Safe Prescribing of Medicines for Physical Disorders in People with Dementia

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Aim

• To investigate the safety of physical health drugs when used in patients with dementia
• To determine their effects on cognitive function and disease progression
• To examine their effects on anti-dementia drugs
• To consider potential drug interactions
• To be aware of which drugs are safe in dementia and which to avoid for various conditions
Prescribing issues in the elderly

• Drugs can have adverse cognitive effects
  – May be a *cause* of MCI (Tannenbaum et al 2012)
  – *Exacerbate* impairments in already established dementia

• Polypharmacy
  – is frequent - average of 8 *drugs* per resident in UK care homes (Shah et al 2012)
  – is dangerous - the more drugs people with dementia take the higher their mortality SHELTER study (2013)
  – Is not necessary - 20% of drugs “potentially inappropriate” in care home residents (Shah et al 2012)
Risks factors in older patients

• Co-morbid diseases
  – Nearly 80% of elderly patients have at least one chronic disease
  – 30% have 3 or more chronic diseases

• Polypharmacy
  – The more drugs combined, the higher the interaction potential:
    – 2 drugs- interaction potential of 5.6%
    – 5 drugs- interaction potential rises to 50%
    – 8 drugs- interaction potential is close to 100%

• Physiological changes occur in old age
• Multiple prescribers
• Patients self medicate with OTC products

High risk for Drug Interactions and Adverse Drug Reactions

Sloan, AFP 1983 Vol 27, No 2 (229-238)
Physiological changes in advanced age affecting pharmacokinetics of drugs

<table>
<thead>
<tr>
<th>Oral absorption</th>
<th>More body fat</th>
<th>Less body water</th>
<th>Less body muscle mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Less gastric acid &amp; blood flow to stomach</td>
<td>• Fat soluble drugs stay in body for longer (more fat to be stored in) eg propranolol</td>
<td>• Higher conc of water soluble drugs (less water to distribute in) eg atenolol</td>
<td>• Depots</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood-brain barrier</th>
<th>Less albumin</th>
<th>Liver</th>
<th>Kidneys</th>
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<tbody>
<tr>
<td>• Changes in permeability- allows more drugs to enter CNS at higher levels</td>
<td>• More free protein bound drugs eg phenytoin</td>
<td>• Decrease blood flow and changes in enzymes</td>
<td>• Function may be impaired with age- can lead to drug accumulation eg lithium</td>
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The Maudsley Prescribing Guidelines – 11th Edition
Pharmacodynamic changes

- As the body ages, changes occur in the number of receptors and also in the binding affinity of some drugs to receptors.
- Such processes may lead to either more or less sensitivity to medication and this is especially true for drugs affecting the cardiovascular or central nervous system.
- Deficits in homeostatic mechanisms and reduced autonomic function seen in the elderly.
Anti-dementia Drugs and potential drug interactions
Mechanism of Action of ACEIs

- Based on cholinergic theory of Alzheimer’s Disease
- Acetylcholine associated with memory + learning
- Progressive loss of cholinergic neurons and decreasing levels of acetylcholine in brain
- Acetylcholinesterase enzyme breaks down ACh
- Inhibiting this enzyme allows a greater concentration of ACh in the brain.
- Thereby improving cholinergic function.
Acetylcholine
AChEIs and Anti-cholinergic drugs

- Up to 50% of patients on concomitant use

- Anti-cholinergic drugs
  - interact negatively with AChEIs
  - Cause confusion, sedation, cognitive impairment, delirium, falls
  - Some suggestion they can increase the risk of dementia and affect the clinical course of AD (Carriere et al 2009; Jessen et al 2010; Lu & tune 2003)
  - Risk factor for onset of psychosis in AD (Cancelli et al 2009)
Anticholinergic drugs

• While some drugs are used for anticholinergic effects
  – eg oxybutynin or hyoscine
• Others have anticholinergic activity not related to their primary mode of action
  – eg ranitidine or carbamazepine
• Cumulative effect
• Anticholinergic risk scales of drugs vary considerably
• Recent systematic review of anticholinergic risk scales
  – Uniform list of drugs (Duran et al 2013)
<table>
<thead>
<tr>
<th>Drugs with unknown anticholinergic potency</th>
<th>Drugs with improbable or no anticholinergic action</th>
<th>Low potency anticholinergic drugs</th>
<th>High potency anticholinergic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colchicine</td>
<td>Allopurinol</td>
<td>Lansoprazole</td>
<td>Amantadine</td>
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<tr>
<td>Digoxin</td>
<td>Amiodipine</td>
<td>Levodopa</td>
<td>Baclofen</td>
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<tr>
<td>Furosemide</td>
<td>Amlodipine</td>
<td>Lisinopril</td>
<td>Bromocriptine</td>
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<td>Metoclopramide</td>
<td>Amoxicillin, Ampicillin</td>
<td>Metoprolol</td>
<td>Carbamazepine</td>
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<td></td>
<td>Aspirin</td>
<td>Betaxol</td>
<td>Cetirizine</td>
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<td></td>
<td>Atenolol</td>
<td>Methotrexate</td>
<td>Cimetiidine</td>
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<td></td>
<td>Atorvastatin</td>
<td>Metformin</td>
<td>Codeine</td>
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<td></td>
<td>Azathioprine</td>
<td>Nifedipine</td>
<td>Disopyramide</td>
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<td></td>
<td>Bisacodyl</td>
<td>Nitroglycerin</td>
<td>Domperidone</td>
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<tr>
<td></td>
<td>Captopril</td>
<td>Omeprazole</td>
<td>Entacapone</td>
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<td></td>
<td>Carbidopa</td>
<td>Paracetamol</td>
<td>Fentanyl</td>
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<td></td>
<td>Cefalexin (+ other cephs)</td>
<td>Phenytoin</td>
<td>Fexofenadine</td>
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<td></td>
<td>Clindamycin</td>
<td>Prednisolone</td>
<td>Hydrocodone</td>
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<td></td>
<td>Clopidogrel</td>
<td>Propranolol</td>
<td>Ketorolac</td>
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<td>Cortisone</td>
<td>Pseudoephedrine</td>
<td>Loperamide</td>
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<td>Dexamethasone</td>
<td>Salmeterol</td>
<td>Loratadine</td>
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<td>Diltiazem</td>
<td>Selegiline</td>
<td>Meperidine</td>
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<td>Dipyriramole</td>
<td>Senna</td>
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<td>Duloxetine</td>
<td>Simvastatin</td>
<td>Methocarbamil</td>
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<td>Enalapril</td>
<td>Spironolactone</td>
<td>Morphine</td>
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<td></td>
<td>Fluticasone</td>
<td>Tamoxifen</td>
<td>Oxcarbazepine</td>
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<td></td>
<td>Gemfibrozil</td>
<td>Terbutaline</td>
<td>Oxycodone</td>
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<td>Gentamicin</td>
<td>Timolol</td>
<td>Prochlorperazine</td>
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<td></td>
<td>Hydrochlorothiazide</td>
<td>Topiramate</td>
<td>Ranitidine</td>
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<td></td>
<td>Hydrocortisone</td>
<td>Trimethoprim</td>
<td>Theophylline</td>
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<td></td>
<td>Ibuprofen</td>
<td>Valproate</td>
<td>Tramadol</td>
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<td></td>
<td>Insulin</td>
<td>Verapamil</td>
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<td></td>
<td>Isosorbide mononitrate</td>
<td>Warfarin</td>
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<td></td>
<td>Ketoprofen</td>
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Anticholinergic drugs

- Cumulative risk of:
  - cognitive impairment + mortality
- “Anticholinergic Cognitive Burden (ACB)” (0-3)
- For each 1 point increase in the ACB
  - a decline in MMSE of 0.33 points over 2 years
  - 26% increase in the risk of death
- Keep ACB to minimum
- Avoid anticholinergic drugs where possible

Urinary Incontinence and bladder anticholinergics

• AChEI- ↑ risk of being on anticholinergic drug
• Opposing actions of drugs - functional decline
• Muscarinic receptors $M_1 - M_5$
• $M_3$ receptors located at neuromuscular junctions in the human bladder detrusor muscle
• $M_1$ receptors, and to lesser extent $M_2$ and $M_4$ receptors in the brain, are involved in cognition and memory
• oxybutynin, tolterodine, fesoterodine and trospium are all non-selective
• Darifenacin selective for $M_3$
• Solifenacin is somewhat selective for $M_3$

Clinical significance of co-administering AChEIs with anticholinergics

- N = 69
- At 2 yrs MMSE scores were significantly worse for pts also receiving anti-cholinergics
The blood-brain barrier

Fig. 1. The histological structure of the blood-brain barrier. Adapted from Francis et al.,[18] 2003 © Cambridge Journals, reproduced with permission.
BBB penetration

- Characteristics of drugs that can pass through BBB

- Small molecules
- Lipid soluble
- Unpolarized

The BBB

• Several conditions can increase the permeability of the BBB:
  – Increasing age
  – Co-morbid disease such as Diabetes, Parkinson’s disease and Alzheimer’s disease, Vascular dementia, Multiple Sclerosis
  – Certain medicines eg Viagra, decongestants
  – Trauma
  – Stress

• As a result the BBB can become “leaky”, allowing compounds through that would not normally be able to penetrate the CNS
Permeability-glycoprotein (P-gp)

• Permeability-glycoprotein (P-gp) is an active CNS efflux transporter which actively pumps agents back into circulation.

• Drugs that are recognised by P-gp are P-gp substrates.

• Darifenacin, Trospium and Fesoterodine are reported to be P-gp substrates.
Structure of the Permeability-glycoprotein (P-gp)

Fig. 2. Representation of the structure and function of the P-glycoprotein efflux pump system. Adapted from Edwards, [71] 2003 © BioMed Central, reproduced with permission.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Muscarinic receptor (M₃:M₁ affinity ratio)</th>
<th>Polarity</th>
<th>Lipophilicity</th>
<th>Molecular weight (kDa)</th>
<th>P-gp substrate</th>
<th>Theoretical ability to cross BBB</th>
<th>Effect on cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>Mainly M₃ (9.3 : 1)</td>
<td>Neutral</td>
<td>High</td>
<td>507.5 (relatively large)</td>
<td>Yes</td>
<td>High (but bladder selective and P-gp substrate)</td>
<td>-</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Non-selective</td>
<td>Neutral</td>
<td>Very low</td>
<td>411.6</td>
<td>Yes</td>
<td>Very low</td>
<td>-</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Non-selective</td>
<td>Neutral</td>
<td>Moderate</td>
<td>357 (relatively small)</td>
<td>No</td>
<td>Moderate/high</td>
<td>+++</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Mainly M₃ (2.5 : 1)</td>
<td>Neutral</td>
<td>Moderate</td>
<td>480.6</td>
<td>No</td>
<td>Moderate</td>
<td>-/+</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Non-selective</td>
<td>Neutral</td>
<td>Low</td>
<td>475.6</td>
<td>No</td>
<td>Low</td>
<td>+</td>
</tr>
<tr>
<td>Trospium Chloride</td>
<td>Non-selective</td>
<td>Positively charged</td>
<td>Not lipophilic</td>
<td>428</td>
<td>Yes</td>
<td>Almost none</td>
<td>-</td>
</tr>
</tbody>
</table>

Taken from The Maudsley Prescribing Guidelines 12th edition (in press)
Drug interactions

• All tertiary amine drugs are metabolised by CYP450 enzymes
  • i.e oxybutynin, tolterodine, fesoterodine and darifenacin
  • CYP450 inhibitors eg erythromycin, fluoxetine can lead to increased serum levels and ADRs
• Metabolism of Trospium is unknown but is not via CYP450 system
Recommendations for treating bladder symptoms in dementia

- 1\textsuperscript{st} line – review bladder anticholinergic, use non-drug measures

- 2\textsuperscript{nd} line: darifenacin (selective and P-gp substrate).
  
  
  trospium (non-selective but poor penetration through BBB, P-gp substrate and no CYP450 function, low risk of interactions)

- 3\textsuperscript{rd} line: solifenacin (somewhat selective but readily penetrates BBB, not P-gp substrate and has potential to cause cognitive impairment).

- Data for fesoterodine is still lacking but it is non-selective, has high central anticholinergic activity but theoretically has low ability to cross BBB
Alpha-blocking agents

• Inhibit the response to sympathetic impulses by blocking the alpha receptor sites of effector organs
• Inhibit the contraction of non-vascular smooth muscle eg at the bladder neck and within prostate
• Commonly used to treat bladder outflow obstruction in men
• Alpha-blockers such as tamsulosin, alfuzosin and prazosin are reported to cause drowsiness, dizziness and depression.
• There is no published literature reporting their effects on cognition and they do not feature on any anticholinergic cognitive burden list (so probably safe in dementia)
Diarrhoea/ constipation

• Loperamide
  – low potency anticholinergic drug
  – cognitive effects have not been investigated
  – no data to suggest worsening of cognitive function
  – may add to anticholinergic cognitive burden

• Laxatives
  – no evidence to suggest negative impact on cognition
  – Since constipation can lead to BPSD, treating it can improve these symptoms in many cases
Anti-emetic

• Hyoscine hydrobromide (Kwells)
  – Scopolamine
  – Centrally acting anticholinergic
  – Lipophilic, penetrates BBB easily
  – **Impairs memory**, speed of processing, disrupts attention
  – Elderly more vulnerable, even at lower doses
    • Confusion, hallucinations
  – Effect on cognition so significant that used in trials to produce memory deficits- to study drugs
    – (The Scopolamine Challenge Test)
Anti-emetics

• Cyclizine- 1\textsuperscript{st} generation antihistamine, weak anticholinergic, \textit{sedative}, penetrates BBB- adds to ACB

• Metoclopramide
  – must be used in caution in elderly patients (D\textsubscript{2} ant)
  – Improbable anticholinergic action (but not known yet)
  – declining hepatic function increases drug exposure, increasing the incidence of \textit{EPSE including TD}
  – Limited data on cognitive function
  – Case reports of prolonged encephalopathy and delirium
Anti-emetics

Prochlorperazine- potent DA antagonist
- Should be avoided in elderly patients with dementia due to risk of EPSE.
- It can cause sedation, hypotension, blurred vision and central nervous system depression.
- It has been associated with increased risk of hospitalisation for hip fracture in elderly patients.

• Domperidone usually doesn’t cross the BBB- but can do so in dementia
  - Case report: induced TD in elderly woman with dementia
Anti-emetics  5HT3 antagonists

- **Cardiovascular warnings** for all - caution in cardiac disease
- Granisetron - insurmountable antagonism of the 5-HT$_3$ receptor over a 24 hour period allowing for od administration
- Metabolism via multiple CYP enzymes including CYP3A and CYP2D6 except granisetron (CYP3A4 only)
- Granisetron drug of choice
- 5HT3 antagonists do not affect cognition negatively
- Study of 232 pts with age associated memory impairment, ondansetron improved some cognitive deficits (neuro tests)
Recommendations

• For people with dementia cyclizine, metoclopramide, and prochlorperazine should not be first line ant-emetics.

• Hyoscine hydrobromide (Kwells) should be avoided

• Domperidone is a good first line choice and 5-HT$_3$ antagonists are also safe to use
Antispasmodics

• Hyoscine Butylbromide (Buscopan)
  – The attachment of the butyl-bromide moiety effectively prevents its movement across the BBB
  – This effectively minimising undesirable CNS side-effects associated with hyoscine.
  – Peripherally acting anticholinergic agent

• Mebeverine and other antipsasmatics-
  – direct intestinal smooth muscle relaxant
  – no effect on cognition

All should be ok in dementia
Hypersalivation

- Oral anticholinergics eg **hyoscine Hbr (Kwells) should be avoided** in the elderly
  - Cognitive impairment
  - Delirium
  - Constipation

- **Pirenzepine**-
  - Relatively selective for $M_1$ and $M_4$ muscarinic receptors
  - Does not cross BBB, **little CNS penetration**

- **Atropine** 1% eye drops used sublingually
  - No data on extent of penetration when used by this route (should be ok in dementia)
Respiratory illness & dementia

- In theory AChEIs can exacerbate asthma/ COPD by inducing bronchoconstriction
- Data is limited and contradictory
- 2 studies- no ↑ risk of adverse pulmonary outcomes (Stephenson et al 2012; Thacker & Schneeweiss 2006)
- 1 French study- significant association with risk of pulmonary diseases including pneumonia, persistent cough, asthma and bronchitis (Helou & Rhalimi 2010)
- Caution in COPD and Asthma - close monitoring recommended
Respiratory Drugs and Dementia

- No evidence to suggest that *inhaled* anticholinergics affect cognitive function
- Poorly absorbed when inhaled
- An RCT comparing ipratropium and theophylline was unable to detect harmful effects of either drug on psychometric tests or performance
- Caution with theophylline
  - Causes N/V as do AChEIs
  - Narrow therapeutic range, metabolised by CYP450
  - Excreted via kidneys
Myasthenia Gravis (MG)

- Caused by antibody-mediated autoimmunity against the nicotinic ACh receptors at the NMJ
- Treatment based on partial restoration of cholinergic balance through AChEIs (e.g. pyridostigmine, neostigmine)
- But these act peripherally, do not cross BBB to minimise unwanted central effects
- No data to support how to manage a patient with AD + MG
- AChEIs in MG act peripherally, AChEIs in AD act centrally
- Combination may add to cholinergic adverse effects eg N/V, diarrhoea, abdominal cramps, increased salivation
- Memantine may be an alternative if AChEIs not tolerated
Pain in dementia

- Common and under-treated (McLachlan et al 2011)
- People with dementia report pain less often (Horgan et al, 1998)
- Pain can worsen cognition (Morrison et al, 2003)
Treating pain in dementia

- NSAIDs cause GI bleeds and fluid retention
- Opiates increase delirium risk 2x
- Codeine and tramadol have unpredictable dose-response
- Tramodol can cause seizures
- Fentanyl patches and long acting opiates risky in opiate naïve patients
How to treat pain in dementia

• Define your target symptom
• Use outcome measures – for pain (e.g. PAIN-AD) and distress (e.g. NPI or CBS)
• Use topical analgesia if appropriate eg NSAID gels
• Have a stepped protocol – for example (Husebo et al 2011):
  1. paracetamol (up to 3g per day)
  2. Morphine (up to 20mg per day)
  3. Buprenorphine patch (max 10mcg per hour)
  4. Pregabalin (max 300mg per day)-if neuropathic pain
Safer opiates in dementia

- **Buprenorphine**- fewer side effects and patch makes administration easier

- **Oxycodone**- short half-life, few drug-drug interactions, predictable dose-response
Antihistamines

- 1st generation H1 blockers (promethazine, chlorpheniramine) cause reduced alertness; 2nd generation ones (cetirizine, loratadine) don’t (Tannenbaum et al 2012)

- Attention and eye-hand coordination most common deficits in healthy volunteers on antihistamines (Van et al, 2010)

- Trend towards increased risk of delirium with antihistamines (Clegg and Young 2011)
Antihistamines

- The older second generation H1 blockers (terfenadine and astemizole) have been withdrawn due to cardiac risk, the newer ones are safe
Antihistamines: recommendations

- Avoid first generation drugs - chlorpheniramine, clemastine, promethazine, cyclizine, cyproheptadine, hydroxyzine
- Second generation drugs are safe - loratadine, fexofenadine, cetirizine
- BNF defines which are sedative and non-sedative
Statins

- No benefit on cognitive function, but no evidence that they are detrimental either (Mc Guinness et al 2013)
- Case reports of subjective memory impairment (Wagstaff et al 2003)
- Simvastatin most likely to cross BBB
- So- use if indicated to treat hyperlipidaemia- but no evidence that they reduce rate of cognitive decline
Digoxin

- Multiple effects on brain, alters catecholamine transport
- Confusional states can occur even with therapeutic drug concentrations
- No evidence that digoxin is a risk factor for delirium (Clegg and Young, 2011)
- Can cause nightmares (Brezis et al, 1980)
- Improves cognitive function in 25% of people with heart failure (Laudisio et al, 2009)
Hypertension in dementia

- Hypertension increases risk of dementia and treating it improves cognition (Duron et al, 2010)

- But no evidence that treating high blood pressure in established dementia improves cognitive or cardiovascular outcomes (Beishon at al, 2013)

- Blood pressure falls as dementia progresses (Qiu et al, 2005)
Anti-hypertensive treatment in dementia

- Calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers all have a beneficial effect on cognition in longitudinal studies.

- ARBs may be more effective in reducing cognitive decline - may reduce amyloid deposition.

- Memory and attention improve more than language impairments, suggesting subcortical perfusion improvements (Marpillat et al, 2013).

- Anti-hypertensives have complex actions on brain other than reducing blood pressure (Duron et al, 2010).

- Link between low blood pressure and orthostatic hypertension and cognitive impairment in the very old (Qiu et al 2005).
Summary

- Avoid polypharmacy
- Stop anything unnecessary
- If you are starting a drug monitor response and stop if no use
- Avoid anti-cholinergic and sedative drugs where possible
- Chose drugs with least central effects
Thank You

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