Medication Burden and Polypharmacy in Chronic Kidney Disease

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Clinical Associate Professor - University of Michigan College of Pharmacy
Clinical Pharmacist Specialist – University of Michigan Health
Disclosures

• No relevant financial relationships to disclose
Objectives

• Explore the implication of polypharmacy in patients living with chronic kidney disease

• Identify approaches to decrease medication burden in patients living with chronic kidney disease
Meet AC

63-year-old female

Problem list:
Heterozygous familial hypercholesterolemia
Hypertension
Hypothyroidism
Obesity (Class 3)
Stage 3 Chronic Kidney Disease
Tobacco use
Type 2 Diabetes Mellitus
## Pertinent Labs

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Patient Case

Vitals

• BP 148/94 mmHg, HR 72 bpm; repeat 146/92 mmHg, HR 70 bpm
  • Home BP log with all readings > 140/90 mmHg
  • Weight 116 kg, Height 60 in, BMI 50 kg/m²

• Social History
  • (+) tobacco: ½ pack per day
  • (+) EtOH: 1-2 glasses wine per week

• Family history
  • Mother died at age 68 from a stroke while on hemodialysis

• Prescription insurance: commercial through her employer
Social Determinants of Health

- Education Access and Quality
- Health Care Access and Quality
- Economic Stability
- Neighborhood and Built Environment
- Social and Community Context

Social Determinants of Health
Healthy People 2030

Copyright-free
## Social Determinants of Health

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<th>Neighborhood</th>
<th>Social</th>
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<td>• Works full time, earns minimum wage</td>
<td>• Lives in high crime area</td>
<td>• Low health literacy</td>
</tr>
<tr>
<td>• Cannot always afford groceries, supplements from food bank</td>
<td>• Does not feel safe walking for exercise in her neighborhood</td>
<td>• Does not discuss her health with family or friends</td>
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Current Medications

- Amlodipine 5 mg daily
- Aspirin 81 mg daily
- Atenolol 25 mg daily
- Atorvastatin 80 mg daily
- Cholecalciferol 2000 units daily
- Empagliflozin 10 mg daily
- Evolocumab 140 mg every 2 weeks
- Ezetimibe 10 mg daily
- Insulin glargine 20 units daily at bedtime
- Irbesartan 150 mg twice daily
- Levothyroxine 112 mcg daily
- Liraglutide 1.8 mg daily
- Metformin 1000 mg twice daily
- Multivitamin daily
- Spironolactone 25 mg daily
Polypharmacy

• Definitions vary
  • Measuring total number of medications
  • Use of high-risk or unnecessary medications

• Most common definition in research: Use of five or more medications

• Hyperpolypharmacy: Use of 10 or more medications
Prevalence of polypharmacy in CKD is greater than 70%
Risks associated with polypharmacy

- Adverse drug events
- Hospital stays
- Polypharmacy
- Impaired function
- Falls
- Cognitive decline
- Mortality
Polypharmacy, CKD, and mortality among older adults

**Objective**
To investigate prospective association between polypharmacy, CKD, and all-cause and cause-specific mortality in adults age ≥ 65

**Design**
Prospective cohort study

**Population**
13,513 adults from National Health and Nutrition Examination Surveys taking ≥ 5 medications

**Outcomes**
Elderly participants with CKD and polypharmacy had a 27% (HR 1.27, 95% CI 1.15-1.39) increase in risk of all-cause mortality and 39% (HR 1.39, 95% CI 1.19-1.62) increase in risk of CVD mortality

Compared with elderly participants without CKD and polypharmacy, those with CKD and polypharmacy had a 34% (HR 1.34, 95% CI 1.21-1.49) increase in risk of all-cause mortality

**Conclusion**
Polypharmacy was associated with elevated risks of all-cause mortality and CVD mortality among older adults with CKD

## Medication choices & monitoring

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<tr>
<th>Nephrotoxin</th>
<th>Mechanism</th>
<th>Potential alternative</th>
</tr>
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<tbody>
<tr>
<td>NSAIDs</td>
<td>Reduction in prostaglandin-dependent kidney blood flow, allergic interstitial nephritis (AIN), nephrotic syndrome</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Acute tubular necrosis (ATN)</td>
<td>Cephalosporins, carbapenems</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Likely related to ATN and possibly AIN</td>
<td>Linezolid, daptomycin</td>
</tr>
<tr>
<td>SMX/TMP</td>
<td>AIN, ATN, crystalluria in distal convoluted tubule, reversible inhibition of tubular creatinine secretion</td>
<td>Clindamycin + primaquine, pentamidine, atovaquone</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Tubulointerstitial nephritis, AIN</td>
<td>H2-receptor antagonists</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Glomerular hemorrhage, oxidative stress, kidney vascular calcification</td>
<td>Non-vitamin K antagonist oral anticoagulants</td>
</tr>
<tr>
<td>Lithium</td>
<td>Nephrogenic diabetes insipidus, chronic tubulointerstitial nephropathy</td>
<td>Aripiprazole, lamotrigine, quetiapine, valproate</td>
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Medication monitoring

- Monitor eGFR, electrolytes, and therapeutic medication levels, when indicated, in people with CKD receiving medications with narrow therapeutic windows, potential adverse effects, or nephrotoxicity, both in outpatient and inpatient settings

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<th>Monitoring parameters</th>
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<td>ACEi, ARB</td>
<td>sCr, K within 2-4 weeks of initiating therapy or changing the dose</td>
</tr>
<tr>
<td>Gentamycin, vancomycin</td>
<td>drug levels, eGFR</td>
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<td>At least annual monitoring of sCr</td>
</tr>
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Medication management

- Review and limit the use of over-the-counter medicines and dietary and herbal supplements that may be harmful for people with CKD
Medication Burden

• Measures have moved from counting medications to standardized instruments
  • STOPP/START criteria
  • Beers Criteria
  • Medication Appropriateness Index
STOPP/START Criteria

Screening Tool of Older Persons’ Prescriptions (133 criteria)

- Examples:
  - Thiazide diuretic with a history of gout
  - Use of tricyclic antidepressants in patients with dementia or constipation
  - NSAID use with chronic renal failure
  - Benzodiazepines in those at risk of falls

Screening Tool to Alert to Right Treatment (57 criteria)

- Examples:
  - ACEi following acute myocardial infarction
  - Calcium and vitamin D supplementation in osteoporosis
  - ACEi or ARB in diabetes with nephropathy

## Beers Criteria

- Potentially inappropriate medication use in older adults

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<th>Rationale</th>
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<td>Non-selective peripheral alpha-1 blockers for treatment of hypertension</td>
<td>High risk of orthostatic hypotension</td>
</tr>
<tr>
<td>(prazosin, doxazosin, terazosin)</td>
<td></td>
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<td>Central alpha-agonists for the treatment of hypertension (clonidine,</td>
<td>High risk of CNS effects; may cause bradycardia and orthostatic hypotension</td>
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<td>guanfacine)</td>
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<td>Antidepressants with strong anticholinergic activity</td>
<td>Highly anticholinergic, sedating, and cause orthostatic hypotension</td>
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<td>(amitriptyline, desipramine, nortriptyline, paroxetine)</td>
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<td>Benzodiazepines</td>
<td>Risk of abuse, misuse, and addiction. Potential for sedation, respiratory depression, especially in</td>
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Medication Appropriateness Index

• 10 questions about each medication
  • Indication?
  • Is the medication effective for the condition?
  • 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 interactions?
  • Is there unnecessary duplication with other drugs?
  • Is the duration of therapy appropriate?
  • Is this drug the least expensive alternative compared to those of equal utility?
High Medication Burden

Adverse events
Nonadherence
Reduced functional status

Medication nonadherence

- 43 to 78% of patients with chronic diseases
- 12 to 53% of patients with Stage 3-4 CKD
- 21 to 74% of patients with ESKD
- 1 in 3 patients with CKD report not taking their antihypertensives

Study of medication adherence, burden, and HRQOL in adults with CKD

- 464 adults
  - Mean age 72 years
  - 67% male
  - Mean eGFR 21 mL/min/1.73m²
  - 79% taking ≥ 5 medications
  - 43% taking ≥ 9 medications

- People who reported medication non-adherence were more likely to report higher perceived medication burden (OR 4.89; 95% CI 1.02-23.5; p=0.02)
Drug stewardship

• Perform medication review periodically and at transitions of care to assess adherence, continued indication, potential drug interactions as patients with CKD often have complex medication regimens and are seen by multiple specialists
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- Ezetimibe 10 mg daily
- Insulin glargine 20 units daily at bedtime
- Irbesartan 150 mg twice daily
- Levothyroxine 112 mcg daily
- Liraglutide 1.8 mg daily
- Metformin 1000 mg twice daily
- Multivitamin daily
- Spironolactone 25 mg daily
Medications by Problem

Uncontrolled T2DM (A1c 8.6%)

- Metformin 1000 mg twice daily
- Empagliflozin 10 mg once daily
- Insulin glargine 20 units once daily
- Liraglutide 1.8 mg once daily

Next steps?
Uncontrolled T2DM – Plan

Uncontrolled T2DM (A1c 8.6%)
- Metformin 1000 mg twice daily → decrease to 500 mg twice daily
- Empagliflozin 10 mg once daily → increase to 25 mg once daily
- Insulin glargine 20 units once daily → increase depending on FBG
- Liraglutide 1.8 mg once daily

But wait…
Never started empagliflozin due to reading online “it could hurt my kidneys”.

Takes insulin glargine 20 units ~3 days per week due to injection burden associated with taking it daily.
Uncontrolled T2DM – Updated Plan

• Metformin 1000 mg twice daily → decrease to 500 mg twice daily
• Empagliflozin 10 mg once daily → counsel on benefits and encourage patient to start taking
• Liraglutide 1.8 mg once daily → switch to a once weekly GLP-1 agonist
• Insulin glargine 20 units once daily → counsel on need for daily dosing initially with potential to decrease the dose depending on response to GLP-1 agonist and SGLT2i
## T2DM – improved treatment burden

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<th>New Treatment</th>
<th>Improvement</th>
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<td>Liraglutide 1.8 mg daily (7 injections per week)</td>
<td>Semaglutide 0.5 mg or dulaglutide 1.5 mg weekly (1 injection per week)</td>
<td>6 fewer injections per week</td>
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<td>Metformin 1000 mg twice daily (taking 2 x 500 mg tablets BID = 28 tablets per week)</td>
<td>Metformin 500 mg twice daily (14 tablets per week)</td>
<td>14 fewer tablets per week</td>
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<td>Empagliflozin 10 mg daily (not taking)</td>
<td>Empagliflozin 10 mg daily (7 tablets per week)</td>
<td>Nephroprotective therapy</td>
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<tr>
<td>Insulin glargine 20 units daily (taking 3 days per week)</td>
<td>After 3 months of taking empagliflozin and uptitration of once weekly GLP-1 agonist to maximum dose, patient is able to stop insulin and has A1c at goal</td>
<td>7 fewer injections per week</td>
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**Net benefit:** A1c at goal, 13 fewer injections per week, 7 fewer tablets per week, nephroprotective therapy that will help with weight loss
Medications by Problem

Uncontrolled HTN (BP 148/94 mmHg, HR 72 bpm; repeat 146/92 mmHg, HR 70 bpm
  • Home BP log with all readings > 140/90 mmHg
  • Atenolol 25 mg once daily
  • Amlodipine 5 mg once daily
  • Irbesartan 150 mg twice daily
  • Spironolactone 25 mg once daily

• Next steps?
Uncontrolled HTN – Plan

Plan
Atenolol 25 mg once daily → change to carvedilol 6.25 mg BID
Amlodipine 5 mg once daily → increase to amlodipine 10 mg daily
Irbesartan 150 mg twice daily → consolidate to 300 mg once daily
Spironolactone 25 mg once daily

But wait...
• Never started amlodipine 5 mg once daily as her mom took it while on dialysis and “always said it caused swollen feet”

• Has not been taking irbesartan for the past month as her prescription ran out of refills and her pharmacy never received a new prescription from her doctor
• Amlodipine 5 mg once daily → counsel patient on benefits of taking and side effects to monitor for

• Irbesartan 150 mg twice daily → consolidate to 300 mg once daily and send new prescription to pharmacy

• Spironolactone 25 mg once daily

• Atenolol 25 mg once daily → change to carvedilol 6.25 mg BID at follow up visit
Medications by Problem

- Worsening hyperlipidemia
  - TC 150 mg/dL → 278 mg/dL
  - LDL 81 → 209 mg/dL
- Atorvastatin 80 mg once daily
- Evolocumab 40 mg every 2 weeks
- Ezetimibe 10 mg daily

- Next steps?
Uncontrolled hyperlipidemia – Plan

• Worsening hyperlipidemia
  • TC 150 mg/dL → 278 mg/dL
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• Atorvastatin 80 mg once daily
• Evolocumab 40 mg every 2 weeks
• Ezetimibe 10 mg daily

• Next steps?
  • Add bempedoic acid?
Uncontrolled hyperlipidemia

Patient report

Has not been taking evolocumab as she became tired of self-administering the injections at home.

Forgets to take atorvastatin 3-4 nights per week.
Uncontrolled hyperlipidemia

Updated Plan

• Atorvastatin 80 mg once daily → counsel patient she can take in the morning

• Evolocumab 40 mg every 2 weeks → switching liraglutide to once weekly GLP-1 agonist decreases injection burden and patient is now willing to take evolocumab

• Ezetimibe 10 mg daily
Can we deprescribe?

• Aspirin 81 mg once daily
  • USPSTF recommends against initiating low dose aspirin for primary prevention of CVD in adults 60 years or older

• Multivitamin once daily
6 months later

- AC presents to primary care clinic for a follow up visit
- Vitals
  - BP 128/78 mmHg, HR 72 bpm
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  - Weight 100 kg, Height 60 in, BMI 43 kg/m²
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- Ezetimibe 10 mg daily
- Irbesartan 300 mg daily
- Levothyroxine 112 mcg daily
- Metformin 500 mg twice daily
- Semaglutide 2 mg once weekly
- Spironolactone 25 mg daily
Barriers to optimal outcomes

- Medication cost
- Medication misconceptions
- Treatment burden
# Programs to help with Medication Cost

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<th>Program</th>
<th>Pros</th>
<th>Cons</th>
</tr>
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| Manufacturer Co-Pay Cards     | • Reduce the cost of brand name medications  
                               | • Can be used in combination with insurance                          | • Can only be used by commercially insured patients  
                               |                                                                      | • Subject to maximums and limited number of uses                  |
| GoodRx                        | • Can be used by anyone (insured or uninsured, government or private insurance) | • Co-pay paid does not count towards insurance deductible  
                               |                                                                      | • Brand name medication co-pays are typically still out of reach   |
| Patient Assistance Programs   | • May provide medications for free  
                               | • Sometimes cover medications for patients with government insurance or uninsured | • Subject to income limits  
                               |                                                                      | • Require written application and sometimes lengthy processing times |
Medication Misconceptions

Counsel patients at the time of prescribing

Provide a written handout in plain language at an appropriate reading level with answers to common misconceptions

Offer contact information for questions/concerns

Follow up on newly started medications
Treatment Burden

• Prescribe once daily medications whenever possible
• Consider combination tablets to decrease pill burden when the treatment regimen is stable
• Deprescribe whenever possible
• Discourage the use of over-the-counter supplements
Adherence Aids

- Pill boxes
- Reminder alarms
- Pill packs/"bubble" packs
- Calendars
- Phone apps
Summary

• Polypharmacy is common in patients living with CKD and has been associated with increased risk of adverse drug events, hospitalizations, and mortality.

• High medication burden may lead to non-adherence.

• Deprescribing unnecessary medications, decreasing the total number of doses per day, addressing medication cost, and use of adherence aids may help to increase patient adherence.
Medication Burden and Polypharmacy in Chronic Kidney Disease

Emily Ashjian, PharmD, BCPS, BCACP, CDCES
Clinical Associate Professor - University of Michigan College of Pharmacy
Clinical Pharmacist Specialist – University of Michigan Health