Time for a reMEDy: A Focus on Medication Use and the Older Adult

Ginah Nightingale, PharmD, BCOP
Associate Professor, Department of Pharmacy Practice
Jefferson College of Pharmacy, Thomas Jefferson University, Jefferson Health
Philadelphia, Pennsylvania

Disclosures

• I do not have any conflicts of interests to declare

Objectives

1. Describe factors associated with under-enrollment of older adults in cancer trials and its impact on treatment decisions
2. Recognize how age-related physiologic changes and functional age can influence the pharmacology of cancer treatments
3. Describe validated tools to screen for ‘inappropriate’ polypharmacy and to identify chemotherapy toxicity risk in older adults
4. Identify the latest research recommendations to improve the generation of evidence for treating older adults

Objectives

Audience Response Question:

Which of the following are considered barriers to accrual of older adults in clinical trials?

A. Comorbidities
B. Regimen complexity
C. Transportation challenges
D. All of the above

Audience Response Question:

Which of the following is a validated tool to assess for ‘inappropriate’ polypharmacy when performing medication reviews?

A. Beers criteria
B. Chemotherapy toxicity calculator
C. Life expectancy
D. Morisky medication adherence survey
Audience Response Question:

Which of the following is a critical domain integrated in the comprehensive geriatric assessment?

A. Age  
B. Cancer stage  
C. Functional status  
D. Organ function

World-Wide Population is Aging

> 20% age 65+

[Link to population-ageing-data]

The Aging Spectrum

Population Requires Unique Skill Sets
- Age-related physiologic changes
- Vulnerability to toxicity
- Dependence in activities of daily living
- Concerns with long-term effects of therapy

[Links to population-ageing-data and peds-milestones]

Does chronologic age = functional age?

[Link to chronologic-age-always=functional-age]

Does chronologic age always = functional age?

[Links to fuel-tank-on-e and chronologic-age-always=functional-age]

Hallmarks of aging: Reduced physiologic reserve

[Links to fuel-tank-on-e and chronologic-age-always=functional-age]
Age-related physiologic changes (Pharmacokinetic)

- **Absorption** is altered due to ↓ gastric emptying, ↓ intestinal motility, ↓ intestinal blood flow and ↓ gastric acid secretion
- **Distribution** is altered due to ↑ percentage of body fat, ↓ muscle mass, ↓ body water, ↓ plasma albumin, altered tissue barriers
- **Metabolism** is altered due to ↓ liver mass (20-30%), ↓ hepatic blood flow and ↓ first pass metabolism
- **Excretion** is altered due to ↓ kidney mass and ↓ blood flow, ↓ glomerular filtration rate (GFR) leads to alterations of renal excretions of drugs

Age-related physiologic changes (Pharmacodynamic)

Pharmacodynamics is defined as the correlation between drug concentration at the receptor and the resulting effect (influenced by variations in receptor number, receptor affinity, cellular response) and by changes in functional organ reserves.

Examples:
- Older adults have increased sensitivity to anthracycline-induced cardiovascular effects, increased risk of cardiomyopathy
- Older adults have reduced bone marrow reserve which increases the risk for chemotherapy-induced myelosuppression

What information exists regarding chronologic age and physiologic changes (e.g. Abiraterone)?

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Renal Adjustment</th>
<th>Hepatic Adjustment</th>
<th>Toxicity and Outcomes data based on chronologic age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone</td>
<td>No adjustment required for mild-severe renal impairment. No adjustment required for end stage renal disease</td>
<td>No adjust required for mild hepatic impairment. Reduce dose to 250mg once daily for moderate hepatic impairment (Child-Pugh class B). Avoid use in severe hepatic impairment (Child-Pugh class C).</td>
<td>Of all patients receiving abiraterone in phase III trials, 73% were aged ≥ 65 years and 30% were aged ≥ 75 years. No overall differences in safety or effectiveness were observed between older adults and younger patients.</td>
</tr>
</tbody>
</table>

Clinical Case: HF is a 74 yo with metastatic castrate resistant prostate cancer

- HF has a past medical history of HTN, dyslipidemia, COPD, insomnia, and arthritis. He was diagnosed with mCRPC (metastasis to the bone) after presenting with a progressive hip pain over the past 2 months.

- Social history: Negative for alcohol, smoking, illicit drugs; Retired attorney, lives alone (wife died 1 year ago) but his daughters live 60 minutes away

- Independent with activities of daily living (e.g. bathing, toileting). HF is independent with housekeeping, grocery shopping, preparing meals and volunteers at a free legal clinic once weekly

- Daughter has expressed that HF needs assistance in paying bills, managing finances and managing medications
**Medications:**

- HCTZ 25mg PO daily, Lisinopril 20mg PO daily, Tiotropium 18mcg inhaled daily, albuterol inhaler prn SOB, diphenhydramine 25mg PO prn sleep, oxycodone 20mg PO prn back pain, senna 2 tablets PO daily, MVI

**Laboratory findings:** Normal Chem-7 (serum creatinine 1.1), normal CBC (Hgb 13.2 g/dL), normal B12, normal folate, normal thyroid tests, normal LFT

- Depression screen is negative, Mini-cog is positive (memory issues)
- Oncologist would like to initiate Abiraterone 1000mg by mouth once daily with prednisone 5mg PO twice daily (continue leuprolide injection)

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**Audience Response Question:**

True/False: HF’s prostate cancer treatment with Abiraterone is appropriate since there are no differences in safety or effectiveness versus younger patients.

A. True
B. False

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**Is there sufficient evidence-based data to support the use of cancer drug therapies in older adults with cancer?**

If so, is the evidence based on chronologic age or functional age?

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**Under-enrollment in Cancer Clinical Trials**

![Graph showing under-enrollment in cancer clinical trials by age group](image)

**Barriers to Accrual of Older Adults in Clinical Trials**

<table>
<thead>
<tr>
<th>Barrier(s)</th>
<th>Frequency ranked (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older patients often do not meet eligibility due to comorbidities</td>
<td>773 (67.5%)</td>
</tr>
<tr>
<td>Regimens are too toxic for older patients</td>
<td>509 (44.4%)</td>
</tr>
<tr>
<td>Long distance to treating center, transportation issues</td>
<td>506 (44.2%)</td>
</tr>
<tr>
<td>Patient and/or family preferences to not enroll on clinical trials</td>
<td>405 (35.3%)</td>
</tr>
<tr>
<td>Concern for limited life expectancy in older adults</td>
<td>310 (27.9%)</td>
</tr>
<tr>
<td>Lack of trials relevant for older adults</td>
<td>286 (25%)</td>
</tr>
<tr>
<td>Lack of patient/family education about clinical trials</td>
<td>206 (18%)</td>
</tr>
</tbody>
</table>

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**Additional factors Associated with under-enrollment**

- Comorbid conditions
  - Increased number and/or severity of comorbidities
  - Reduced functional status (e.g. ADL, IADL, cognitive impairment)
- Lack of social support
- Decreased access to comprehensive medical care
- Concomitant Medication Use
  - Polypharmacy
  - Potentially inappropriate medications (e.g. 2019 Beers)
Polypharmacy in Older Adults with Cancer

Results from a pharmacist-led medication assessment among ambulatory older adults with cancer (N=234, mean age 80 years)

<table>
<thead>
<tr>
<th>Medication Variable</th>
<th>Mean (SD) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of medications</td>
<td>9.2 (4.79)</td>
</tr>
<tr>
<td>Prescription medications</td>
<td>6.1 (3.58)</td>
</tr>
<tr>
<td>Non-prescription medications</td>
<td>2.8 (2.11)</td>
</tr>
<tr>
<td>Polypharmacy (5-9 medications)</td>
<td>41%</td>
</tr>
<tr>
<td>Excessive polypharmacy (≥10 medications)</td>
<td>43%</td>
</tr>
</tbody>
</table>


Polypharmacy: The Other Drug Problem

Problem #1: Many medications
- ≥5 concurrent medications (prescription, non-prescription)
- Unnecessary medications (no clear indication)

Problem #2: Potentially ‘inappropriate’ medications
- Any medication that has a greater risk than benefit
- Medications with significant adverse drug reactions
- Drug-drug interactions or drug-disease interaction


Have Drug Interactions Impacted Survival in Older Adults with Cancer?

- Retrospective study (Medicare data, 2007 through 2012)
- N=12,538 (median age 76) [lung, liver, renal, pancreas, CML]
- Prevalence of TKI-PPI interaction was 22.7%
- Polypharmacy was a predictor of concomitant TKI-PPI use
- TKI-PPI use decreased survival in 90 day and 1 year follow up


Potentially Inappropriate Medications in Older Adults with Solid Tumor Malignancies

Problematic medications: amitriptyline, megestrol, promethazine


I know this slide is text heavy but the article did not have any illustrations that I could insert.

Ginah Nightingale, 5/23/2019
**What Discussions Exist Around Medication Management at Your Institution?**

- What’s polypharmacy?
- These meds are needed for all their conditions, right?
- Should we consult with pharmacy?
- Now that you mention it, these are a lot of meds!
- We didn’t prescribe those meds so we shouldn’t meddle.

**Valuable Tools to Screen for ‘Inappropriate’ Medications**

- Beers criteria (NEW 2019)
- Screening tool of older persons’ potentially inappropriate prescriptions (STOPP) criteria
- Screening Tool to Alert doctors to Right Treatment (START) criteria
- Medication Appropriateness Index (MAI)

**Beers Criteria: Drugs to avoid**

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>Rationale</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>Highly anticholinergic. Clearance reduced with advanced age. Greater risk of confusion, hallucinations, sleepiness, blurred vision, difficulty urinating, dry mouth and constipation</td>
<td>Avoid use of diphenhydramine for treating severe allergic reactions may be appropriate</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meclizine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**START Criteria**

- **Cardiovascular system**
  - Antihypertensive therapy where systolic blood pressure consistently > 160
  - Statin therapy for primary prevention of cardiovascular disease in diabetes

- **Endocrine system**
  - Metformin with type 2 diabetes +/- metabolic syndrome ([-]renal impairment)
  - Antiplatelet therapy with type 2 diabetes for primary prevention of CVD

- **Musculoskeletal system**
  - Bisphosphonate + Calcium-vitamin D with known osteoporosis

**Medication Appropriate Index Criteria**

- Is there an indication for the drug? Is the medication effective?
- Is the dosage correct?
- Are the directions correct? Are the directions practical?
- Are there clinically significant drug-drug interactions?
- Are there clinically significant drug-disease condition interactions?
- Is there unnecessary duplication with other drugs?
- Is the duration of therapy acceptable?
- Is this drug the least expensive compared with others of equal usefulness?

**HF’s Medication List: Polypharmacy?**

1. Lisinopril-HCTZ 20-12.5mg PO QD
2. Metformin 1000mg PO TID
3. Tiotropium 18mcg inhaled QD
4. Albuterol inhaler prn SOB
5. Diphenhydramine 25mg PO prn HS
6. Senna 2 tablets PO daily
7. MVI PO daily
8. Oxycodone 20mg PO prn pain
9. Abiraterone 1000mg PO QD
10. Prednisone 5mg PO BID
### HF’s Medication List: ‘Inappropriate’ Meds?

1. Lisinopril-HCTZ 20-12.5mg PO QD  
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### HF’s Medication List: START criteria?

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### Senior Adult Oncology Center – Sidney Kimmel Cancer Center Approach

**National guidelines recommend medication evaluations as a standard component of the geriatric assessment**

**Brown bag medication review**
- Indication (medication-condition matching)
- Dosage, duration, duplication, drug interactions
- Medication adherence
- Comorbidities, functional status, life expectancy
- Social, cultural, and economic factors

### What are the latest research recommendations for treating older adults with cancer?

- Comprehensive Geriatric Assessment (CGA)

  **Key Domains for Assessment**
  - Functional status
  - Comorbid medical conditions
  - Nutritional status
  - Cognitive function
  - Psychological state
  - Social support
  - Medications (polypharmacy)

  **FIT**
  - Minimal co-morbidities
  - Independence with ADLs/IADLs*
  - Similar to younger age counterparts

  **Vulnerable**
  - Controlled co-morbidities
  - Some dependence with ADLs/IADLs
  - Geriatric syndrome

  **High Risk**
  - Several co-morbidities
  - Dependence with ADLs
  - Significant geriatric syndromes

- **Comprehensive Geriatric Assessment: HF**
  - Functional status – needs assistance with medication management
  - Comorbidities – has cardiovascular disease (drug-disease interaction)
  - Cognition – has mild cognitive impairment (does not impact ADL)
  - Socioeconomic – has daughter who lives 60 minutes away (support?)
  - Polypharmacy – on high risk medication (diphenhydramine), potential drug-drug interaction (oxycodone + diphenhydramine)
Can a geriatric assessment predict chemotherapy toxicity in older adults?

Predicting Chemotherapy Toxicity in Older Adults

Eligibility criteria
- Age 65 or older
- Diagnosis of cancer
- To start a new chemotherapy regimen

Timepoint 1: Pre-chemotherapy Geriatric Assessment
Timepoint 2: Geriatric Assessment
Chemotherapy: toxicity grading at each visit

* Sample size: 500 patients (chemotherapy alone)
* 7 participating institutions (Cancer and Aging Research Group)

Predicting Chemotherapy Toxicity in Older Adults

- Age ≥ 72 years old (2 points)
- GI/GU malignancies (2 points)
- Standard dose chemotherapy (2 points)
- Polychemotherapy (2 points)
- Hemoglobin (male < 11g/dl; female < 10g/dl) (2 points)
- Creatine clearance (Jelliffe < 34 ml/min) (2 points)
- Falls (last 6 months) (2 points)
- Hearing impairment (2 points)
- Limited in walking 1 block (2 points)
- Assistance required with med intake (2 points)
- Decreased social activity (2 points)

Chemotherapy Toxicity Risk Calculator

Chemotherapy Toxicity Risk Tools: Limitations

- Treatment regimens were limited to single-, multi-agent conventional therapies
- Treatment regimens did not include high dose chemotherapy regimens
- Treatment regimens did not include monoclonal antibodies, oral chemotherapy, hormonal therapy or immunotherapies
- Predictive models focused on grade 3-5 toxicity but grade 2 toxicity may be equally important in an older population
**Summary: Key Take-away Points**

- Age-related physiologic changes and functional age can influence the pharmacology of cancer treatments
- Several barriers exist that influence under-enrollment of older adults in cancer trials
- Validated tools are available to identify 'inappropriate' medications and identify predictors for chemotherapy toxicity
- Resources are available to identify recommendations to improve the treatment of older adults with cancer

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**Audience Response Question:**

True/False: HF’s prostate cancer treatment should be assessed using a chemotherapy toxicity calculator in order to predict risk for toxicity.

A. True
B. False

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