Polypharmacy in HIV and Aging

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Educational Objectives
By the end of the session, learners will be able to:

1. Describe one feature that distinguishes polypharmacy in HIV-infected patients from that in the general population.
2. Outline two adverse effects of polypharmacy on the health of HIV-infected patients.
3. Apply a systematic approach to the evaluation and management of polypharmacy in HIV-infected patients.

Suggested reading:

CASE ONE:

Mrs. Pill is a 70-year-old woman with chronic HIV infection who recently moved to your town and comes with her daughter to establish care with you as her new HIV provider. She has a history of non-traumatic hip fracture, hypertension, hyperlipidemia, coronary artery disease s/p stent placement 5 years ago, and chronic kidney disease (CKD) stage II (creatinine clearance (CrCl) of 65 mL/min).

Her daughter brings up a concern that Mrs. Pill takes too many medications and she believes her mother often forgets to take all of them as prescribed since she often finds extra pills around the house.

Questions:

1. How many pills are considered too many? What is polypharmacy?

   - Polypharmacy is strictly defined as the use of multiple medications by a patient. The precise minimum number used to defined polypharmacy is variable (ranges from 5-10) (1), although multiple studies have shown that the cutoff of 5 medications has been consistently associated with negative health outcomes (2).
- More practically, polypharmacy can be characterized by the following features:
  - Prescribing medications that are inappropriate for the patient’s medical condition
  - The use of medications that cause adverse drug events
  - Underutilization of beneficial therapy
- Based on the information above, there is no specific cutoff for the appropriate number of pills, since this number will be different in each patient. One pill can be too many if the patient does not need to take it.

2. How is polypharmacy different in HIV-infected patients compared to the general population?
- Comorbid conditions: Due to chronic HIV infection, certain health conditions are more common and present earlier in HIV-infected patients than in the general population, such as osteoporosis or cardiovascular disease.
- Organ system injury: HIV-infected patients may have higher rates of organ system injury (such as kidney or liver dysfunction) stemming from chronic use of ART or comorbid conditions with HIV. As a result, they may be more susceptible to medication toxicity.

3. How common is polypharmacy in HIV-infected patients? What is the effect of polypharmacy on their health?
- The prevalence of polypharmacy among HIV-infected patients varies across multiple studies, with most report excluding non-prescription medications and therefore likely an underestimate of the true prevalence. Data from the Swiss HIV Cohort Study (3) focusing on patients over 65 years old found the prevalence of polypharmacy to be about 14%.
- Polypharmacy has been found to affect the following:
  - Nonadherence: A meta-analysis by Atkinson et al (4) found that a pill burden of >10 pills/day was associated with higher nonadherence in HIV-infected patients (odds ratio 1.5, 95% CI 1.3-1.7).
  - Adverse drug events: A prospective study in HIV-uninfected patients receiving outpatient care (5) showed that the only factor associated with the occurrence of adverse drug events was the number of medications. The mean number of events per patient increased by 10% (95% CI 6%-15%) for each additional medication.
  - Geriatric syndromes: Data is limited in HIV-infected patients, but increased pill burden correlates with increased falls and decreased cognitive function in the general population. A meta-analysis by Erlandson et al (6) found that for each additional medication, there was a 5% increase risk in falls among community-dwelling older HIV-uninfected adults. Additionally, another study by Jyrkka et al (7) showed that HIV-uninfected older adults taking 10 or more drugs demonstrated decreased cognitive function over 3 years compared to those on 5 medications or less.
Mortality: Multiple studies have found an association between polypharmacy and mortality, although it is unclear whether polypharmacy is a marker of increased comorbid conditions/poor health or an independent risk factor for mortality.

4. How would you address the daughter’s concern?
   - The first step is to review the patient’s current medications, making sure to include over-the-counter products, ointments, vitamins, ophthalmic solutions, and herbal medicines, since many patients do not consider these to be medications. One of the best ways to ensure all medications are reviewed is “the brown bag method,” in which patients are asked to bring all bottles of everything they are taking to the visit to be reviewed with the physician.
   - It is important to review medications in a systematic manner, as outlined below (8):
     o Review current therapy for drug interactions
     o Discontinue potentially unnecessary therapy
     o Consider adverse drug events as a potential cause for any new symptom
     o Consider non-pharmacological approaches
     o Substitute with safer alternatives
     o Ensure appropriate dosing of all medications
     o Simplify the dosing regimen
     o Prescribe beneficial therapy
   - To reduce the risk of polypharmacy, Mrs. Pill should utilize only one pharmacy, preferably with integrated pharmacy computer network and experience in caring for HIV-infected patients. Utilizing a specialty pharmacy has been shown to reduce contraindicated medications and improve adherence in HIV-infected patients (9).
   - After the list of appropriate medications is determined, it is important to monitor for compliance and resolve any barriers that may prevent patients from taking medications as prescribed. Afterwards, the medication list should be reviewed periodically, and at least when the following occurs:
     o A change in severity of disease or renal/liver function at which time medication dosing needs to be adjusted
     o A new symptom which may be secondary to a medication side effect
     o A change in goals of care at which time certain medications may no longer be in line with the patient’s wishes

CASE ONE CONTINUED:

The daughter brought all of Mrs. Pill’s bottles from home. Her medications include: lisinopril 20mg daily, amlodipine 10mg daily, furosemide 40mg on Monday/Tuesday/Friday, simvastatin 20mg daily, aspirin 325mg daily, clopidogrel 75mg daily, esomeprazole 40mg daily, abacavir 600mg daily, lamivudine 300mg daily, atazanavir 300mg daily, ritonavir 100mg daily. She does not take any over-
the-counter medications or herbal supplements. However, she has multiple bottles of expired medications, including a bottle of lorazepam 1mg, which she has been taking on and off as a sleep aid.

Mrs. Pill states that she started taking clopidogrel after her stent placement 5 years ago. She also mentions that she started developing leg swelling after she started amlodipine. The heart doctor put her on furosemide to try and reduce the swelling, although she does not notice an improvement.

5. After reviewing her medication list in a systematic manner, how would you adjust Mrs. Pill’s medications?

- To help screen for inappropriate medications, validated instruments such as the Beers criteria from the American Geriatrics Society (10) or the STOPP criteria (Screening Tool of Older Person’s Prescriptions) (11) are available.

- Review current therapy for drug interactions:
  - Because atazanavir requires gastric acid for absorption, its level may decrease when taken with esomeprazole. This can be reduced if esomeprazole is taken at least 12 hours apart from atazanavir.
  - Esomeprazole inhibits hepatic metabolism through the CYP2C19 pathway, which may decrease conversion of clopidogrel to active metabolite. Since clopidogrel is unnecessary 5 years after a stent placement, stopping clopidogrel would be a sensible option.

- Discontinue potentially unnecessary therapy:
  - Clopidogrel is usually given for up to 1 month in bare-metal stents and up to 1 year in drug-eluting stents. Because Mrs. Pill’s stent was placed 5 years prior, clopidogrel is no longer necessary.

- Consider adverse drug events as a potential cause for any new symptom:
  - The swelling in Mrs. Pill’s legs can result from amlodipine, which can cause up to 15% of peripheral edema in female patients. This result in a “prescribing cascade,” in which side effects of a medication are misdiagnosed as symptoms of another problem (in this case leg swelling) resulting in further prescriptions, further side effects and further drug reactions.
  - Discontinue amlodipine to determine if it is the cause of the swelling. If the swelling improves, furosemide can also be stopped, which will reduce the overall pill burden for Mrs. Pill.

- Consider non-pharmacological approaches:
  - Lorazepam is not an appropriate medication for sleep aid in the elderly due to increased risk of falls and delirium. Non-pharmacologic interventions if possible are preferred to avoid side effects and drug interactions. For example, sleep hygiene including maintaining a regular sleep schedule and avoiding caffeinated beverages after lunch can help with insomnia, especially in Mrs. Pill whose symptoms only occur occasionally.

- Substitute with safer alternatives:
Because ritonavir and atazanavir can increase simvastatin level due to inhibited hepatic metabolism, combining protease inhibitors with simvastatin increases risk of myopathy and rhabdomyolysis. Simvastatin should be substituted with safer statins such as rosvastatin, pravastatin or atorvastatin.

If Mrs. Pill were ART-naïve, it would be sensible to prescribe a regimen with integrase inhibitor as the third agent, since it is more lipid-neutral than protease inhibitors. However, because Mrs. Pill does not have indications for changing antiretroviral therapy (such as virologic failure or difficulty adhering to regimen), it would not be appropriate to switch her regimen at this time.

- **Ensure appropriate dosing of all medications:**
  - The appropriate dose of aspirin for coronary artery disease is 81mg daily. As a result, her current aspirin dose should be decreased to reduce the side effect of bleeding.

- **Simplify the dosing regimen:**
  - Furosemide 40mg on Monday/Tuesday/Friday might be too complicated for elderly patients, especially those with cognitive impairment. Alternatively, the regimen can be simplified to 20mg daily to make things easier to remember.

- **Prescribe beneficial therapy:**
  - Because patient has a history of hip fracture, she likely has osteoporosis with a high risk of future non-traumatic fractures. She should be treated aggressively for osteoporosis with bisphosphonates, calcium and vitamin D supplementation.

**CASE ONE CONTINUED:**

You made adjustments to Mrs. Pill’s regimen, but the daughter is still concerned that her mother will not be able to sort through her pill bottles and remember to take all of them.

6. **How would you address her daughter’s concern? What questions would you ask to help you formulate a plan that increases compliance?**
   - An appropriate medication regimen is not effective if Mrs. Pill does not take it as prescribed. As a result, removing barriers to medication administration is important in ensuring compliance, especially regarding her ARV.
   - The first step to addressing the daughter’s concern is to take further history regarding how the patient takes her medications. Relevant questions include:
     - When does she usually take her medications?
     - Who manages her medications?
     - If the patient lives alone, who ensures that the patient accurately takes her medications?
CASE ONE CONTINUED:

The daughter states that patient lives alone and manages her own medications, although when asked, the patient seems unclear about the timing and the purpose of her medications. The patient feels bad throwing medications away, so she has multiple bottles of expired medications stashed away in the same cabinet as her current pills. The daughter is not convinced that the patient is taking medications appropriately, because she often finds leftover pills in bottles and on the floor of the apartment. The patient agrees that taking medications has been challenging and would like some help.

7. What options do you have to increase medication compliance at home?
   - There are multiple options to help with medication management and increase compliance in the home:
     - If the daughter is willing, you could ask her to obtain a pillbox, so that she can prepours Mrs. Pill’s medications by week. Alternatively, Visiting Nurse Services can also prepour medications. Every week at prepour time, she can make sure that all the pills in the box are gone which may indicate, but does not confirm, compliance.
     - Certain pharmacies also offer a blister pack service, in which the pharmacy prepours medications into a bubble pack for patients, who only have to open the pack and take the pills within.
     - Electronic automated medication reminder and dispenser can also be purchased for the home. They can remind patients to take medications by voice, dispense the correct combination of pills for the appropriate time of day, and send email notifications to caretakers to let them know that the medications have been taken out of the machine to monitor for compliance.
     - The only way to ensure complete compliance is to observe patient taking her medications. This can be done at home by family members or at an assisted living facility where medications can be dispensed by a health care provider.

CASE ONE CONTINUED:

Mrs. Pill’s daughter volunteers to prepour medications in a pillbox and to stop by Mrs. Pill’s apartment everyday to make sure that the medications are taken correctly.

At 3 months follow-up, you discover that Mrs. Pill’s CKD has worsened. Her CrCl is now 30mL/min.
8. **What would you do at this point?**

- *All of Mrs. Pill’s medications needs to be reviewed and adjusted based on the newly decreased CrCl. For example, her lamivudine should be decreased to 150mg daily. Enlisting the help of a pharmacist might be helpful.*

- *If reversible causes are ruled out, Mrs. Pill’s worsening CrCl indicates a progression of her CKD. At this point, it would be reasonable to consult a nephrologist, but to also sit down with Mrs. Pill and her daughter to discuss goals of care, since hemodialysis may not lead to the quality of life that Mrs. Pill wants. If the goals of care change from prolonging her current medical state to focusing on comforts, her medication list should be adjusted to reduce unnecessary pill burden and to add beneficial therapy that may help control symptoms commonly experienced in patients with CKD at the end of life. Consulting a palliative care provider may be helpful in this situation.*
Additional reference:
2. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol 65.9 (2012):989–95