Rational Pharmacotherapy for LUTS in Older People

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Frailty

• Frailty = state of increased vulnerability resulting from aging-associated decline in reserve and function

• NOT synonymous with disability or comorbidity

• Associated with negative health outcomes
  • Falls
  • Hospitalization
  • Mortality

The great success of modern medicine is to create an awful lot of old people
Multimorbidity

Lancet 2007; 370: 797-799
Multimorbidity in LUTS

Number of Comorbid Conditions (n=111)
Polypharmacy

Increasing burden

Application of single disease guidelines to persons with multimorbidity may lead to excessive burden...
For example...

• Mrs A: A 78-year-old woman with previous MI, type 2 diabetes, osteoarthritis, COPD and depression.
Mrs. A

- 11 medications as a minimum
- Up to 10 other drugs routinely recommended
- She would be advised to routinely engage in nine self care/lifestyle alterations.
- 8–10 routine primary care appointments
- 4–6 GP appointments
- 8–30 psychosocial intervention appointments for her depression
- Multipla appointments for smoking cessation support and pulmonary rehabilitation
Older people handle drugs differently...
<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Changes</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>↓ Gastric secretion</td>
<td>Many drugs are more slowly absorbed</td>
</tr>
<tr>
<td></td>
<td>↑ Gastric pH</td>
<td>Delayed time of onset of action</td>
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<tr>
<td></td>
<td>↓ GI Motility</td>
<td>Least clinically significant change</td>
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<tr>
<td></td>
<td>↓ GI blood flow</td>
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</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>↓ Total body water</td>
<td>Increased volume of distribution of lipid-soluble drugs</td>
</tr>
<tr>
<td></td>
<td>↓ Lean body weight</td>
<td>Increased free fraction of drug</td>
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<tr>
<td></td>
<td>↓ Albumin</td>
<td></td>
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<tr>
<td></td>
<td>↑ Body fat</td>
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<tr>
<td><strong>Metabolism</strong></td>
<td>↓ Enzyme induction</td>
<td>Reduced hepatic clearance</td>
</tr>
<tr>
<td></td>
<td>↓ Hepatic mass</td>
<td>Reduced prodrug → drug metabolism</td>
</tr>
<tr>
<td></td>
<td>↓ Hepatic blood flow</td>
<td>Increased potential for drug:drug interaction</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>↓ Glomerular filtration rate</td>
<td>Reduced clearance of renally excreted drugs</td>
</tr>
<tr>
<td></td>
<td>↓ Renal blood flow</td>
<td></td>
</tr>
<tr>
<td><strong>Blood-brain barrier</strong></td>
<td>↑ permeability to drugs</td>
<td>Probably not significant in the absence of disease</td>
</tr>
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Muscarinic ACh receptors

<table>
<thead>
<tr>
<th>Subtype</th>
<th>General Distribution in the CNS</th>
<th>Non-CNS Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_1$</td>
<td>Abundant in cerebral cortex, hippocampus, and neostriatum; constitute 40–50% of total acetylcholine receptors</td>
<td>Salivary glands, sympathetic ganglia</td>
</tr>
<tr>
<td>$M_2$</td>
<td>Located throughout brain</td>
<td>Smooth muscle, cardiac muscle</td>
</tr>
<tr>
<td>$M_3$</td>
<td>Low levels throughout brain</td>
<td>Smooth muscle, salivary glands, eyes</td>
</tr>
<tr>
<td>$M_4$</td>
<td>Abundant in neostriatum, cortex, and hippocampus</td>
<td>Salivary glands</td>
</tr>
<tr>
<td>$M_5$</td>
<td>Projection neurons of substantia nigra pars, compacta and ventral tegmental area, and hippocampus</td>
<td>Eyes (ciliary muscle)</td>
</tr>
</tbody>
</table>
Anticholinergic burden

• Many drugs have anticholinergic activity
• Higher anticholinergic burden correlates with risk of cognitive decline
• Risk assessment tools exist
  • Anticholinergic Cognitive Burden Scale (ACB)
  • Anticholinergic Risk Scale (ARS)
  • Anticholinergic Drug Scale (ADS)
  • AC component of the Drug Burden Index (DBI-ACh)
  • Summated Anticholinergic Medication Scale (SAMS)
• Drugs for OAB are intentionally anticholinergic
Pharmacological options in OAB
Drugs for incontinence

• Oxybutynin - 1975
• Tolterodine - 1998
• Solifenacin - 2004
• Darifenacin – 2004
• Fesoterodine - 2008
• Mirabegron – 2012
• Obobotulinum Toxin – 2013 (2000)
Adverse effects of Antimuscarinics

• Dry mouth
• Constipation
• Blurred vision
• Cognitive effects
Oxybutynin

• Introduced in the 1970s
• Efficacious in reducing urgency and urgency incontinence
• Non-selective antagonist of the muscarinic acetylcholine receptor
Oxybutynin / Oxybutynin ER

• Commonest prescribed agent in UK
• RCT suggest efficacy at high (5mg tds) dose
  • SE leading to withdrawal $\approx 22\text{-}40\%$

• Efficacy at lower doses also shown (2.5 - 3mg bd) - withdrawal $\approx 10\%$
  • enhanced tolerability and reduced side effects  BUT after 1 year only 10-30\%
    of patients still on treatment

Cardozo LD. Neurourol Urodyn 1987;6: 256-7

Oxybutynin

- Elderly do as well as young
  
  Szonyi G Age & Ageing 1995; 24: 287-91

- Adverse effect on cognition recognised
  

- Efficacy in relation to behavioural techniques established - but conflicting
  
  Szonyi G. Age & Ageing 1995;24: 287-91
## Oxybutynin with prompted voiding in NH

<table>
<thead>
<tr>
<th></th>
<th>Placebo +PV</th>
<th>Oxybutynin +PV</th>
<th>P (Chi sq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wet checks</td>
<td>23.7%</td>
<td>20.2%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Frequency of incontinence</td>
<td>12 (19%)</td>
<td>20 (32%)</td>
<td>0.48</td>
</tr>
<tr>
<td>(&gt;1/3 checks “wet”)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved “continence” criterion</td>
<td>11 (18%)</td>
<td>25 (40%)</td>
<td>0.005</td>
</tr>
<tr>
<td>(1 or less wet per day)</td>
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Two things determine CNS effects

- Affinity for CNS muscarinic receptors
- Drug levels within the CNS
  - Influx (BBB permeability)
  - Efflux
    - pGP system
So oxybutynin

• Gets into the CNS
• Stays in the CNS
• Antagonises M1 receptors
• Risk of CNS side effects
This is clinically relevant

• Single dose of oxybutynin caused deterioration in 7 cognitive domains
• Deterioration in face-name test following 20mg of oxybutynin daily
  • Subjects were unaware of this decline
• Patients with dementia treated with cholinesterase inhibitors and bladder
  antimuscarinics deteriorated 50% faster than those on cholinesterase inhibitors
  alone
Other side effects

- Antimuscarinic ADEs are common with all BAMs
  - Constipation
  - Dry Mouth
  - Blurred vision
- Occur in up to 80% of people taking oxybutynin
- Long-term concordance is poor
- Oxybutynin taken for less time than solifenacin
  - Median 119 days vs 187 days
- Newer, bladder-specific drugs are better tolerated in general
Is oxybutynin cheaper?

- Lowest acquisition cost of all bladder antimuscarinics
- But;
  - Oxy vs tolterodine, $9,000pa more (US)
  - Oxy vs solifenacin, $1,831 more (CAD)
  - Oxy vs all newer BAMs €42,000/QALY more
- Product use, healthcare use, laundry

- NICE (UK) - “should offer” oxybuynin first line
Alternatives

- Solifenacin
  - Data in mild cognitive impairment

- Fesoterodine
  - Data in frail elderly (not cognitive data)

- Mirabegron
  - No antimuscarinic ADEs
  - Little data in the elderly

- Early data is encouraging
FORTA (Fit fOR The Aged) Classification

FORTA was introduced in 2008:¹

• To guide physicians in their screening process for inappropriate or harmful medications and drug omissions in older patients¹
  • Aimed at individual indications (implicit listing requiring patient characteristics/diagnoses)¹
  • Involves a two-step Delphi process and rating by 20-25 experts¹,²
• First classification system in which both negative and positive labelling are combined at the level of individual drugs or drug groups¹
• There is currently a FORTA list of >200 different drugs/drug groups for >20 therapeutic areas with relevance to older people²
  • The list is continuously expanded/refined²

FORTA Classifications


Class A (Absolutely)
- Indispensable drug, clear-cut benefit in terms of efficacy/safety ratio proven in elderly patients for a given indication

Class B (Beneficial)
- Drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns

Class C (Careful)
- Drugs with questionable efficacy/safety profiles in the elderly, to be avoided or omitted in the presence of too many drugs, lack of benefits or emerging side effects; review/find alternatives

Class D (Don’t)
- Avoid in the elderly, omit first, review/find alternatives
### Key Findings on Urological Drug Appropriateness

<table>
<thead>
<tr>
<th>LUTS Drug Class</th>
<th>FORTA-A (Absolutely)</th>
<th>FORTA-B (Beneficial)</th>
<th>FORTA-C (Careful)</th>
<th>FORTA-D (Don’t)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-Blocker</strong></td>
<td></td>
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<tr>
<td>Antimuscarinics</td>
<td></td>
<td>Fesoterodine</td>
<td>Darifenacin</td>
<td>Alfuzosin, Doxazosin, Terazosin</td>
</tr>
<tr>
<td>5α-Reductase inhibitors</td>
<td></td>
<td>Dutasteride, Finasteride</td>
<td>Oxybutynin ER, Solafenacin, Trospium, Tolterodine</td>
<td></td>
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<tr>
<td>PDE5 Inhibitors</td>
<td></td>
<td></td>
<td>Tadalafil</td>
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<tr>
<td>β-Agonists</td>
<td></td>
<td></td>
<td>Mirabegron</td>
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In general

• Try non-pharmacological methods first
• Newer antimuscarinics in preference to oxybutynin
• Review and stop other drugs if possible
• Minimise anticholinergic burden