The Culture and Science of Polypharmacy

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Research Interests:
Decision Making Re Medication Use

- Consumers
- Patients
- Caregivers
- Physicians
- Nurses
- Pharmacist
- PT, OT, RT
- Hidden impact of polypharmacy

The “hidden” impact of polypharmacy
What is Polypharmacy?

• 5 or more medications taken simultaneously
• More medications used than are clinically warranted.
• A Random Uncontrolled Experiment

• Types of Polypharmacy
  • Too many drugs
  • Inappropriate choices
  • Inappropriate combinations
  • Administration errors
  • Way off label use
  • Inappropriate dosing
  • Inappropriate prescriber
Polypharmacy: A Silent Epidemic

A side effect of modern medical care
- 15-minute office visit/Hospital visit
- Cornerstone of guideline driven care (GDC)
  - “lifestyle changes, and if LC ineffective”
  - X
  - Y
  - Z
- GC derived mostly from clinical drug studies (CDS)
- CDS are efficacy trials against placebo
  - Set up for consumerism not necessarily for superior intervention discovery
- Example: current dementia treatments
- New drugs added annually and marketed direct.
- Multiple specialists
- Over the counter products and supplements proliferation

Tai-Seale and McGuire 2012; Tai-Seale, McGuire et al. 2007
Young, Burge et al. 2018
## Polypharmacy: A Silent Epidemic

106,000; medication related problems*

* A conservative (very) estimate

### United States Annual Causes of Death

<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>2,712,630</td>
</tr>
<tr>
<td>1. Heart Disease</td>
<td>633,842</td>
</tr>
<tr>
<td>2. Cancer</td>
<td>595,930</td>
</tr>
<tr>
<td>3. Lower Respiratory Disease</td>
<td>155,041</td>
</tr>
<tr>
<td>4. Accidents</td>
<td>146,571</td>
</tr>
<tr>
<td>5. Cerebral Vascular Disease</td>
<td>140,323</td>
</tr>
<tr>
<td>6. Alzheimer’s Disease</td>
<td>110,561</td>
</tr>
<tr>
<td>7. Diabetes Mellitus</td>
<td>79,535</td>
</tr>
<tr>
<td>8. Influenza and Pneumonia</td>
<td>57,062</td>
</tr>
<tr>
<td>9. Nephritis</td>
<td>49,959</td>
</tr>
</tbody>
</table>

* A conservative (very) estimate

-Center for Managing Chronic Disease
-CDC National Health Statistics tables 2015 [https://www.cdc.gov/nchs/fastats/deaths.htm](https://www.cdc.gov/nchs/fastats/deaths.htm)
Errors leading to ADEs in ambulatory older adults (mean age 75): 65-80

Adherence:
- HC system obsessed
- Strongest driver = the belief that the product works for a problem the patient is concerned about.
- Cochran review concludes despite multiple complex interventions, none have yet to successfully improve adherence.


Clifford, S., 2008.
85 drugs pulled off market since...... ever.

+ Over the Counter Products, Supplements and Vitamins

- PDR in 1969 = 1425 pages Rx and OTC
- PDR in 2012 = 3151 very different pages plus a separate 800-page OTC product book.

<table>
<thead>
<tr>
<th>Year</th>
<th># FDA approved drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>59</td>
</tr>
<tr>
<td>2017</td>
<td>46</td>
</tr>
<tr>
<td>2016</td>
<td>22</td>
</tr>
<tr>
<td>2015</td>
<td>45</td>
</tr>
<tr>
<td>2014</td>
<td>44</td>
</tr>
<tr>
<td>2013</td>
<td>27</td>
</tr>
<tr>
<td>2012</td>
<td>43</td>
</tr>
</tbody>
</table>

- FDA New Molecular Entities 2016
- FDA Approved Drugs 2016
- Center Watch: [https://www.centerwatch.com/drug-information/fda-approved-drugs/year/2016](https://www.centerwatch.com/drug-information/fda-approved-drugs/year/2016)
- US Government Publishing Office: [https://www.ecfr.gov/cgi-bin/text-idx?SID=9f72be9eddb31ec17e76f977678b42878&mc=true&node=se21.4.216_124&rgn=div8](https://www.ecfr.gov/cgi-bin/text-idx?SID=9f72be9eddb31ec17e76f977678b42878&mc=true&node=se21.4.216_124&rgn=div8)
What’s The Concern?

% Patients with Adverse Medication Reactions vs Number of Medications Prescribed

Denham 1990
Is total drug burden important?

**Intervention:** Discontinuation of average 2.8 drugs per patient. 119 patient in geriatric nursing care in Israel vs age, gender and co-morbidity matched controls in the same facility.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year mortality rate</td>
<td>21%</td>
</tr>
<tr>
<td>Annual referral to ED</td>
<td>11.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of medication discontinued</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example of meds discontinued</strong></td>
<td></td>
</tr>
<tr>
<td>Nitrates in patients who had no chest pain for 3 months. Failure defined as return of symptoms or ECG changes.</td>
<td>22 patients had nitrates discontinued with no clinical or ECG changes.</td>
</tr>
<tr>
<td>H2 blockers in patients with no proven peptic ulcer, gastrointestinal bleeding or dyspepsia for 1 year. Failure defined as return of UGI bleed.</td>
<td>Discontinuation of H2 blockers did not cause UGI symptoms in 94% of patients.</td>
</tr>
<tr>
<td>When several antihypertensive agents were used, they tried to remove only one while maintaining the dosage of others. Failure defined as increase in dbp &gt; 90mmHG or sbp&gt;140 mmHG</td>
<td>Discontinuation of blood pressure medications did not cause increased bp in 82% (42/51) of patients.</td>
</tr>
</tbody>
</table>

(Garfinkel, Zur-Gil et al. 2007)
Obesity map is nearly identical to this scripts per capita map

Henry J Kaiser Family Foundation State Health Facts 2018
### Is Polypharmacy a Harmful Syndrome for All?

**> or = to 20 years of age (median age 49)**
- None, 1-3, 4-6, 7-9, 10 or >
- Not consistently linked with increased hospitalization among multi-morbidity patients.
- “Hyperpolypharmacy” associated with increased hospitalization risk across patient groups with any number of co-morbidities.

Payne, Abel et al. 2014

**Middle Aged Adults (45-64 years)**
- PROMPT Criteria for Middle Aged Adults
  - Example: Esomeprazole or Omeprazole should not be used in combination with clopidogrel.
  - Example: PPIs should not be prescribed at doses above the recommended maintenance dosage for > 8 weeks.
- Conflicting studies regarding the associations of polypharmacy in adults <60 years.

Cooper, Ryan et al. 2014
Calderon-Larranaga, Gimeno-Feliu et al. 2013

**Older Adults**
- > or = to 5 medications
- Poor outcomes; frailty, disability, mortality, and falls.

Nobili, Licata et al. 2011
Franchi, Marcucci et al. 2016
How do stakeholders view medication use?

"If you remember, I did mention possible side-effects."
Efficacy is great but what about toxicity? Pharmacology and Toxicology go hand in hand... or they’re supposed to at least.
Perhaps a Shift in Approach to Research is Needed Too

<table>
<thead>
<tr>
<th>Medications</th>
<th>ATS Hold Protocol</th>
<th>UL hold Protocol</th>
<th>$T_{1/2}$ (expected elimination for adults)</th>
<th>$T_{1/2}$ (expected elimination for older adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>48 hrs</td>
<td>48 hrs (Advair 24 hrs)</td>
<td>5.5 hrs (27.5 hrs)</td>
<td>Increased $T_{1/2}$ with high drug burden of CYP3A4 metabolized medications.</td>
</tr>
<tr>
<td>Formoterol</td>
<td>48 hrs</td>
<td>48 hrs (Symbicort 24 hrs)</td>
<td>7-10 hrs (35-50 hrs)</td>
<td>$60^\circ$: 11 hrs (55 hrs) $80^\circ$: 12 hrs (60 hrs) $90^\circ$: 13 hrs (65 hrs)</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>48 hrs</td>
<td>48 hrs</td>
<td>2 hrs (10 hrs)</td>
<td>2 hrs (10 hrs)</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>48 hrs</td>
<td>48 hrs</td>
<td>Solution [Asthma]: 44 hrs (220 hrs)</td>
<td>Solution [asthma]: $60^\circ$: 48.4 hrs (242 hrs) $70^\circ$: 52.8 hrs (264 hrs) $80^\circ$: 57.2 hrs (286 hrs)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>12-24 hrs</td>
<td>12-48 hrs</td>
<td>8.7 hrs (43.5 hrs)</td>
<td>9.8 hrs (49 hrs)</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>12-14 hrs</td>
<td>72 hrs</td>
<td>8 hrs (40 hrs)</td>
<td>$T_{1/2}$ will increase with renal impairment</td>
</tr>
</tbody>
</table>

Antimisiaris D., Ingram I. 2018
William Osler

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

What’s up in your world regarding Polypharmacy?