First do no harm:
reducing morbidity and mortality from polypharmacy in modern medicine

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Disclosures

Dr. Cara Tannenbaum has previously consulted for Pfizer, Astellas, Allergen, Watson and Ferring Pharmaceuticals but reports no conflict of interest for this presentation.
Women & men’s top 5 health concerns

- **Medication**
- **Memory loss**
- **Vision**
- **Weakness**
- **Pain**

Proportion of men and women aged 55+ who are concerned n=5000

- **Women**
- **Men**

Tannenbaum et al. CMAJ 2005
Tannenbaum Aging Male 2012
What constitutes polypharmacy?

1. The long-term simultaneous use of two or more medications
2. The concomitant use of three or more medications
3. Use of 5 or more medications
4. Use of 10 or more medications
Determining the cutoff threshold that increases the risk of harm

Drugs or Diseases?

- Confounding by number of co-morbid conditions

Confounding = when a third factor (other than the exposure of interest) is responsible for all or part of the observed effect
Multimorbidity and its association with polypharmacy

In Canada:

- 1-in-4 seniors has ≥ 3 conditions
- Persons with 1-2 chronic conditions take 3-4 prescription medications
- Persons with 3 or more conditions take 6 different medications on average

*Canadian Institute for Health Information. Seniors and the Health Care System: What is the Impact of Multiple Chronic Conditions. Ottawa, Ontario, 2011.*
Multimorbidity

- 314 primary care practices in Scotland n= 1,751,841
  - Although the prevalence of multimorbidity increases with age, the absolute number of people with multimorbidity is higher in those younger than 65 years

![Figure 1: Number of chronic disorders by age-group](image)
Polypharmacy as an independent risk factor for adverse outcomes

- Increased risk of mortality (OR 1.09, 95% CI 1.04-1.15), with each additional medication when adjusted for age, self-reported medical conditions and depression (Gnjidic et al. J Clin Epi 2012;65:989-995)

- Increased risk of drug-related visits to the ER (OR 1.07, 95% CI 1.01-1.13), with each additional medication when adjusted for the number of comorbidities and prescribers (Zed et al. CMAJ 2008;178:1563-1569)

- Significant association with adverse drug events (OR 1.88 (95% CI 1.58-2.25) (Bourgeois et al. Pharmacoepidemiol Drug Saf 2010;19:901-910)
Mechanism of causality

POLYPHARMACY → Adverse Drug Events → MORBIDITY AND MORTALITY

40% PREVENTABLE

Zed et al. CMAJ 2008;178:1563-1569
Adverse drug events

An adverse drug event is defined as an injury resulting from administration of a drug

- account for 5% (1-in-20) of all emergency department visits in Canada
- cost ~$35.7 million Canadian dollars for seniors alone (>80% of costs due to hospitalization)
- are estimated to be the 4th - 6th leading cause of death in hospitalised patients

Which drugs are most to blame?

- For ER visits
- For drug-related hospitalisation
- For unnecessary mortality
Proportion of ER visits for adverse drug events requiring hospitalisation

Commonly implicated medications

265,802 ER visits/yr for adverse drug events in U.S. adults 65+, 37% of which required hospitalisation

Frequency of hospitalisation by drug class

99,628 emergency hospitalisations/yr for adverse drug events in U.S. adults 65+

Commonly implicated medications

Canadian Institute for Health Information reports on hospitalisations due to adverse drug events in seniors

*Seniors accounted for 57% of all ADE-related hospitalisations

Number of hospitalisations per year

- Anticoagulants
- NSAIDS
- Opioids
- Diuretics
- Antineoplastic agents (neutropenia)
- Beta-blockers and digoxin (bradycardia)

Polypharmacy increases the risk of drug-related hospitalisation.

Top 5 culprit drug classes

Account for 88% of drug-related hospitalizations

- Hematologic agents
  - Warfarin, ASA, NSAIDS
- Endocrine agents
  - Insulin, oral hypoglycemics
- Cardiovascular drugs
  - Digoxin, ACE inhibitors, diuretics, beta-blockers
- Central nervous system agents
  - Benzodiazepines, opioids, antipsychotic agents
- Anti-infective agents

*Budnitz et al. Emergency hospitalizations due to adverse drug events in older Americans. NEJM 2011; 365: 2002-2012*
Avoid “Inappropriate” Prescriptions: Risk > Benefit, alternative therapies exist

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Non-benzodiazepine sedative hypnotics</th>
<th>Tricyclic antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam</td>
<td>Zolpidem</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Zopiclone</td>
<td>Imipramine</td>
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<tr>
<td>Lorazepam</td>
<td>Zaleplon</td>
<td></td>
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<tr>
<td>Alprazolam</td>
<td></td>
<td>1st generation antihistamines</td>
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<tr>
<td>Clonazepam</td>
<td></td>
<td>Hydroxyzine</td>
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<tr>
<td>Diazepam</td>
<td>Sulfonylurea oral hypoglycemics</td>
<td>Diphenhydramine</td>
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<tr>
<td>Flurazepam</td>
<td>Glyburide</td>
<td></td>
</tr>
<tr>
<td>Chlorazepam</td>
<td>Glipizide</td>
<td>Cardiovascular/diuretic agents</td>
</tr>
<tr>
<td>All antipsychotics</td>
<td>Chlorpropamide</td>
<td>Amiodarone</td>
</tr>
</tbody>
</table>

http://www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/2012
Risk ≠ Adverse Event
Drug interaction as an explanatory factor

- POLYPHARMACY
- Adverse Drug Events (Idiosyncratic)
- Drug-drug interactions
  - PREVENTABLE
- MORBIDITY AND MORTALITY
More medications = more interactions

- Low risk of drug-drug interactions
- 4-fold greater risk of drug-drug interactions
- 8-fold greater risk of drug-drug interactions

- 2-4 medications
- 5-7 medications
- 8-10 medications

Johnell & Klarin. Drug Safety 2007
Which drug interactions should be avoided?

- Interactions that change the intended bioavailability of the object drug by altering its pharmacokinetics, and consequently, its serum levels.

![Graph showing concentration over time with labels Maximum Tolerated Concentration (MTC) and Minimum Effective Concentration (MEC).]

- Toxicity
- Therapeutic range
- Therapeutic failure
Toxicity due to pharmacokinetic drug-drug interactions

- Warfarin + CYP2C9 inhibitors ➔ Bleeding
- Oral hypoglycemic agents + CYP2C9 inhibitors ➔ Hypoglycemia
Warfarin + sulfamethoxazole increase the risk of hospitalization for GI bleeding

CYP2C9 = main enzyme responsible for metabolizing S-warfarin (responsible for 60-70% of warfarin’s activity) in the liver

- Sulfamethoxazole = inhibits cytochrome CYP2C9

Glyburide + sulfamethoxazole increase the risk of hospitalization for hypoglycemia

CYP2C9 = main enzyme responsible for metabolizing glyburide in the liver
- Sulfamethoxazole = inhibits cytochrome CYP2C9

New on the Beers List

Therapeutic failure due to pharmacokinetic drug-drug interactions

Tamoxifen + CYP2D6 inhibitors → Increased risk of death from breast cancer
Tamoxifen + paroxetine increase risk of death from breast cancer

Tamoxifen is a prodrug that must be activated by CYP2D6 in order to exert its therapeutic effect.

- Paroxetine inhibits CYP2D6 → no active tamoxifen metabolite → therapeutic failure

![Graph showing the hazard ratio for death due to breast cancer in women treated with tamoxifen, with different proportions of time patients were concurrently treated with paroxetine.]

Kelly CM et al. BMJ 2010;340:c693
Pair-wise versus multiple simultaneous cytochrome-mediated drug-drug interactions
80% prevalence of potential CYP450 DDIs in older hospitalized patients

Among 100 patients aged 65+ with 5+ medications (mean 12, range 5-27)

<table>
<thead>
<tr>
<th>Cytochrome</th>
<th>Proportion of interactions n=80 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A4</td>
<td>70.1</td>
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<tr>
<td>2D6</td>
<td>22.7</td>
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<tr>
<td>2C9</td>
<td>3.4</td>
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<tr>
<td>2C19</td>
<td>2.1</td>
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<tr>
<td>1A2</td>
<td>1.7</td>
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<tr>
<td>2B6</td>
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</tbody>
</table>

238 different interactions among 100 patients

The number of potential CYP450 drug-drug interactions increases as a function of the number of drugs consumed.

A typical patient with multimorbidity

8 medical conditions

- Cardiovascular disease – STEMI 10 & 2 years ago, admitted last year for heart failure, EF 30%
- Hypertension x 20 years
- Diabetes Type 2 x 15 years
- Dyslipidemia x 15 years
- Prostate cancer x 10 years, prostatectomy 2 years ago
- Osteoporosis x 8 years
- Urinary incontinence x 1 year
- Depression x 6 months

Mr C. 79 years old
A typical patient with multimorbidity

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- Cardiovascular disease – STEMI 10 & 2 years ago, admitted last year for heart failure, EF 30%
- Hypertension x 20 years
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- Prostate cancer x 10 years, prostatectomy 2 years ago
- Osteoporosis x 8 years
- Urinary incontinence x 1 year
- Depression x 6 months

Mr C. 79 years old
Mr. C. – 12 medications

- Candasartan 8 mg daily, Metoprolol 50 mg bid
- Furosemide 40 mg bid, Aldactone 25 mg po bid
- ASA 80 mg daily
- Atorvastatin 10 mg po daily
- Metformin 500 bid, Glyburide 5 mg bid
- Alendronate 70 mg/wk, Calcium carbonate 1000 mg + vitamin D 800 IU/day
- Pantoprazole 40 mg daily
- Zopiclone 7.5 mg po qhs
- Started on venlafaxine 7.5 mg daily 6 months ago

79 years old
Just following the guidelines!

**Chronic heart failure** → ACE inhibitor/ARB and diuretics  
(2012 Canadian Cardiovascular Society guidelines)

**Hypertension target 130/80** → ACE inhibitor/ARB and beta-blocker  
(2011 Canadian Hypertension Education Program recommendations for patients with diabetes and cardiovascular disease)

**Diabetes target HbA1C < 7%** → Oral hypoglycemic agents  
(2008 Canadian Diabetes Association clinical practice guidelines)

**Dyslipidemia target LDL-C < 2.0 mmol/L** → Statin  
(2008 Canadian Diabetes Association clinical practice guidelines for high risk diabetic patients)

**Osteoporosis** → Bisphosphonate, Calcium, Vitamin D  
(2010 Canadian Osteoporosis Society guidelines)

**Use of ASA in elderly** → Proton Pump Inhibitor to reduce GI bleeding  
(2009 Canadian Association of Gastroenterology Consensus Group on long-term NSAID therapy and gastroprotection)

**Urinary incontinence** → Kegel exercises!  
(2012 International Consultation on Incontinence)
16 potential cytochrome-mediated interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>CYP 1A2</th>
<th>CYP 2B6</th>
<th>CYP 2C8</th>
<th>CYP 2C9</th>
<th>CYP 2C19</th>
<th>CYP 2D6</th>
<th>CYP 3A4</th>
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<tbody>
<tr>
<td>Metoprolol</td>
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<td>Venlafaxine</td>
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<td>Glyburide</td>
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<td>Candasartan</td>
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<td>Atorvastatin</td>
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<td>Zopiclone</td>
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<td>Pantoprazole</td>
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<td>Metformin</td>
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<td>Moderate inhibitor</td>
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<td>Alendronate</td>
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<td>No cytochrome metabolism</td>
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<td>ASA</td>
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Moderate inhibitor | Weak inhibitor

http://ws-ddi.intermed-rx.ca//default_fr.fwx
Toxicity and therapeutic failure due to pharmacodynamic drug-drug interactions

- Angiotension II receptor blocker and potassium sparing diuretic ➔ hyperkalemia
- Benzodiazepine/Non-benzo + other CNS medication ➔ Risk of falls and hip fractures
- Proton pump inhibitors and bisphosphonates ➔ Therapeutic failure
Warfarin + NSAIDs increase the risk of hospitalization for GI bleeding

Additive bleeding risk due to anticoagulant and antiplatelet action

- NSAIDS inhibit cyclooxygenase, which decreases gastric pH and causes gastric erosions

**High frequency of unreported over-the-counter NSAID use**

ACE inhibitors, potassium-sparing diuretics and admissions for hyperkalemia

Patients treated with an ACE inhibitor/ARB admitted with a diagnosis of hyperkalemia are 20 times more likely to have been treated with a potassium sparing diuretic in the previous week (OR 20.3 (95% CI 13.4-30.7)).

*Juurlink et al. JAMA 2003;289:1652-1658*
*Juurlink et al. NEJM 2004;351:543-551*
ACE inhibitors, potassium-sparing diuretics and hospital death associated with hyperkalemia

Patients treated with an ACE inhibitor/ARB and spironolactone had higher anticipated rates of in-hospital death from hyperkalemia

Release of RALES (Randomised Aldactone Evaluation Study showing improved outcomes in patients with severe heart failure)

Juurink et al. JAMA 2003;289:1652-1658
Juurink et al. NEJM 2004;351:543-551
Mr. C. - Risk of pharmacodynamic drug-drug interactions

- Candasartan + Aldactone
- Zopiclone
  - + prn hydroxyzine for dry itchy skin
Benzodiazepine/non-BDZ hypnotics + other interacting agents and risk of hip fracture

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<tr>
<th>Drug combination</th>
<th>Risk of hip fracture (95% CI)</th>
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</tr>
<tr>
<td>Alone</td>
<td>0.92 (0.78 – 1.08)</td>
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<td>CYP3A4 inh + other CNS drugs*</td>
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*Antihistamines, opioids, trazodone, anticonvulsants, antidepressants

## Benzodiazepine/non-BDZ hypnotics + other interacting agents and risk of hip fracture

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Dose and duration of BDZ use affect the risk of hip fracture

<table>
<thead>
<tr>
<th></th>
<th>Relative risk of hip fracture adjusted for age, sex, comorbidity RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td></td>
</tr>
<tr>
<td>Low (≤ 0.5 DDD)</td>
<td>1.09 (1.02 – 1.17)</td>
</tr>
<tr>
<td>Medium</td>
<td>1.21 (1.11 – 1.31)</td>
</tr>
<tr>
<td>High (&gt; 1.0 DDD)</td>
<td>1.32 (1.17 – 1.48)</td>
</tr>
<tr>
<td><strong>Duration (date of first prescription in relation to the hip fracture)</strong></td>
<td></td>
</tr>
<tr>
<td>0-14 days (new users)</td>
<td>2.05 (1.52 – 2.77)</td>
</tr>
<tr>
<td>15-30 days</td>
<td>1.42 (1.03 – 1.96)</td>
</tr>
<tr>
<td>31-60 days</td>
<td>1.34 (1.02 – 1.77)</td>
</tr>
<tr>
<td>180-270 days</td>
<td>1.53 (1.31 – 1.78)</td>
</tr>
<tr>
<td>271-365 days</td>
<td>1.10 (1.04 – 1.17)</td>
</tr>
</tbody>
</table>

Neurotransmitter pathways involved in attention, response time, executive function.

Drug-induced amnestic vs. non-amnestic cognitive dysfunction

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Amnestic deficits: short or long-term memory</th>
<th>Non-amnestic deficits: concentration/information processing/planning/psychomotor speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>✓✓✓</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Non-benzodiazepines</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>1st generation antihistamines</td>
<td>✓</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>✓</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Other anticholinergics</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Opioid drugs</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Proton pump inhibitors reduce antifracture efficacy of bisphosphonates


*17% of the population studied was male
Solutions: what can we do to reduce the risks associated with polypharmacy?

3 targets:

- Physician
- Pharmacist
- Patient
Avoid starting patients on inappropriate prescriptions!

Uncovering the source of new benzodiazepine prescriptions in community-dwelling older adults’

Alex S. Halme¹, Sarah-Gabrielle Beland¹, Michel Previle² and Cara Tannenbaum¹

RESULTS: Incident benzodiazepine use was 11% over a 2-year period among 1189 older adults enrolled in the Étude sur la Santé des Aînés.

Being hospitalized was a risk factor for a new benzodiazepine prescription:

2.7-fold greater risk than during an outpatient visit (OR 2.7, 95% CI 1.8–4.0)
ABIM Choosing Wisely Campaign

An initiative led by the American Board of Internal Medicine

- Each specialty suggests the top 5 UNNECESSARY tests or treatments to be questioned by physicians and patients

4/5 recommendations by the American Board of Geriatric Medicine involve the use of medicines

1. Don’t use antipsychotics as first choice to treat behavioral symptoms of dementia
2. Avoid using medications to achieve hemoglobin A1c < 7.5% in most adults aged 65 years and older
3. Don’t use benzodiazepines or other sedative hypnotics as first choice for insomnia
4. Don’t use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present
Recognize dangerous drug-drug interactions

Pharmacokinetic drug-drug interactions

CYP2C9: Warfarin, glyburide, SMX/TMP
CYP3A4, 2D6 : most common multidrug

- Use **drug alert software** and **pay attention** to the warnings
  - Substitute with drugs not metabolized by the same cytochrome
  - Diminish the dose of the drug that is expected to accumulate because of insufficient metabolism
  - Replace medication with non-pharmacologic therapy

Beware common pharmacodynamic drug-drug interactions

- Benzodiazepines – 32% prevalence among older adults in Quebec
  - Concomitant use with over-the-counter antihistamines and prescription antidepressants, other pain medication

- ACE-inhibitors/ARBs and potassium-sparing diuretics in patients with low ejection fraction heart failure
  - Both are recommended in the 2012 CCS guidelines for the management of heart failure with reduced ejection fraction, though the guidelines state there is little evidence on combined use

Interprofessional collaboration with pharmacists

- Untapped resource
- Ask for help!
  - Polypharmacy and drug-drug interaction consult
- Principle of demand and supply
  - Changing scope of pharmacist practice across Canada

Tannenbaum & Tsuyuki. CMAJ 2013 in press
Educate patients

- Randomised trial testing whether patient education results in discontinuation of inappropriate prescriptions

- Preliminary findings suggest that 50% of patients change their risk perceptions after receiving the educational intervention

Risk is a matter of perspective: What is better or worse?
Be unreasonable

“The reasonable man adapts himself to the world; the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man.”

George Bernard Shaw (1903)

DARE TO DE-PRESCRIBE

“It is an art of no little importance to administer medicines properly; but it is an art of much greater and more difficult acquisition to know when to suspend or altogether omit them.”

Philippe Pinel (1745-1826)
What to do first?

- Decide what should be tapered or stopped
- Stop the easy ones (no longer needed, have long half-lives, don’t cause adverse drug withdrawal events)
  - Alendronate
- Stop the drugs causing side effects
- Remember that drugs that can cause adverse drug withdrawal events need to be **tapered**:
  - Beta-blockers
  - Benzodiazepines
  - SSRIs
  - Proton pump inhibitors
  - Diuretics
  - Narcotics, anticonvulsants, antipsychotics
Mr. C’s medication changes

**Week 1**
- Switch candasartan to valsartan (not metabolized by CYP 2C9)
- Start aldactone taper 25 daily
- Start glyburide taper 2.5 mg bid
- Stop prn hydroxyzine

**Month 2**
- Switch metoprolol to bisoprolol (not metabolized by CYP 450)
- Provide sleep hygiene education
- Teach heart failure self-management

**Month 4**
- Begin 20-week zopiclone taper
- Stop alendronate
- Stop glyburide
- Monitor glucose
- Stop aldactone
Mr. C’s medication changes

- **Month 6**
  - Switch atorvastatin to rosuvastatin (CYP2C9)
  - Decrease pantoprazole to 20 mg daily
  - Start elastic stockings

- **Month 8**
  - Start furosemide taper 20 mg bid
  - Increase dose of metformin 500 tid
  - Begin venlafaxine taper

- **Month 10**
  - Discontinue zopiclone and venlafaxine
  - Continue furosemide taper 20 mg daily alternating with 40 mg daily prn
At 1 year follow-up

**Mr. C’s medications**
- Bisoprolol 5 mg daily
- Valsartan 80 mg bid
- Lasix 20 mg alt with 40 mg
- Metformin 750 mg tid
- Rosuvastatin 10 mg daily
- ASA 80 mg daily
- Pantoprazole 20 mg daily
- Calcium and Vitamin D
- Schedule repeat bone density in 1 year

**Mr. C’s life:**
- Urge incontinence resolved
- Depression resolved
- Lower risk of hyperkalemia
- Lower risk of hypoglycemia
- Lower risk of falls
Questions

Thank you!