Drug Therapy in the Elderly

Jerry H. Gurwitz, M.D.
The Prescribing Casade

B.F. is an 80 year-old female nursing home resident with a history of Parkinson’s Disease treated with long-term Sinemet therapy (25-100 TID). She has suffered occasional hallucinations attributed to the Sinemet therapy, which have recently increased in frequency. The hallucinations sometimes involve large animals and can be quite terrifying.
The Prescribing Cascade

The resident is initiated on olanzapine 2.5 mg at bedtime. Due to agitation and continued hallucinations, the olanzapine dose is increased to 5 mg and lorazepam 0.5 mg po q4 hours prn is added to the medication regimen. The hallucinations continue and the evening dose of olanzapine is increased to 7.5 mg.
The resident is noted by the nursing staff to be shaky and stiff, but no change is made in the olanzapine dose. She becomes increasingly lethargic. She is described as rigid and stooped over with ambulation and begins to have more difficulty with activities of daily living including bathing, dressing, toileting, and transferring. She begins to require a wheelchair.
The Prescribing Cascade

The resident’s functional decline is attributed to Parkinson’s Disease...
It is much easier to write upon a disease than upon a remedy. The former is in the hands of nature and a faithful observer with an eye of tolerable judgement cannot fail to delineate a likeness. The latter will ever be subject to the whim, the inaccuracies and the blunder of mankind.

William Withering (1741-1799)
A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals.

Sir William Osler, 1891
In the elderly, less medication is always better.
Prescription of Drug Therapy
National Ambulatory Medical Care Survey
(3 or more prescribed drugs)
Drug Use in the Elderly

- 40% of all elderly use > 5 drugs per week
- 12% of elderly use > 10 drugs per week
“I know of no way to end an office visit as satisfactorily and as efficiently as by writing a prescription. The patient knows that the visit is over and is expected to leave. He has something in his hand that he thinks will help him and obtaining it required an office visit.”

Marcus Reidenberg, MD
Editor Emeritus, CP&T
Is there evidence of inappropriate drug prescribing to the elderly?

- The Beers list
- List of 33 drugs
  - Drugs that should *always be avoided*
  - Drugs that are *rarely appropriate*
  - Drugs with *some indications*, but that are often misused
11 drugs that should always be avoided in the elderly:

- Barbiturates
- Chlorpropamide
- Flurazepam
- Meperidine
- Meprobamate
- Pentazocine
- Belladonna alkaloids
- Dicyclomine
- Hyoscyamine
- Propantheline
- Trimethobenzamide

Zhan et al. *JAMA* 2001
Use of “Always Avoid” Drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996 U.S.</td>
<td>2.6%</td>
</tr>
<tr>
<td>1996 Ontario</td>
<td>2.9%</td>
</tr>
<tr>
<td>2000-2001 US HMOs</td>
<td>5.1%</td>
</tr>
</tbody>
</table>
“The Other Quality Problem”

**Underuse**

- Beta blockers, ACE inhibitors, and aspirin post-MI
- Warfarin for stroke prevention in atrial fibrillation
- Calcium, vitamin D, and other agents for osteoporosis prevention
- Antidepressant therapy in nursing homes
Use of Statins in US Elderly with CAD

Federman et al, *JAMA*, 2001

![Bar chart showing the percentage of drug coverage for elderly with CAD in the US. The chart indicates that 27% of patients are covered, while 4% are not.](image-url)
“Have you taken less medication than was prescribed for you because of the cost?”

<table>
<thead>
<tr>
<th>Drug Coverage</th>
<th>None</th>
<th>Partial</th>
<th>Full</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>8%</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Steinman et al, *JGIM* 2001
1995-1996 data
Antihypertensive Drug Therapy and Quality of Life

Physician’s Assessment

Jachuck et al, 1982
Antihypertensive Drug Therapy and Quality of Life

*Patient’s Assessment*

Jachuck et al, 1982
Antihypertensive Drug Therapy and Quality of Life

Relative’s Assessment

Jachuck et al, 1982
Factors Influencing Drug Effects and Risk of Adverse Effects in the Elderly

- Multiple co-existing illnesses
- Polypharmacy: redundant effects and drug-drug interactions
- Adverse drug effects nonspecific
- Pharmacologic changes with aging
- Limited knowledge base
- Medical errors
Pharmacokinetics
Changes with Aging

• Absorption
• Distribution
• Metabolism
• Excretion
Body Composition Changes in Adult Men with Aging

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Body Weight (kg)</th>
<th>Body Fat (kg)</th>
<th>Muscle Mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>80</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>30-49</td>
<td>81</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>60-69</td>
<td>79</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>70-79</td>
<td>80</td>
<td>25</td>
<td>13</td>
</tr>
</tbody>
</table>

Data adapted from Cohn et al, 1980
Hepatic Metabolism of Drugs
*Changes with Aging*

- **Phase I reactions** - primarily oxidative reactions
  - Decline in efficiency with aging
- **Phase II reactions** - conjugation reactions
  - No decline in efficiency with aging
Renal Function Changes with Aging
\[ t_{1/2} \sim \frac{V_d}{\text{Clearance}} \]
DIAZEPAM $\xrightarrow{\text{N-DEALKYLLATION}}$ DESMETHYLDIAZEPAM
Pharmacodynamics
Changes with Aging
Figure 19.1. Relationship between age and serum diazepam concentration that causes failure to respond to vocal but not painful stimuli.
Factors Influencing Drug Effects and Risk of Adverse Effects in the Elderly

- Multiple co-existing illnesses
- Polypharmacy: redundant effects and drug-drug interactions
- Adverse drug effects nonspecific
- Pharmacologic changes with aging
- **Limited knowledge base**
The Limited Knowledge Base
Exclusion of the Elderly from Clinical Trials

• Advanced age has been a primary reason for ineligibility
• Systematic exclusion of patients over the age of 75
Exclusion of Elderly Patients from Clinical Trials of Acute Coronary Syndromes

*Age >75 Exclusion*

Lee et al *JAMA* 2001
Exclusion of Elderly Patients from Clinical Trials of Acute Coronary Syndromes

Trials not enrolling any patients >75 years old

Lee et al. *JAMA* 2001
Exclusion of Elderly Patients from Clinical Trials of Acute Coronary Syndromes

*Mean Age of Trial Participants*

<table>
<thead>
<tr>
<th>Year Interval</th>
<th>Mean Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981-1990</td>
<td>58</td>
</tr>
<tr>
<td>1991-1995</td>
<td>61</td>
</tr>
<tr>
<td>1996-2000</td>
<td>62</td>
</tr>
</tbody>
</table>

Lee et al *JAMA* 2001
Exclusion of Elderly Patients from Clinical Trials of Acute Coronary Syndromes

“Attempts at making cardiovascular trials more inclusive appear to have had limited success; thus elderly persons remain underrepresented in published trial literature relative to their disease prevalence. Because safety and efficacy can vary as a function of sex and age, these enrollment biases undermine efforts to provide evidence-based care to elderly patients.”

Lee et al.  JAMA  2001
You can observe a lot just by watching.

Yogi Berra
The Prescribing Cascade

Drug 1

ADE

Drug 2
DRUG 2 = PROXY FOR ADE
The New Jersey Medicaid Database

• Program for the disadvantaged
• Medical care
• Covered services include drugs
• Complex frail elderly
Case-Control Study Design

CLASSIFY/COMPARE

Drug Exposure: Yes or No?

BEGIN

Cases (ADE)

Controls

Drug Exposure: Yes or No?
The Prescribing Cascade

Metoclopramide

Extrapyramidal Effects

Levodopa Rx
Case-Control Study Design

CLASSIFY/COMPARE

Metoclopramide: Yes or No?

BEGIN

L-dopa Rx

Controls

Metoclopramide: Yes or No?
Metoclopramide and L-dopa Rx

- **Study population**: New Jersey Medicaid enrollees ≥ age 65
- **Cases**: 1,253 new users of L-dopa therapy
- **Controls**: 16,435 non-users of L-dopa therapy
- **Drug exposure of interest**: metoclopramide
Results

Metoclopramide users were over three times more likely to begin use of L-dopa therapy compared with non-users (OR=3.09; 95% CI 2.25 to 4.26).
Likelihood of L-dopa Treatment by Metoclopramide Dose
Conclusion

Metoclopramide confers an increased risk for the initiation of treatment generally reserved for the management of idiopathic Parkinson’s disease.
The Prescribing Cascade

Drug 1

ADE

Drug 2
The Incidence and Preventability of Adverse Drug Events in Two Large Academic Long-term Care Facilities

Funded by AHRQ
Adverse Drug Events

Medication Errors

Preventable

ADEs
Results - Event Rates

• Adverse drug events
  – Events: 815
  – Rate: 9.8 per 100 resident-months

• Preventable adverse drug events
  – Events: 338
  – Rate: 4.1 per 100 resident-months
### Adverse Drug Events by Severity (n=815)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>4</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>33</td>
<td>4%</td>
</tr>
<tr>
<td>Serious</td>
<td>188</td>
<td>23%</td>
</tr>
<tr>
<td>Less serious</td>
<td>590</td>
<td>72%</td>
</tr>
</tbody>
</table>
Preventability of Adverse Drug Events

Of fatal, life-threatening & serious events
Preventable 61%

Of less serious events
Preventable 34%
## Error Stage for Preventable ADEs (n=338 preventable ADEs)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordering</td>
<td>198</td>
<td>59%</td>
</tr>
<tr>
<td>Dispensing</td>
<td>16</td>
<td>5%</td>
</tr>
<tr>
<td>Administration</td>
<td>43</td>
<td>13%</td>
</tr>
<tr>
<td>Monitoring</td>
<td>271</td>
<td>80%</td>
</tr>
</tbody>
</table>
Event Categories - Preventable

Neuropsychiatric  29%
Hemorrhagic       16%
Gastrointestinal  16%
Renal/electrolytes 12%
Fall with injury  5%
Cardiovascular    4%
Fall without injury 3%
EPS               2%
Syncope/dizziness  2%
## Drug Categories

### Preventable events

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>12%</td>
</tr>
<tr>
<td>Atypical antipsych</td>
<td>12%</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>10%</td>
</tr>
<tr>
<td>Benzos (intermediate)</td>
<td>9%</td>
</tr>
<tr>
<td>Opioids</td>
<td>8%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>8%</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>7%</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>7%</td>
</tr>
<tr>
<td>Insulin</td>
<td>5%</td>
</tr>
<tr>
<td>Laxatives</td>
<td>5%</td>
</tr>
</tbody>
</table>
What does this mean at the national level?

- Extrapolation to total US nursing home population (n=1.6 million)
  - 1,900,000 ADEs per year in nursing home setting (40% preventable)
  - 86,000 life threatening or fatal ADEs (70% preventable)
Drug Therapy in the Elderly

- Pharmacology
- Health Care Quality
- Epidemiology
- Patient Safety
Goals for the Future

• Increase the knowledge base around drug therapy in the elderly—include more elderly in RCTs
• Enhance efforts to identify and analyze adverse drug events
• Test and implement new technological approaches—CPOE with clinical decision support
• Team approach to the care of elderly patients: physicians, pharmacists, nurses, etc.
• Provision of affordable drug coverage