly patient
Questions & Discussions