Polypharmacy: Untangling a Complex Pharmacologic Imbroglio

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Henry Palmer CE Finale  
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Dennis J Chapron reports no real or potential conflicts of interest relevant to this lecture.
Learning Objectives

• Define the terms polypharmacy, hyperpolypharmacy and extreme polypharmacy.

• Discuss the clinical consequences of polypharmacy.

• Discuss the factors that are stimulating the polypharmacy epidemic.

• Review the concepts of cascading iatrogenesis and drug burden index.

• Describe benefit-risk stratification when accessing a polymedicine profile.

The Washington Post

Sandra G. Boodman, December 17, 2017

The other big drug problem: Older people taking too many pills
Medications are probably the single most important health care technology in preventing illness, disability, and death in the geriatric populations.

Dr. Jerry Avorn, MD, 1995
Harvard Medical School

The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.

Sir William Osler
Polypharmacy Definitions

• Polypharmacy - ≥ 5 medications

• Hyperpolypharmacy - ≥ 10 medications

• Extreme polypharmacy - ≥ 20 medications

Polypharmacy is an International Phenomena Community-Dwelling Elderly

• United States- 39%

• Australia – 37.7%

• Germany – 39.1 %
Trends in Prescription Drug Use Among Adults in the United States From 1999-2012

Elizabeth D. Kantor, PhD, MPH; Colin D. Rehm, PhD, MPH; Jennifer S. Haas, MD, MSc; Andrew T. Chan, MD, MPH; Edward L. Giovannucci, MD, ScD

The prevalence of polypharmacy (use of ≥ 5 prescription drugs) increased from an estimated 8.2% in 1999-2000 to 15% in 2011-2012 (difference 6.6% [95% CI, 4.4%-8.2%]; P for trend < .001)

JAMA. 2015;314(17):1818-1831
The concept of “appropriate polypharmacy” recognizes that patients can benefit from multiple medications provided that prescribing is evidence based, reflects patients’ clinical conditions and considers potential drug interactions.

What is stimulating the polypharmacy epidemic?

- Accumulating co-morbidities in an aging population
- Newer and more effective medications
- Enhanced efficacy with combination therapy
- Availability of Clinical Practice Guidelines and their use as a quality of care indicator
- Clinical Practice Guidelines often recommend two or more drugs for treatment of a single condition
- Treatment intensification
- Fragmentation of medical care
- Overdiagnosis / Misdiagnosis
- Prescribing cascade
Aging – Population

Increased Prevalence of Disease

Polymedications

Elderly

HTN  OA  OP  PUD  GERD
COPD  CAD  Cancer  CHF  BPH  CVA  AD  PD  Glaucoma  CKD
Depression  DM  Gout  Hypo-T4  Constip
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Clinical Practice Guidelines

• Based on clinical evidence and expert consensus
• Defines standards of care
• Improves quality of care
• Reduce undesirable variations in care
• Assists with decision making about treating specific diseases
• Addresses single diseases with a focus on intercepting pathophysiological processes.

Evidence-based clinical practice guidelines often recommend several drugs for treatment of a single condition:

- Diabetes mellitus
- Heart failure
- Osteoporosis
- Osteoarthritis
- Hypertension
Issues on the Applicability of Clinical Practice Guidelines (CPG) in the Elderly

- What is the quality of evidence for patients 75 years or older with multiple comorbidities?
- Are there recommendations on the modification of treatment goals in the setting of several comorbidities?
- What are the risks of medication complications, especially if influenced by age and comorbidities?
- Have you considered the burden of comprehensive treatment on patients and caregivers—drugs, diets, exercise, follow-up office visits, specialty care, lab test monitoring, and environmental changes?
- What is the duration of therapy necessary to achieve benefit in the context of life expectancy?
- Is there explicit information on the number needed to treat to obtain a specified benefit?
- What are the potential drug-drug and drug-disease interactions when applying several CPG to a patient?

Clinical Practice Guidelines and Polymedications – Room for Improvements

- Include explicit information on the number needed to treat to obtain a specified benefit.
- Patient specific factors such as age, estimated life expectancy, and comorbidities should be considered in benefit estimations.
- Risk of medication complications should be provided, especially if influenced by age and comorbidities.
- Effect of additional medications in the complexity of the preexisting therapeutic regimen.
- Patient preference
What is stimulating the polypharmacy epidemic?

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A Randomized Trial of Intensive versus Standard Blood-Pressure Control

**SBP ≤ 120 vs ≤ 140 mm Hg**

**Conclusions**
Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01206062.)

From a public health standpoint a NNT of 61 means that several hundred thousand patients may benefit from more intensive treatment.

From an individual standpoint, life expectancy and co-morbid vulnerabilities need to be considered. Patients need to be told that he/she needs to be treated with three medications with a higher risk of significant side effects to achieve a one-in-61 chance of being benefited.
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Overdiagnosis: Bad for You, Good for Business

"The biggest problem is that overdiagnosis triggers overtreatment, and all of our treatments carry some harm," says H. Gilbert Welch, this year's William J. Beekman Lecturer in Public Health. Photo courtesy of Dartmouth College.
Introduction to “Over-Diagnosed”

- From time to time my blood pressure runs a little high. This is particularly true when I measure it at work (where blood pressure machines are readily available).
  
  **Diagnosis: borderline hypertension**

- I’m six foot four and weigh 205 pounds; my body mass index (BMI) is 25. (A “normal” BMI ranges from 20 to 24.9.)
  
  **Diagnosis: overweight**

- Occasionally, I’ll get an intense burning sensation in my midchest after eating or drinking. (Apple juice and apple cider are particularly problematic for me.)
  
  **Diagnosis: gastroesophageal reflux disease**

- I often wake up once a night and need to go to the bathroom.
  
  **Diagnosis: benign prostatic hyperplasia**

- I wake up in the morning with stiff joints and it takes me a while to loosen up.
  
  **Diagnosis: degenerative joint disease**
CONCLUSIONS AND RELEVANCE In this prospectively planned analysis of data from 2 clinical trials involving adults aged 80 years and older with subclinical hypothyroidism, treatment with levothyroxine, compared with placebo, was not significantly associated with improvement in hypothyroid symptoms or fatigue. These findings do not support routine use of levothyroxine for treatment of subclinical hypothyroidism in adults aged 80 years and older.
How Many Patients with Diagnosed COPD Truly Have It?
David J. Amrol, MD


Diagnoses of chronic obstructive pulmonary disease were incorrect in about 62% of cases.

Pharmacy Education Needs to Address Diagnostic Safety
Mark L. Graber, MD; Gloria R Grice, PharmD; Louis J. Ling, MD; Jeannine M. Conway, PharmD; Andrew Olsson, MD
Am J Pharm Educ. 2019;83(6):7442

Abstract and Introduction
Abstract
The American Association of Colleges of Pharmacy, the Accreditation Council for Pharmacy Education, and the Center for the Advancement of Pharmacy Education frame patient safety from the perspective of medication management, which is also the current focus of pharmacy education and training. With the growing appreciation that diagnostic errors represent an urgent and actionable patient safety concern, the National Academy of Medicine has recommended diagnostic safety training for all health care professions. The Society to Improve Diagnosis in Medicine has worked with an interprofessional consensus group to identify a set of 12 key competencies necessary to achieve diagnostic quality and safety that focuses on individual, team-based, and system-related competencies. Much of this already exists in pharmacy education, but pharmacy training programs need to give graduates more guidance on how they contribute to the diagnostic process and the prevention and detection of diagnostic errors. We describe the current state of progress in this regard, and what steps are needed by training programs to provide content and assessment so that graduates achieve the requisite competencies. Governing and advisory bodies need to expand the expectations around patient safety to include diagnostic safety.
What is stimulating the polypharmacy epidemic?

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The Prescribing Cascading
A simple prescribing cascade

Cholinesterase inhibitors $\rightarrow$ Urinary incontinence $\rightarrow$ Oxybutynin

Haloperidol $\rightarrow$ Parkinsonism $\rightarrow$ Trihexyphenidyl

Hydrochlorothiazide $\rightarrow$ Hyperuricemia $\rightarrow$ Allopurinol

Oxycodone $\rightarrow$ Constipation $\rightarrow$ Laxative

DPP-4 Inhibitors

• Saxagliptin
• Sitagliptin
• Linagliptin
• Alogliptin
DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient(s)</th>
</tr>
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<tbody>
<tr>
<td>Januvia</td>
<td>sitagliptin</td>
</tr>
<tr>
<td>Janumet</td>
<td>sitagliptin and metformin</td>
</tr>
<tr>
<td>Janumet XR</td>
<td>sitagliptin and metformin extended release</td>
</tr>
<tr>
<td>Onglyza</td>
<td>saxagliptin</td>
</tr>
<tr>
<td>Kombiglyze XR</td>
<td>saxagliptin and metformin extended release</td>
</tr>
<tr>
<td>Tradjenta</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Glyxambi</td>
<td>linagliptin and empagliflozin</td>
</tr>
<tr>
<td>Jentadueto</td>
<td>linagliptin and metformin</td>
</tr>
<tr>
<td>Nesina</td>
<td>alogliptin</td>
</tr>
<tr>
<td>Kazano</td>
<td>alogliptin and metformin</td>
</tr>
<tr>
<td>Oseni</td>
<td>alogliptin and pioglitazone</td>
</tr>
</tbody>
</table>

FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling. We have added a new Warning and Precaution about this risk to the labels of all medicines in this drug class, called dipeptidyl peptidase-4 (DPP-4) inhibitors.

Patients should not stop taking their DPP-4 inhibitor medicine, but should contact their health care professional right away if they experience severe and persistent joint pain. Health care professionals should consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue the drug if appropriate.

DPP-4 inhibitors are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. These medicines are available as single-ingredient products and in combination with other diabetes medicines such as metformin (see Table 1 below).

In a search of the FDA Adverse Event Reporting System (FAERS) database and the medical literature, we identified cases of severe joint pain associated with the use of DPP-4 inhibitors. Patients started having symptoms from 1 day to years after they started taking a DPP-4 inhibitor. After the patients discontinued the DPP-4 inhibitor medicine, their symptoms were relieved, usually in less than a month. Some patients developed severe joint pain again when they restarted the same medicine or another DPP-4 inhibitor.

We urge health care professionals and patients to report side effects involving DPP-4 inhibitors to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.
Cases of severe, sometimes disabling, arthralgia (joint pain) have been reported with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors. Patients are advised not to discontinue therapy but to contact their health care professional immediately if they experience severe and persistent joint pain while taking any of the DPP-4 inhibitors. These medications should be considered as a possible cause of joint pain and discontinued if appropriate. The FDA has identified 33 cases of severe arthralgia with the use of DPP-4 inhibitors, all of which resulted in substantial reduction of the patient’s prior level of activity and, in 10 cases, required hospitalization. In the reported cases, the onset of symptoms occurred from 1 day to several years after the start of therapy with a DPP-4 inhibitor. Symptoms resolved with discontinuation of therapy, usually in less than a month; however, some patients experienced a recurrence of joint pain when restarting the same drug or switching to another DPP-4 inhibitor. Twenty-one of the 33 patients were treated for arthritis with drug therapies that included corticosteroids, nonsteroidal anti-inflammatory drugs, methotrexate, and immune-modulating drugs.
Rx with DDP-Inhibitor

New onset joint pain

oral NSAID prescribed

PPI added as prophylaxis

Systolic BP increased

dose of antihypertensive med increased or new AH med added

Patient experiences a fall with trauma
Clinical Consequences of Polypharmacy

- Adverse drug events (excessive dosing, monitoring lapses, drug-drug interactions, drug-disease interactions)
- Medication non-adherence
- Increase cost of healthcare (drugs, monitoring, office visits, etc)
- Increased risk of a medication error (med rec)
- Falls
- Functional decline
- Cognitive impairment
- Increased mortality
- Increased risk for “prescribing cascade” – polypharmacy begetting more polypharmacy

Adverse Drug Reaction- Spectrum

- Overt: hypotension, GI bleeding, acute kidney injury, delirium

- Less overt/subtle: incontinence, cognitive impairment, anorexia, weight loss, dizziness, weakness, gait imbalance with falling
Development and Validation of a Score to Assess Risk of Adverse Drug Reactions Among In-Hospital Patients 65 Years or Older

The GerontoNet ADR Risk Score

Graziano Onder, MD, PhD; Mirko Petrovic, MD, PhD; Balamursugan Tangisuran, MPharm, PhD; Marieke C. Meinders, MD; Wim F. Markito-Notenboom, MD; Annemie Somers, MPharm; Chakravarthi Rajkumar, MD, PhD; Roberto Bernabei, MD; Tisha J. M. van der Cammen, MD, PhD

Conclusions: This study proposes a practical and simple method of identifying patients who are at an increased risk of an ADR. This approach may be useful in clinical practice as a tool to identify patients at risk and in research to target a population that can benefit from interventions aimed to reduce drug-related illness.

Arch Intern Med. 2010;170(13):1142-1148

Table 2. Variables Included in the Scorea

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4 Comorbid conditions</td>
<td>1.31 (1.04-1.64)</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.79 (1.39-2.30)</td>
<td>1</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.36 (1.06-1.74)</td>
<td>1</td>
</tr>
<tr>
<td>No. of drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>1 [Reference]</td>
<td>0</td>
</tr>
<tr>
<td>5-7</td>
<td>1.90 (1.35-2.68)</td>
<td>1</td>
</tr>
<tr>
<td>≥8</td>
<td>4.07 (2.93-5.65)</td>
<td>4</td>
</tr>
<tr>
<td>Previous ADR</td>
<td>2.41 (1.79-3.23)</td>
<td>2</td>
</tr>
<tr>
<td>Renal failureb</td>
<td>1.21 (0.96-1.51)</td>
<td>1</td>
</tr>
</tbody>
</table>

Arch Intern Med. 2010;170(13):1142-1148
The strongest predictors for an adverse drug event are the (1) number of drugs prescribed and (2) a prior history of an adverse drug event.
Clinical Consequences of Polypharmacy

- Adverse drug events (excessive dosing, monitoring lapses, drug-drug interactions, drug-disease interactions)
  - Medication non-adherence
  - Increase cost of healthcare (drugs, monitoring, office visits, etc)
  - Increased risk of a medication error (med rec)
  - Falls
  - Functional decline
  - Cognitive impairment
  - Increased mortality
  - Increased risk for “prescribing cascade” – polypharmacy begetting more polypharmacy

The truth is that few drugs that cause problems for elderly persons are inherently bad; when drugs do cause problems, it is because they are prescribed, dosed, taken, or monitored inappropriately.

Jerry H. Gurwitz and Paula Rochon
Arch Internal Medicine 2002;162:1670.
Annals of Internal Medicine

Medication Use Leading to Emergency Department Visits for Adverse Drug Events in Older Adults

Daniel S. Budnitz, MD, MPH; Nadine Shehab, PharmD; Scott R. Kegler, PhD; and Chesley L. Richards, MD, MPH

Background: The Beers criteria identify inappropriate use of medications in older adults. The number of and risk for adverse events from these medications are unknown.

Objective: To estimate the number of and risk for emergency department visits for adverse events involving Beers criteria medications compared with other medications.

Design: Nationally representative, public health surveillance of adverse drug events and a cross-sectional survey of outpatient medical visits.


Participants: Persons 65 years of age or older seeking emergency department and outpatient care.

Measurements: Estimated number of and risks for emergency department visits for adverse drug events involving Beers criteria medications and other medications.

Results: Among U.S. patients 65 years of age or older, an estimated 177,504 emergency department visits (95% CI, 100,155 to 254,854 visits) for adverse drug events occurred both years. An estimated 3.6% (CI, 2.8% to 4.5%) of these visits were for adverse events medications considered to be always potentially inappropriate; according to the Beers criteria, and 33.3% (CI, 27.8% to 38.7%) of visits were for adverse events from 3 other medications (warfarin [17.3%], insulin [13.0%], and digoxin [3.2%]). Accounting for outpatient prescription frequency, the risk for emergency department visits for adverse events due to these 3 medications was 35 times (CI, 9.6 to 61) greater than that for medications considered to be always potentially inappropriate.

Limitation: Adverse events were identified only in emergency departments.

Conclusion: Compared with other medications, Beers criteria medications caused low numbers of and few risks for emergency department visits for adverse events. Performance measures and interventions targeting warfarin, insulin, and digoxin use could prevent more emergency department visits for adverse events.

For author affiliations, see end of text.
Clinical Consequences of Polypharmacy

- Adverse drug events (excessive dosing, monitoring lapses, drug-drug interactions, drug-disease interactions, drug-burden indexes)
- Medication non-adherence
- Increase cost of healthcare (drugs, monitoring, office visits, etc)
- Increased risk of a medication error (med rec)
- Falls
- Functional decline
- Cognitive impairment
- Increased mortality
- Increased risk for “prescribing cascade” – polypharmacy begetting more polypharmacy
Drug-Disease Interactions

American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel

Beers Criteria is an explicit list of potentially inappropriate medications (PIM) best avoided in older adults in general and in those with certain disease states or conditions, or if needed prescribed at reduced dose and carefully monitored.

Table 3 - 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Due to Drug-Drug or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndromes

**Disease or Syndrome** | **Drug(s)** | **Rationale** | **Recommendation** | **Quality of Evidence** | **Strength of Recommendation**
--- | --- | --- | --- | --- | ---
Cardiovascular |diabetes and QRS > 0.11 seconds | sodium-channel blockers, calcium-channel blockers, beta blockers | Avoid | Moderate | Strong
| hypertension with heart failure | ACE inhibitors, angiotensin receptor blockers | POTENTIAL TO INCREASE RISK OF HEART FAILURE | Avoid | Moderate | Strong
| diabetic nephropathy, QT prolongation, ventricular arrhythmias | clopidogrel, aspirin | COX-2 inhibitors, nonsteroidal anti-inflammatory drugs | COX-2 inhibitors, nonsteroidal anti-inflammatory drugs | Moderate | Moderate
| advanced chronic heart failure | ACE inhibitors, beta blockers | POTENTIAL TO INCREASE RISK OF HEART FAILURE | Avoid | Moderate | Strong

**Sympathetic nervous system**

| Drug(s) | Rationale | Recommendation | Quality of Evidence | Strength of Recommendation
| --- | --- | --- | --- | ---
| peripheral alpha-1 blockers | INCREASES RISK OF HYPERTENSION | Avoid | Peripheral alpha-1 blockers | Strong
| peripheral alpha-1 blockers | INCREASES RISK OF HYPERTENSION | Avoid | Peripheral alpha-1 blockers | Strong
| TCA, selective serotonin reuptake inhibitors | INCREASES RISK OF HYPERTENSION | Avoid | TCA, selective serotonin reuptake inhibitors | Strong
| antipsychotics | INCREASES RISK OF HYPERTENSION | Avoid | Antipsychotics | Strong

**Central nervous system**

| Drug(s) | Rationale | Recommendation | Quality of Evidence | Strength of Recommendation
| --- | --- | --- | --- | ---
| lithium | LOWERED DISEASE TREATMENT, MAY NOT BE ACCEPTABLE IN INDIVIDUALS WITH MULTIPLE DISEASES | Avoid | Lithium | Strong

**Delirium**

| Drug(s) | Rationale | Recommendation | Quality of Evidence | Strength of Recommendation
| --- | --- | --- | --- | ---
| benzodiazepines, selective serotonin reuptake inhibitors | AVOID IN ELDERLY ADULTS WITH OR AT HIGH RISK OF DELIRIUM | Avoid | Benzodiazepines, selective serotonin reuptake inhibitors | Strong
| antipsychotics, selective serotonin reuptake inhibitors | AVOID IN ELDERLY ADULTS WITH OR AT HIGH RISK OF DELIRIUM | Avoid | Antipsychotics, selective serotonin reuptake inhibitors | Strong
| antipsychotics, selective serotonin reuptake inhibitors | AVOID IN ELDERLY ADULTS WITH OR AT HIGH RISK OF DELIRIUM | Avoid | Antipsychotics, selective serotonin reuptake inhibitors | Strong
| antipsychotics, selective serotonin reuptake inhibitors | AVOID IN ELDERLY ADULTS WITH OR AT HIGH RISK OF DELIRIUM | Avoid | Antipsychotics, selective serotonin reuptake inhibitors | Strong

Table 3 (Continued)
One fifth of older Americans receive medications that may adversely coexisting conditions. Effects on coexisting conditions should be considered when prescribing medications.
| Indicated Condition* | Competing Condition | Competing condition present
n/N (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>COPD Hypertension</td>
<td>335/846 (39.6)</td>
<td></td>
</tr>
<tr>
<td>COPD CAD</td>
<td>160/433 (37.0)</td>
<td></td>
</tr>
<tr>
<td>COPD Atrial Fibrillation</td>
<td>86/225 (38.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Beta-agonist* [35–37]

Drug-Drug Interactions
### Medication Elimination

- **Response**
- **Medication → Gut → [Circulating blood]**
- **Elimination**
  - Kidneys
  - Liver

### Table

<table>
<thead>
<tr>
<th>Number of Drugs</th>
<th>Number of Combinations</th>
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<tbody>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
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<td>4</td>
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<td>6</td>
<td>15</td>
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<tr>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>66</td>
</tr>
</tbody>
</table>
Class D = combination should be avoided

Fig. 2. Prevalence of potentially serious (type D) drug-drug interactions (DDIs) as a function of number of dispensed drugs among 630 743 people aged ≥75 years from the Swedish Prescribed Drug Register, 2005.

Table IV. Adjusted odds ratios (ORs) with 95% confidence intervals for potentially serious drug-drug interactions (type D) among elderly from the Swedish Prescribed Drug Register, 2005

<table>
<thead>
<tr>
<th>Number of dispensed drugs</th>
<th>Ref</th>
<th>5–7</th>
<th>8–10</th>
<th>11–13</th>
<th>14–16</th>
<th>17–19</th>
<th>≥20</th>
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<tr>
<td>2–4</td>
<td>Ref</td>
<td>3.76</td>
<td>7.78</td>
<td>12.95</td>
<td>20.64</td>
<td>32.12</td>
<td>55.75</td>
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<tr>
<td>5–7</td>
<td>3.76</td>
<td>(3.60, 3.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>7.78</td>
<td>(7.45, 8.11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11–13</td>
<td>12.95</td>
<td>(12.38, 13.55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–16</td>
<td>20.64</td>
<td>(19.60, 21.73)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17–19</td>
<td>32.12</td>
<td>(30.12, 34.25)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥20</td>
<td>55.75</td>
<td>(51.59, 60.25)</td>
<td></td>
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Drug Burden Index
a consequence of
Pharmacodynamic Interactions

In a polymedicine drug profile, the cumulative impact of drugs with overlapping secondary adverse effects is often underappreciated.
Medications $\rightarrow$ Gut $\rightarrow$ [Circulating blood] $\rightarrow$ Elimination $\rightarrow$ Kidneys $\rightarrow$ Liver

[Serum anticholinergic activity]

- Nortriptyline
- Hydroxyzine
- Paroxetine
- Desipramine
- Oxybutynin
- Citalopram
- Clonidine
- Trazodone
- Cyclobenzaprine
- Diphenhydramine
Anticholinergic Drug Exposure and the Risk of Dementia
A Nested Case-Control Study

Carol A.C. Coupland, PhD; Trevor Hill, MSc; Tom Denier, MD; Richard Morris, MD;
Michael Moore, MSc; Julia Hippisley-Cox, MD

CONCLUSIONS AND RELEVANCE Exposure to several types of strong anticholinergic drugs is
associated with an increased risk of dementia. These findings highlight the importance of
reducing exposure to anticholinergic drugs in middle-aged and older people.

Key Points

Question  Is the risk of dementia among persons 55 years or older associated with the use of different types of anticholinergic medication?

Findings  In this nested case-control study of 58,769 patients with a diagnosis of dementia and 225,574 matched controls, there were statistically significant associations of dementia risk with exposure to anticholinergic antidepressants, antiparkinson drugs, antipsychotic drugs, bladder antimuscarinics, and antiepileptic drugs after adjusting for confounding variables.

Meaning  The associations observed for specific types of anticholinergic medication suggest that these drugs should be prescribed with caution in middle-aged and older adults.
## Drugs with ACB Score of 1

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimemazine</td>
<td>Theralon™</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Xanax™</td>
</tr>
<tr>
<td>Arpiprazole</td>
<td>Ability™</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris™</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Tenormin™</td>
</tr>
<tr>
<td>BuPROPION</td>
<td>Wellbutrin™, Zyban™</td>
</tr>
<tr>
<td>Captopril</td>
<td>Capoten™</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>Zyrtec™</td>
</tr>
<tr>
<td>Chlorothalidone</td>
<td>Diuril™, Hygroton™</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Tagamet™</td>
</tr>
<tr>
<td>Clidinium</td>
<td>Librax™</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Tranxene™</td>
</tr>
<tr>
<td>Codeine</td>
<td>Cotrol™</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Colchic™</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>Clarinex™</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Valium™</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>Pantoprazole™</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Persantine™</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Pertol™</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Duragesic™, Actiq™</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Lasix™</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox™</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol™</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Apresoline™</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Cortef™, Cortaid™</td>
</tr>
</tbody>
</table>

*Note: The Aging Brain Care program developed the Anticholinergic Cognitive Burden Scale (ACB) to help caregivers identify and manage medications that might cause cognitive difficulties.*
### Drugs with ACB Score of 2

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Symmetrel™</td>
</tr>
<tr>
<td>Belladonna</td>
<td>Multiple</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tegretol™</td>
</tr>
<tr>
<td>Cyclobenzapr ine</td>
<td>Flexeril™</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>Periactin™</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane™</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Demerol™</td>
</tr>
<tr>
<td>Methotrimeprazine</td>
<td>Levoprome™</td>
</tr>
<tr>
<td>Molindone</td>
<td>Moban™</td>
</tr>
<tr>
<td>Nefopam</td>
<td>Nefogesic™</td>
</tr>
<tr>
<td>Oxicarbazepine</td>
<td>Trileptal™</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap™</td>
</tr>
</tbody>
</table>

### Drugs with ACB Score of 3

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Elavil™</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Asendin™</td>
</tr>
<tr>
<td>Atropine</td>
<td>Sol-Tropine™</td>
</tr>
<tr>
<td>Benztropine</td>
<td>Cogentin™</td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>Dimetapp™</td>
</tr>
<tr>
<td>Carinobenzamine</td>
<td>Histex™, Carbistat™</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Chlor-Trimehton™</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine™</td>
</tr>
<tr>
<td>Clemastine</td>
<td>Tavist™</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafrin™</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozantil™</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Endep™</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramin™</td>
</tr>
<tr>
<td>Diocyclomine</td>
<td>Benyl™</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Dramamine™, others</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Benedryl™, others</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Sinequan™</td>
</tr>
<tr>
<td>Doxylamine</td>
<td>Unisom™, others</td>
</tr>
<tr>
<td>Feosorexidine</td>
<td>Toviaz™</td>
</tr>
<tr>
<td>Fluvastate</td>
<td>Urtasp™</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Atarax™, Vistaril™</td>
</tr>
<tr>
<td>Hyoscine</td>
<td>Anaspaz™, Levsin™</td>
</tr>
</tbody>
</table>
An unexpected example of the anticholinergic burden issue:

Postsurgical patient note: Avoid if possible escalating the doses of opiates because of an intestinal motility issue of hypoactive bowels sounds, negative flatus and no bowel movement since surgery.
### Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>11/21/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam (ATIVAN) 2 MG/ML injection 1 mg</td>
<td>5932</td>
</tr>
<tr>
<td>Lorazepam (ATIVAN) 2 MG/ML injection 0.5 mg</td>
<td>5932</td>
</tr>
<tr>
<td>Hydroxyzine (VISTIZINE) injection 60 mg</td>
<td>5808</td>
</tr>
<tr>
<td>Hydroxyzine (VISTIZINE) injection 50 mg</td>
<td>1593</td>
</tr>
<tr>
<td>Hydroxyzine (VISTIZINE) injection 25 mg</td>
<td>1446</td>
</tr>
<tr>
<td>Dimenhydrinate (Dramamine) 25 mg in sodium chloride (NS) 0.9 % 50 mL</td>
<td>5831</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid) injection 0.5 mg</td>
<td>1456</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid) injection 0.1 mg</td>
<td>1456</td>
</tr>
<tr>
<td>Oxycodone (OXYCONTIN) 5 MG tablet 5 mg</td>
<td>1593</td>
</tr>
<tr>
<td>Oxycodone (OXYCONTIN) 5 MG tablet 10 mg</td>
<td>1593</td>
</tr>
</tbody>
</table>

### Cumulative Effects Leading to Sedation

- Flexeril
- Zoloft
- Clonidine
- Seroquel
- Ativan
- Requip
- Antivert
- Ultram

Sedation

---

11/27/2019
Consider other burden indexes

Polypharmacy and Bleeding:

Gastrointestinal

Genitourinary
Drug Burden and Bleeding

Risk of Adverse GI Events
When NSAIDs Are Given
With Other Medications
CONCLUSIONS:
Based on a case series analysis, concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRIs significantly increases the risk of UGIB. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants produces significant excess risk of UGIB.

Gastroenterology 2014;147:784–792
Drugs Associated with Bone Loss

- Phenytoin, carbamazepine, phenobarbital
- Glucocorticoids
- SGLT-2 inhibitors
- Furosemide
- Leuprolide
- Aromatase inhibitors
- Proton pump inhibitors
- SSRIs and SNRIs
- Heparin
- Aluminum hydroxide
- Glitazones

An 85 year-old man was evaluated in hospital for a fall at home and a resulting hip fracture. He has a past fracture history that includes three spinal compression fractures and a wrist fracture. Past medical history includes GERD for many years, a post stroke seizure 5 years ago, hypertension for 20 yrs, prostate cancer, temporal arteritis, diabetes type II and depression. Medications include lansoprazole 30 mg daily, phenytoin 300 mg daily, furosemide 40 mg daily, nifedipine XL 60 mg, leuprolide depot every 3 months, citalopram 20 mg daily, metformin 500 mg bid, pioglitazone 5 mg daily and prednisone 7.5 mg daily.
Excess Renal Excretion of Calcium | Decreased GI Calcium Absorption | Decreased Estrogen and Testosterone | Decreased Osteoblastic Activity
---|---|---|---
Furosemide | Lansoprazole | Leuprolide | Prednisone
Prednisone | Prednisone | Prednisone | Citalopram
Phenytoin | | | Pioglitazone

**Drug Burden Index and Potassium Retention**
iStat K > 9, scr 3.6 receiving emergent dialysis - dmw

PMH: CAD/afib/DM/HTN PTA meds: coumadin/diovan/lopressor/lasix/imdur/aldaconone/coreg?/glipizide/celebrex/ASA - dmw

INR 2.2, coumadin 3.5mg tonight; daily reminder ordered - dmw

Angiotensin converting enzyme inhibitors

↓

Al → All

↓

Adrenal gland

Na channel blockers

Inhibition of renin release

NSAIDs
Beta Blockers
Cyclosporine

↓

Juxtaglomerular cell

↑

Renin

↓

Inhibition of aldosterone metabolism

Heparin
Ketoconazole
Aminoglutethamide

Aldosterone

↓

Aldosterone receptor blocker

Spironolactone

↓

K

Na

Amiloride
Triamterene
Trimethoprim
Pentamidine
### Drug Burden Index

<table>
<thead>
<tr>
<th>Renin Release (JG cells)</th>
<th>ACE</th>
<th>Adrenal Aldosterone Blockade or Decreased Aldo Biosynthesis</th>
<th>Aldo Receptor or Na Channel Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td></td>
<td>Valsartan</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Metoprolol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Polypharmacy and Metabolic Drug-Drug Interactions
Response

Medication → Gut → [Circulating blood] → Elimination

Kidneys    Liver

Fig. 1. Proportion of drugs metabolized by the major cytochrome P450 (CYP) isoenzymes.
Complications of Treatment

The role of drug-drug interactions in prostate cancer treatment: Focus on abiraterone acetate/prednisone and enzalutamide

Marzia Del Re 1, Stefano Fogli 1, Lisa Derosa 1, Francesco Massari 2, Paul De Souza 1, Stefania Crucitta 3, Sergio Bracarda 1, Daniele Santini 1, Romano Danesi 1,4,8

Elderly patients with cancer may have comorbidities, each requiring additional pharmacologic treatment. Therefore, the occurrence of pharmacokinetic (PK) and pharmacodynamic (PD) interactions is very likely, and the risk of adverse reactions (ADRs), due to the narrow therapeutic window of anticancer drugs, is increased. Drug-drug interactions (DDIs) may occur in prostate cancer patients due to inhibition by abiraterone of liver cytochrome P450 (CYP)–dependent enzymes CYP2C8 and 2D6, which are involved in the metabolism of approximately 25% of all drugs, and induction by enzalutamide of CYP3A4, 2C9 and 2C19, which metabolize up to 50% of medications. Therefore, abiraterone may increase plasma levels of CYP2D6 substrates, including amitriptyline, oxaprozin and rizatriptan, as well as of CYP2C8 substrates including amiodarone and carbamazepine. Since enzalutamide is extensively metabolized by CYP2C8, its plasma levels are likely to be raised if coadministered with strong CYP2C8 inhibitors such as gemfibrozil or pioglitazone. Inducers of CYP2C8 (i.e., rifampicin) may reduce the effectiveness of enzalutamide and hence should be avoided. Enzalutamide may decrease plasma levels of CYP3A4, 2C9 and 2C19 substrates including diltiazem, quetiapine, quinidine and warfarin. Growing awareness of the importance of DDIs in cancer patients is now reflected in the variety of web-based sources offering information and guidance. However, the evaluation of the clinical relevance of DDIs is the result of a comprehensive evaluation of many factors, including therapeutic index, amplitude of therapeutic range and presence of comorbidities, requiring a specific expertise in clinical pharmacology.

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DRUG INTERACTIONS

Drug–drug interaction potential in men treated with enzalutamide: Mind the gap

A high prevalence of potential drug-drug interactions was found. … which might require intensive monitoring or alternative treatment strategies to prevent suboptimal treatment of co-morbidities in patients treated with Enzalutamide.
Enzalutamide metabolism: CYP2C8

CYP450 isoforms induced by enzalutamide:
3A4, 2D6, 2C9, 2C19

CYP substrates at risk of enzalutamide-DDIs:
+ immunosuppressants (e.g., sirolimus)
+ HIV antivirals (e.g., atazanavir)
+ Anticoagulants (e.g., rivaroxaban)
+ Antiplatelet drugs (e.g., clopidogrel)
+ CNS drugs (fentanyl, pimozide, midazolam)
Introducing an antibiotic in a polypharmacy regimen
Acute tx on chronic tx

Abiraterone metabolism:
CYP3A4

CYP450 isoforms inhibited by abiraterone:
1A2, 2C8, 2D6, 2C9, 2C19

CYP substrates at risk of abiraterone-DDIs:
+ Analgesics (e.g., hydrocodone, codeine)
+ Antidepressants (e.g., venlafaxine)
+ Cardiovascular drugs (e.g., metoprolol)
+ Antidiabetics (pioglitazone)
+ Lipid-lowering drug (atorvastatin)
Some Prescription Plans- A setup for compromised DDI monitoring

• Acute medications (ie., antibiotics) can be filled at a local pharmacy.
• Long-term maintenance medications must be filled at a mail order pharmacy.

Antimicrobial Agent Drug-Drug Interactions

- Antimicrobial Agent | Effected CYP or Transporter
- Ciprofloxacin | CYP-1A2, CYP-3A4
- Clarithromycin | CYP3A4, PGP, OAT
- Co-trimoxazole | CYP-2C8, CYP-2C9
- Erythromycin | CYP-3A4, OAT
- Fluconazole | CYP-2C9, CYP-2C19, CYP-3A4
- Isoniazid | CYP-2C19, CYP-3A4
- Itraconazole/ketoconazole | CYP-3A4, PGP
- Metronidazole | CYP-2C9, 2A6
- Nafcillin/Dicloxacillin | Inducer - CYP-2C9 and CYP-3A4
- Posaconazole | CYP-3A4, PGP
- Rifampin | Inducer - CYPs 2C8, 2C9, 2C19, 3A4, PGP
- Voriconazole | CYP-2C9, CYP-2C19, CYP-3A4
Patients admitted with digoxin toxicity (n=1051) were about 12 time more likely to have been treated with clarithromycin (adjusted odds ratio 11.7; CI 7.5-18.2) in the previous week.

909 elderly patients receiving glyburide were admitted with a diagnosis of hypoglycemia. Those admitted for hypoglycemia were six times more likely to have been treated with co-trimoxazole (Bactrim©) the previous week (adjusted odds ratio 6.6; CI 4.5-9.7).
Polypharmacy and Drug Safety

Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial

Although major bleeding rates were consistently lower with apixaban than with warfarin, the magnitude of benefit with apixaban seemed to decrease with the increasing number of concomitant drug treatments.

BMJ 2016;353:i2868
Renal dysfunction and Polypharmacy and Metabolic Drug-Drug Interactions
Renal

[Drug]

Hepatic

Renal

[Drug]

Drug-drug interactions inhibitors
Metabolic/transporters

Hepatic
Renal

[Drug]

Hepatic

Drug-drug interactions inhibitors
Metabolic/transporters
Approaches to therapeutic drug debridement

Improving Prescribing Quality

- Polypharmacy should be in the problem list.
- Need to have a comprehensive, portable and truly accurate medication list, which is reviewed at every patient encounter.
- Establish a team approach to monitoring medication effectiveness and adverse effects, and stopping medications determined to be ineffective or noxious.
- Encourage patient engagement and shared decision making.
- Develop electronic systems to compile drug burden indexes and to assist in the process of drug debridement.
Standardized Assessment of Polypharmacy

- Beers Criteria
- STOPP/START Criteria
- Medication Appropriateness Index
- Sort Medications According to Specific Drug Burden indices
- Rate medications according to benefit vs risk matrix

American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel

Beers Criteria is an explicit list of potentially inappropriate medications (PIM) best avoided in older adults in general and in those with certain disease states or conditions, or if needed prescribed at reduced dose and carefully monitored.

Standardized Assessment of Polypharmacy

- Beers Criteria
- STOPP/START Criteria
- Medication Appropriateness Index
- Sort Medications According to Specific Drug Burden indices
- Rate medications according to benefit vs risk matrix

Assessing Prescribing Appropriateness

- Is there an indication for the drug?
- 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 acceptable?
- Is this drug the least expensive alternative compared to others of equal utility?
- Can the cause of any symptoms be drug-related?
- With evolving frailty, has the need for medication reduction been considered?
- Are medications being monitored with assigned efficacy and safety endpoints.
Standardized Assessment of Polypharmacy

- Beers Criteria
- STOPP/START Criteria
- Medication Appropriateness Index
- Sort Medications According to Specific Drug Burden indices
- Rate medications according to benefit vs risk matrix

Benefit- Risk Stratification in Polypharmacy
Rating Drugs According to Selected Therapeutic Characteristics

- Relative efficacy or effectiveness
- Therapeutic Index
- Range of toxicity (mild to severe to fatal)
- Narrow therapeutic range
- Accumulation profile
- Multiple sites of action – primary vs secondary effects
- Degree of interactivity with other co-prescribed medications

<table>
<thead>
<tr>
<th>Risk</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Amiodarone, Digoxin,</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Clopidogrel, Tramadol</td>
</tr>
<tr>
<td>Low</td>
<td>Thyroxine, Famotidine,</td>
</tr>
<tr>
<td></td>
<td>Docusate</td>
</tr>
</tbody>
</table>
Deprescribing and Deintensification

Deprescribing

• The process of withdrawing inappropriate medications, supervised by a health-care professional with the goal of managing polypharmacy and improving patient outcomes.
• Little guidance is available for tapering or discontinuing medications in elderly patients burdened with polypharmacy.
The High-Risk Patient is a Priority for Deprescribing

• 8 or more medications
• > 75 years old
• Receiving high-risk medications (CNS, cardiovascular, antithrombotic)
• Selective morbidities- CRF, CLF, CHF

Some Components of the Deprescribing Process

• Determine all current medication use
• Identify high risk patients
• Confirm indications for medication use
• Assess effectiveness
• Estimate their life expectancy
• Prioritize overall goals in context of life expectancy
• Determine latency of the beneficial effect
• Assess the balance between harm and benefit.
Multiple Choice Questions:

1. Extreme polypharmacy is defined as:
   a. ≥5 medications
   b. ≥7 medications
   c. ≥10 medications
   d. ≥20 medications

2. The following medications, oxybutynin, diphenhydramine, desipramine and cyclobenzaprine would be described as contributing to which drug burden?
   a. Hypotensive
   b. Hyperkalemic
   c. Hemorrhagic
   d. Anticholinergic

3. All of the following are components of the deprescribing process except:
   a. Confirm indications for medication use.
   b. Determine effectiveness of medications in use.
   c. Provide see-through medication containers for adherence improvement.
   d. Determine all medication use (prescription and nonprescription).

4. Which of the following is not considered a contributor to the epidemic of polypharmacy.
   a. Overdiagnosis/misdiagnosis
   b. Combination products with enhanced efficacy
   c. Excess opioid prescribing
   d. Treatment intensification
5. Which adverse effect of DPP-4 inhibitors can initiate a prescribing cascade?
   a. Urinary incontinence.
   b. Hypoactive delirium.
   c. Joint pain
   d. Dyspepsia

Answer key:
1. d
2. d
3. c
4. c
5. c
END