Polypharmacy and Deprescribing: A Guide for Hospitalists

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Objectives:

- Define polypharmacy and its impact on the elderly population
- Effects of aging on pharmacokinetics
- Deprescribing: Benefits and barriers
- Developing a deprescribing protocol
Polypharmacy in the Elderly
Polypharmacy

- No clear definition:
  - Taking 4 or more medications
  - Administration of more medicines than are clinically indicated, representing unnecessary use¹

- Common in geriatric population (≥65 years)
  - 40% take 5-9 medications, 18% take ≥10 ²
  - (UK): Avg # of medications prescribed to adults >65 yrs doubled (21.2 to 40.8 items per year) between 1996 and 2006³
  - 1/5 drugs commonly used in older people may be inappropriate→ increases to 1/3 in patients living in aged care facilities⁴

Polypharmacy

- Polypharmacy ↑ risk for adverse drug events (ADE)\(^1,3\)
  - With 2 medications: 13%
  - With 5 medications: 58%
  - >7 medications: 82%

- Older adults are nearly 7x as likely as younger persons to have adverse drug events requiring hospitalization\(^3\)

- 80% of ADEs among ambulatory patients who were hospitalized and up to 90% of ADEs among inpatients were preventable\(^3\)

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Evaluated data from National Electronic Injury Surveillance Cooperative Adverse Drug Event Survey (NEISS-CADES) from patients ≥65 years old treated for conditions directly related to drug or drug-specific adverse effect²
ED visits and ADEs:

- Estimated 265,802 ED visits (CI 95%, 184,040 to 347,563) for ADEs occurred annually from 2007-2009
- 37.5% of visits (99,629 visits; 95% CI, 55,531 to 143,724) required hospitalizations (inpatient admission, observation, or transfer to another hospital)
  - Half of hospitalizations for ADEs involved adults ≥ 80 years old
  - Rate of hospitalizations for ADEs was 3.5x higher among patients >85 years old compared to patients ages 65-69 years
- ED visits resulting in hospitalization more likely to involve unintentional overdoses and ≥ 5 concomitant medications compared to visits not resulting in hospitalization
Hematologic, endocrine, cardiovascular, CNS, and antimicrobial agents → 88.3% of hospitalizations for ADEs
Accounted for 2/3 of hospitalizations!

<table>
<thead>
<tr>
<th>Medication</th>
<th>Annual National Estimate of Hospitalizations (N = 99,628)</th>
<th>Proportion of Emergency Department Visits Resulting in Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Most commonly implicated medications†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>33,171</td>
<td>33.3 (28.0–38.5)</td>
</tr>
<tr>
<td>Insulins</td>
<td>13,854</td>
<td>13.9 (9.8–18.0)</td>
</tr>
<tr>
<td>Oral antiplatelet agents</td>
<td>13,263‡</td>
<td>13.3 (7.5–19.1)</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>10,656</td>
<td>10.7 (8.1–13.3)</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>4,778</td>
<td>4.8 (3.5–6.1)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>4,205</td>
<td>4.2 (2.9–5.5)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>3,465</td>
<td>3.5 (1.9–5.0)</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>3,329‡</td>
<td>3.3 (0.9–5.8)</td>
</tr>
<tr>
<td>Antiadrenergic agents</td>
<td>2,899</td>
<td>2.9 (2.1–3.7)</td>
</tr>
<tr>
<td>Renin–angiotensin inhibitors</td>
<td>2,870</td>
<td>2.9 (1.7–4.1)</td>
</tr>
<tr>
<td>Sedative or hypnotic agents</td>
<td>2,469</td>
<td>2.5 (1.6–3.3)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>1,653</td>
<td>1.7 (0.9–2.4)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1,071‡</td>
<td>1.1 (0.4–1.8)</td>
</tr>
<tr>
<td>High-risk or potentially inappropriate medications§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEDIS high-risk medications</td>
<td>1,207</td>
<td>1.2 (0.7–1.7)</td>
</tr>
<tr>
<td>Beers-criteria potentially inappropriate medications</td>
<td>6,607</td>
<td>6.6 (4.4–8.9)</td>
</tr>
<tr>
<td>Beers-criteria potentially inappropriate medications, excluding digoxin</td>
<td>3,170</td>
<td>3.2 (2.3–4.1)</td>
</tr>
</tbody>
</table>

Factors contributing to polypharmacy and adverse drug events:

- Multiple comorbidities
- Prescribing cascade
- Applicability of literature to elderly population
- Unclear guidelines regarding deprescribing
- Medications started while inpatient are continued indefinitely (antipsychotics for insomnia or delirium, PPIs for NSAID use, etc.)
- Altered pharmacokinetics
Pharmacokinetics and Aging
Pharmacokinetics

- Aging has effects on all of the following\(^5\):
  - Absorption
  - Distribution
  - Metabolism
  - Elimination

Absorption

- Decreased rate of absorption through GI tract
  - Lower peak serum concentration, delayed time to reach peak

- Influence of other medications:
  - Fluoroquinolones and divalent cations (Ca++, Mg++, iron)
  - Enteral feeds and levothyroxine
  - Increased pH from PPIs → ↑↓ absorption of other drugs
    - ↑ absorption (nifedipine, amoxicillin)
    - ↓ absorption (antifungals, ampicillin, cyanocobalamin)
  - ΔGI motility (laxatives, motility agents) → Δamount of time spent in GI tract → Alters amount of drug absorbed
Distribution

- **△Body composition**: Decreased body water and lean body mass, increased fat stores → different volumes of distribution (Vd)
  - Hydrophilic meds = Low Vd
    - Ethanol, lithium, digoxin
  - Lipophilic meds = increased Vd → Longer time to reach steady-state, longer time to be eliminated
    - Diazepam, Flurazepam, Trazodone

- Binding to plasma proteins: Albumin decreased in older adults → Increases proportion of drug that is unbound and pharmacologically active
  - Ceftriaxone, diazepam, lorazepam, phenytoin, valproic acid, warfarin
Metabolism

- Most drug metabolism occurs in liver → hepatic flow decreases with age → Decreased metabolism
  - Decreased phase I pathways: hydroxylation, oxidation, dealkylation, reduction
    - Variable effects on parent drug

- Phase II pathways: Convert medications to inactive compounds
  - Glucuronidation, conjugation, acetylation
  - Medications that utilize phase II pathway preferred!

- Affects on cytochrome P-450 system:
  - CYP3A4 substrate: Induced by rifampin, phenytoin, carbamazepine, etc.
    - Inhibited by macrolides, nefazodone, itroconazole, ketoconazole, grapefruit juice, etc.
Elimination

- Usually dependent on kidneys → GFR decreases with age

- Difficulty estimating GFR in older adults → serum creatinine not always reflection of true creatinine clearance
  - Decreased lean muscle mass
  - eGFR for estimated CrCl can lead to dosing errors
  - Cockcroft-Gault equation preferred (takes age into account)
    - Still not completely accurate as a low creatinine can overestimate CrCl
Deprescribing: Benefits and Barriers
Deprescribing

- Scott et al\textsuperscript{4}: Systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient’s care goals, current level of functioning, life expectancy, values, and preferences
  - Not about denying effective treatment to eligible patients
  - Positive, patient-centered intervention, requires shared decision making, informed patient consent, close monitoring of effects (same as when a drug is prescribed!)
Barriers to Deprescribing

- Resistance from patients or family members
- Fear of losing patient-provider relationship
- Concern from clinicians to discontinue medications started by another provider
- Time expenditure
- Fear of drug-withdrawal side effects
- Lack of resources (i.e., clinical pharmacist, database availability)
Is Deprescribing Beneficial?

- Previous systematic reviews evaluating numerous studies in a variety of locations and several categories of interventions found weak quality of evidence to interpret effectiveness on intervention strategies\(^1,^3\)
  - Unclear if any significant decrease in mortality
  - Complex interventions, limited information on study designs, wide variability of methods, and lack of reproducibility
  - Wide variety of medications being evaluated, and therefore a wide range of endpoints

Deprescribing benefits, cont.

- Systematic review (Page et al, 2016): Evaluated studies involving patients >65 years prescribed one or more meds at beginning of study⁶
  - Deprescribing single medications was most common intervention type
  - Wide range of medication targets:
    - Included antihypertensives, potassium supplements, antiplatelet/anticoagulation meds, digoxin, diuretics, statins, PPIs, bisphosphonates

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Results and Conclusions:

- No significant impact on mortality across studies
  - Mortality significantly reduced when patient-specific (rather than education-specific) interventions were applied (OR 0.62, 95% CI 0.43-0.88; participants = 1906; studies 8)
  - No change in mortality in patients >80 yrs but decreased mortality in 65-80 yr old group

Secondary end points:

- Adverse Drug Withdrawal Events: Not increased with deprescribing
  - Deprescribing feasible and safe
- Falls:
  - No change in number of people who fell; did reduce the number of falls experienced
Conclusions:

- Deprescribing is feasible and can be done safely
- Mortality is reduced when patient-specific approaches are utilized
  - Effect more pronounced between ages 65-80
- Health outcomes vary with target medication
- Reinforces importance of individualized approach to medication use in older adults
Developing a Deprescribing Protocol
Deprescribing Protocol:

- Scott et al: 10 step protocol → simplified to a 5 step protocol and algorithm in 2015, published in JAMA

Special Communication | LESS IS MORE

Reducing Inappropriate Polypharmacy
The Process of Deprescribing

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Tips for Deprescribing in the Nursing Home

Linda M Liu, DNP, ANP-BC, GNP-BC, ACHPN • Irene G Campbell, MSN, APRN, GNP

  - Checklist designed for nursing home, may be useful for inpatient setting (SNF often continuum for acute care setting)
1. Ascertain all drugs patient is currently taking and reasons for each one

- Need patient (or family member) to bring all drugs (prescribed, complimentary and alternative medications and OTC meds)
- Clarify how/when/if patient is taking medication
- Consider involving pharmacy to perform med reconciliation (may involve contacting patient’s pharmacy, employing pill counts, etc)
2. Consider overall risk of drug-induced harm in individual patients in determining required intensity of deprescribing interventions

- Assess for risk factors, including:
  - Number of drugs (single most important predictor)
  - Use of high-risk drugs (Beer’s criteria)
  - Past or current toxicity
  - Patient factors:
    - age >80 years
    - cognitive impairment/dementia
    - multiple comorbidities
    - geriatric syndromes (falls, weight loss, delirium, etc)
    - substance abuse
    - multiple prescribers
    - past or current nonadherence
    - renal impairment
Common Geriatric Syndromes: Often due to drug toxicity!

Table 2. Geriatric Presentations Commonly Caused by Medications

<table>
<thead>
<tr>
<th>Geriatric Presentation</th>
<th>Medication-Related Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls, dizziness, syncope</td>
<td>Sedatives, hypnotics, cholinesterase inhibitors, antihypertensives, antidepressants, anticholinergics¹²²</td>
</tr>
<tr>
<td>Confusion, delirium, cognitive impairment, Constipation</td>
<td>Antiparkinsonian, anticholinergics, anticonvulsants, antisisperminic, corticosteroids, antiarrhythmics, opioids, sedatives/hypnotics¹</td>
</tr>
<tr>
<td></td>
<td>Anticholinergics, calcium, calcium channel blockers, opioids, tricyclic antidepressants²³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effect: altered taste or smell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol, ACE inhibitors, antibiotics, anticholinergics, antihistamines, calcium channel blockers, levodopa, propranolol, spironolactone²³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effect: anorexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine, antibiotics, anticonvulsants, antipsychotics, benzodiazepines, digoxin, levodopa, cholinesterase inhibitors, memantine, metformin, opiates, SSRIs²³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effect: dry mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics, antihistamines, clonidine, loop diuretics²³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effect: dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates, doxycycline, iron, NSAIDs, potassium²³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effect: nausea/vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine, antibiotics, bisphosphonates, digoxin, dopamine agonists, metformin, SSRIs, statins, tricyclic antidepressants²³</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

3. Assess each drug for its eligibility to be discontinued

- No valid indication and/or contraindications:
  - Diagnosis in doubt or not confirmed
  - Confirmed diagnosis but no evidence in literature to support efficacy of treatment

- Risks > benefits of continuing medication:
  - Beer’s criteria
    - Benzodiazapines
    - Psychotropics
    - Narcotics
    - NSAIDs
    - Anticoagulants
    - Digoxin
    - Cardiovascular drugs
    - Insulins/hypoglycemics
    - Anticholinergic meds

- “High-risk” drug combinations → Increase level of toxicity (i.e. NSAID + diuretic + ACE inhibitor in CKD)
Drug discontinuation, cont.

- Time to benefit of medication > patient’s expected lifespan
  - Statins, bisphosphonates
  - Evaluate utility of preventative medications in patients with severe dementia, metastatic cancer, end-stage organ failure

- Part of prescribing cascade:
Table 3. Common Examples of Prescribing Cascades

<table>
<thead>
<tr>
<th>Initial Medication</th>
<th>Adverse Effect</th>
<th>Subsequent Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil, rivastigmine, Galantamine</td>
<td>Urinary incontinence</td>
<td>Antimuscarinic agent (eg, oxybutinin, tolterodine, solifenacin, etc(^1,24))</td>
</tr>
<tr>
<td>Antimuscarinic agents, Vasodilators, diuretics, calcium channel blockers, (\beta)-blockers, ACE inhibitors, NSAIDs, opioid analgesics, sedatives, statins</td>
<td>Dizziness</td>
<td>Meclizine(^24)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Hypertension</td>
<td>Antihypertensive(^24)</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Edema</td>
<td>Furosemide(^1)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Gout</td>
<td>Allopurinol or colchicine(^24)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>EPS</td>
<td>Carbidopa/levodopa(^24)</td>
</tr>
<tr>
<td>Digoxin, opioids, NSAIDs, nitrates, ACE inhibitors, diuretics, oral corticosteroids</td>
<td>Nausea</td>
<td>Prochlorperazine, proton pump inhibitor(^24)</td>
</tr>
<tr>
<td>Memantine, rivastigmine, etc</td>
<td>Agitation</td>
<td>Antipsychotic, sedative/hypnotic(^25)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Urinary retention</td>
<td>Tamulosin(^26)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; EPS, extrapyramidal symptoms; NSAID, nonsteroidal anti-inflammatory drug.
Drug discontinuation, cont.

- Disease or symptom control drug ineffective or symptoms have resolved
  - Sliding scale insulin, oral hypoglycemics in older diabetic patients with multiple comorbidities
  - Antihypertensive use in frail older patients
  - Ongoing anti-emetic use following resolved episode of nausea/vomiting
  - Ongoing PPI use following cessation of NSAIDs or corticosteroid therapy
  - Antihypertensive use if normo→hypotensive with lifestyle modifications
  - Antidepressants for previous but resolved episode of reactive depression
  - Antipsychotics for agitation in dementia
Table 1. Common Examples of Medications That May No Longer Be Indicated

<table>
<thead>
<tr>
<th>Medications</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Statins                                 | Consider discontinuing in patients with limited life expectancy (< 5 years)\(^{14}\)  
                                          | Check lipid panels; often times elderly patients continue on statin when no longer needed  
                                          | Consider discontinuing in patients with no known cardiac disease\(^{10}\)                                                                 |
| Antihypertensives                       | Monitor BPs: target BP < 150/90 mm hg for patients aged 60 or older\(^{15}\)                                                          |
| Bisphosphonates after 5 years           | No evidence of effectiveness after 5 years of continuous use\(^{16}\)                                                                  |
| NSAIDs                                  | Intended for short-term use\(^{17}\)                                                                                                  |
| PPI/H\(_2\) antagonists                 | Typically intended for short-term use\(^{17}\)                                                                                         |
| Acetaminophen                           | Typically intended for short-term use\(^{18,19}\)                                                                                     |
| Ferrous sulfate, folic acid, B\(_{12}\) | Check levels such as iron, B\(_{12}\) levels, etc, to determine ongoing need\(^{18,19}\)                                             |
| Laxatives                               | Review diet, fluid intake, exercise, and medications contributing to constipation\(^{19}\)                                          
                                          | Consider discontinuing docusate sodium, especially if already on other laxatives\(^{19}\)                                          |
| Diuretics                               | Stop if not used for heart failure or hypertension\(^{18,19}\)                                                                       |
| Cholinesterase inhibitors and memantine | Discontinue in patients with advanced dementia, weight loss, syncope, falls, bradycardia, GI side effects, or agitation\(^{20}\) |
| Vitamins                                | May no longer be indicated in those consuming a well-balanced diet\(^{18}\)                                                            |
| Antipsychotics                          | Behaviors may no longer be present; consider safer alternatives\(^{19}\)                                                             |
| Oral hypoglycemic agents                | Avoid long-acting sulfonylureas; target HbA\(_{1c}\) < 8\%\(^{21}\)                                                                   |
| Antiemetics                             | Rarely needed long-term; trial discontinue\(^{18}\)                                                                                   |

Abbreviations: BP, blood pressure; GI, gastrointestinal; HbA\(_{1c}\), hemoglobin A\(_{1c}\); NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.
4. Prioritize drugs for discontinuation

- Medications with greatest harm and least benefit
  - Focus on medications that could contributing to reason for admission

- Medications easiest to discontinue

- Medications patient is most willing to discontinue

- (Inpatient setting): Medications with potentially harmful/life-threatening side effects if discontinued rapidly
  - Benefit from inpatient monitoring
  - Benzodiazepines, antipsychotics
Benefit of inpatient monitoring: Ability to slowly taper in supervised setting → often difficult to initiate in the outpatient setting

5. Implement and monitor drug discontinuation regimen

- Benefit of inpatient stay → Ability to monitor for withdrawal
- Shared decision making between patient and provider (patient/family member barriers)
- Discontinue one medication at a time (if monitoring for withdrawal)
- COMMUNICATION IS KEY!!!
  - Communicate plan to other health care prescribers and other relevant parties (family members, caregivers)
  - Discharge planning: Ensure plan for removal of meds in patient’s home
- Document reasons for and outcomes of deprescribing
Deprescribing Resources:

  - 5-Step Protocol and algorithm

  - Tip sheet and useful medication tables

- American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
  - americangeriatrics.org
    - Online access (non-members): $5 for 1 year
    - Print (25 cards per order): $25

- Uptodate.com:
  - Lists side effects, drug-drug interactions, pharmacokinetics, as well as renal and geriatric dosing of medications
Conclusions

- Polypharmacy affects more than half of the elderly population

- Adverse drug effects are a major contributor of ED visits and inpatient hospitalizations in this population:
  - Antiplatelet meds, anticoagulants, hypoglycemic meds and insulins a major culprit!

- Aging has effects on drug metabolism
  - Absorption; Distribution; Metabolism; Elimination
Conclusion

- Deprescribing → mixed evidence regarding decrease in mortality (due to wide range of study designs and targets) but more pronounced when patient-centered approach utilized:
  - Deprescribing shown to be feasible and safe

- Following a simplified protocol and algorithm can help provider safely remove unnecessary and unsafe medications:
  - Inpatient: Focus on medications potentially contributing to reason for admission
  - Consider slow titration of medications with potential withdrawal effects during hospitalization
  - Limit short term medications at discharge: Place stop dates, limit # refills
  - Communication is KEY
Special Thanks to:

- Mark A. Supiano, MD
- Carole A. Baraldi, MD
- Philip Kithas, MD PhD
- Natalie Sanders, MD
References:

1. Patterson, S. M. *et al.* in *Cochrane Database of Systematic Reviews* (John Wiley & Sons, Ltd, 2014).


Thank you!