Adapting Prescribing for Symptom Management in Dementia

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Consultant – St Catherine’s Hospice
Outline

- Context & prevalence
- Why adapt prescribing in dementia?
- The brainy bits
- Prescribing pitfalls & principles
- Anticipated symptoms & adapting prescribing
• Prevalence of dementia
  – 815,000 in UK (2013)
  – 42,000 under 65y (2013)
• Affects 1 in 6 over 80y
• Two thirds live at home and one third in care home setting, with increasing move to care home setting as disease progresses
• 80% care home residents have dementia or significant cognitive impairment
• Approx 60,000 deaths annually attributed to dementia
## Prevalence of dementia & symptom clusters

### (McKeith & Cummings 2005)

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimers</td>
<td>67%</td>
<td>Apathy, agitation, anxiety, depression</td>
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<tr>
<td>Vascular</td>
<td>17%</td>
<td>Behavioural disturbance (delusions &amp; hallucinations less common)</td>
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<tr>
<td>Mixed</td>
<td>10%</td>
<td>Apathy, depression, delusions, emotional lability. BPSD higher than AD. Increased dyspraxia and falls</td>
</tr>
<tr>
<td>Lewy body</td>
<td>4%</td>
<td>Visual hallucinations, delusions, depression, sleep disturbance (REM sleep-behaviour disorder)</td>
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<tr>
<td>Parkinson’s</td>
<td>2%</td>
<td>Apathy, disinhibition</td>
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<tr>
<td>Frontotemporal</td>
<td>2%</td>
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</tr>
</tbody>
</table>
Prevalence of BPSD in advanced dementia

BPSD very common ~ 85% have some aspect in advanced dementia

- Agitation / aggression 50%
- Depression 45%
- Withdrawal / lethargy 41%
Prevalence of multi-morbidities in >75y (Barnett et al 2012)

- Hypertension 61.9%
- Ischaemic heart disease 31.2%
- Pain 23.6%
- CKD 18.5%
- Depression
- Diabetes & thyroid disease
- COPD
- Hearing & visual impairment

Dementia

- Vascular diseases – cardiac arrythmias or failure, multiple CVA
- Parkinson’s disease & other neurological conditions (MS, MND, PSP, corticobasal syndrome)
Factors to consider

- Dementia as one of several co-morbidities
- Frailty & complex psychosocial context
- Challenges of assessment
- Safe drug administration
- Consent & decision making
Pharmacological Factors to consider

Altered organ function affects pharmaco-kinetics

- Reduced liver size 25-35%, reduced hepatic blood flow 40%, affecting first pass metabolism & drug clearance

- GFR affected by ageing & vascular diseases. By age 70 ~40% reduction in nephrons

- Weight loss, malnutrition & relative dehydration > reduce vol of distribution > higher serum conc for water sol drugs (Warfarin, Alcohol)

- Obesity – increased vol of distribution for lipophilic drugs (Diazepam, Amitryptiline)
Other factors to consider

• Vulnerability to adverse drug effects:
  – Frailty & falls risk
  – Cognitive impairment lowers threshold for sedation & delirium
  – Impaired baroreceptor response > greater risk of postural hypotension

• Polypharmacy (>$5$ drugs) and adverse drug events

• Guidelines written assuming single disease states & therefore need adjusting for multi-morbidities
Brief neurochemistry next...

To make sense of the drugs
Acetyl Choline

- Cholinergic neurones relax vascular tone and improve blood flow.
- Higher levels Ach correlate to better MMSE scores
- AD – Generalised loss Ach receptors assoc with greater tangles and cognitive impairment
- Reduced cholinergic activity post stoke may cause impaired function in VascD
- DLB – Ach loss > AD

- Treatments: Cholinesterase inhibitors increase Ach available at receptors
Brief neurochemistry of dementia

Serotonin
• Important in controlling mood, aggression, behaviour and memory
• Reduced levels found in VascD, FTD & AD (although increased 5HT receptors in AD)

Dopamine (D1-5, D2 most important)
• Reduced Dopamine receptors in PDD and DLB, probably explains reduced response to dopaminergic drugs
• Reduced DA may account for dyspraxic gait in Vasc D
• Reduced in FTD > apathy, rigidity & flattened affect
Glutamate & GABA

- Glutamate main excitatory neurotransmitter
- Important in stimulating processes, learning & memory
- Vasc D - reduced in brain tissue post CVA
- AD - both excess and too little glutamate at different times

- Memantine stimulates Glutamate transmission;
- now recommended for the treatment of core or associated symptoms in people with moderate dementia (NICE guidance 2011)
Jane, 84, Advanced dementia (mixed)
Hypertension, previous MI, AF, Osteoporosis & OA hip

- PS 4, Increased tone with foot drop
- Pressure sore on hip (G2)
- Limited oral intake
- Tendency to constipation
- Poor sleep
- Variable taking meds
- Agitated and calling out repeatedly
Prescribing hazards – which drugs might be problematic?

**Medication**
- Bisprolol
- Warfarin
- Ramipril
- Statin
- Baclofen
- Trazodone
- Lactulose
- Tramadol
- Zopiclone

**PRN:** Paracetamol, Oramorph, Lorazepam, Haloperidol
Which drugs might cause problems?

The Good guys
- Bisoprolol
- Paracetamol

Needs improving
- Lactulose,
- Oramorph,

Trouble
- Warfarin
- Ramipril
- Baclofen
- Trazodone
- Lorazepam
- Haloperidol
- Tramadol
- Zopiclone

why am I here?
- Statin
Prescribing hazards
Polypharmacy

- Substantial evidence that >5 drugs increases risk of ADR, delirium, falls etc and further inc risk in dementia
- Particular drug groups increase risk, many used in management of chronic conditions and palliative care
  - Opioids
  - Benzodiazepines
  - Neuroleptics
  - Anticholinergics
  - Antihistamines
Prescribing hazards
Polypharmacy

**Medications that increase the risk of delirium**

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Odds Ratio</th>
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</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>2.5</td>
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<tr>
<td>Benzodiazepines</td>
<td>3</td>
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<tr>
<td>Calcium channel blocker</td>
<td>2.4</td>
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<tr>
<td>Antihistamines</td>
<td>1.8</td>
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</tbody>
</table>

Davies & Mahoney, Br J Clin Pharmacol / 80:4 / 799
Prescribing hazards
Anticholinergic burden

• Elderly people, particularly those with dementia, sensitive to adverse anticholinergic drug effects
• Often manifests as symptoms of delirium
• Higher risks in dementia due to polypharmacy prescribing for co-morbidities
• Study in Australia community patients 2015:
  – ~60% dementia & 40% non-dementia patients receiving anticholinergic drugs (Mate 2015)
• Importance in considering prescribing for this patient group, particularly for agitation, nausea, pain
Table 1: Commonly used medicines with anticholinergic effects in older veterans\textsuperscript{12,18}

<table>
<thead>
<tr>
<th></th>
<th>Antipsychotics</th>
<th>Antidepressants</th>
<th>Bladder antispasmodics</th>
<th>Antihistamines</th>
<th>Opioids</th>
<th>Inhaled medicines</th>
<th>Other medicines</th>
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</thead>
<tbody>
<tr>
<td><strong>Higher anticholinergic effects</strong></td>
<td>chlorpromazine</td>
<td>amitriptyline</td>
<td>darifenacin*</td>
<td>cyproheptadine</td>
<td>tapentadol</td>
<td>aclidinium</td>
<td>benztrapine</td>
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<td></td>
<td>clozapine</td>
<td>clomipramine</td>
<td>oxybutynin</td>
<td>promethazine</td>
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<td>doxepin</td>
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<td>ipratropium</td>
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<td>imipramine</td>
<td>solifenacin*</td>
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<td>tiotropium</td>
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<td></td>
<td></td>
<td>nortriptyline</td>
<td>tolterodine*</td>
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<tr>
<td><strong>Lower anticholinergic effects</strong></td>
<td>haloperidol</td>
<td>citalopram</td>
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<td>fluoxetine</td>
<td>fexofenadine</td>
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<td>olanzapine</td>
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<td>theophylline</td>
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Note: The list of medicines is based on Duran et al.'s 2013 Systematic review of anticholinergic risk scales in older adults (reviewing 7 studies, one of which was Australian), the Australian Medicines Handbook, Martindale: The Complete Drug Reference and expert opinion.

Note: *these medicines are not available on the PBS/RPBS
## Drugs on the Anticholinergic Burden (ACB) scale

(A total ACB scale score of three or more is considered clinically relevant)

<table>
<thead>
<tr>
<th>ACB Score 1 (mild)</th>
<th>ACB Score 2 (moderate)</th>
<th>ACB Score 3 (severe)</th>
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</thead>
<tbody>
<tr>
<td>Alimemazine</td>
<td>Amantadine</td>
<td>Amitriptyline</td>
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<tr>
<td>Alprazolam</td>
<td>Belladonna alkaloids</td>
<td>Amoxapine</td>
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<td>Alverine</td>
<td>Carbamazepine</td>
<td>Atropine</td>
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<tr>
<td>Atenolol</td>
<td>Cyclobenzaprine</td>
<td>Benztrpine</td>
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<tr>
<td>Beclometasone dipropionate</td>
<td>Cyproleptadine</td>
<td>Chlorpheniramine</td>
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<tr>
<td>Bupropion hydrochloride</td>
<td>Loxapine</td>
<td>Chlorpromazine</td>
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<tr>
<td>Captoril</td>
<td>Meperidine</td>
<td>Clemastine</td>
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<tr>
<td>Chloralhydrate</td>
<td>Methotrimeprazine</td>
<td>Clomipramine</td>
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<tr>
<td>Cimetidine hydrochloride</td>
<td>Molindone</td>
<td>Clozapine</td>
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<tr>
<td>Clorazepate</td>
<td>Oxcarbazepine</td>
<td>Darifenacin</td>
</tr>
<tr>
<td>Codeine</td>
<td>Pethidine hydrochloride</td>
<td>Desipramine</td>
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<tr>
<td>Colchicine</td>
<td>Pimozide</td>
<td>Dicyclomine</td>
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<tr>
<td>Dextropropoxyphene</td>
<td></td>
<td>Diphenhydramine</td>
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<td>Diazepam</td>
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<td>Doxepin</td>
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<td>Digoxin</td>
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<td>Flavoxate</td>
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<td>Dipyridamole</td>
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<td>Hydroxyazine</td>
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<td>Disopyramide phosphate</td>
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<td>Hyoscymine</td>
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<td>Fentanyl</td>
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<td>Imipramine</td>
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<td>Fluvoxamine</td>
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<td>Mediclazine</td>
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<td>Furosemide</td>
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<td>Nortriptyline</td>
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<td>Haloperidol</td>
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<td>Orphenadrine</td>
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<td>Hyaluridine</td>
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<td>Oxybutynin</td>
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<td>Hydrocortisone</td>
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<td>Paroxetine</td>
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<td>Isosorbide preparations</td>
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<td>Loperamide</td>
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<td>Procyclidine</td>
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<td>Metoprolol</td>
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<td>Promazine</td>
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<td>Morphine</td>
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<td>Nifedipine</td>
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<td>Propentheline</td>
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<td>Prednisone/Prednisolone</td>
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<td>Pyrimidine</td>
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<td>Quinidine</td>
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<td>Scopolamine</td>
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<tr>
<td>Ranitidine</td>
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<td>Thiortazone (withdrawn)</td>
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<td>Toterodine</td>
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<td>Timolol maleate</td>
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<td>Trifluoperazine</td>
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<tr>
<td>Trazodone</td>
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<td>Trihexyphenidyl</td>
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<tr>
<td>Triamterene</td>
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<td>Trimipramine</td>
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<tr>
<td>Warfarin</td>
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</table>
• Increased falls, sedation, EPS, CVA and death from all causes (Ballard 2006)
• Up to 60% patient with DLB develop EPS toxicity

• ‘Time for Action’, (Banerjee 2009) highlighted neuroleptic prescribing in Dementia, questioned benefits; recommended significant reduction & use of non-pharmacological measures for BPSD
• National Dementia and anti-psychotic prescribing audit 2012: 51.8% reduction 2008>2010.

• Inappropriate prescribing still likely - need caution and clear rationale for use
Prescribing hazards neuroleptics

- Atypicals – some benefit in aggression & psychosis in AD, however evidence of inc risk of CVA (Risperidone) and prolonged QT (Olanzapine)

- Haloperidol – some benefit in aggression but EPS limits use (SIGN 2006)

- Trazodone – insufficient evidence for aggression; may be useful for agitation associated with depression (SIGN 2006)
7 steps (Polypharmacy, NHS Scotland)
1. Identify aims and objectives of drug therapy.
2. Identify essential drug therapy.
3. Does the patient take unnecessary drug therapy?
4. Are therapeutic objectives being achieved?
5. Is the patient at risk of ADRs or suffering actual ADRs?
6. Is drug therapy cost-effective?
7. Is the patient willing and able to take drug therapy as intended?

STOPP/START criteria
STOPP 65 clinical criteria for potentially inappropriate prescribing in older people, emphasizes potential adverse drug-drug interaction and duplicate drug class prescriptions

BEERS criteria – less helpful as focused on US medications and prescribing (overlaps with STOPP)
Neuroleptics

- Stop if dementia with cardiac or cerebrovascular risk—risk of CVA
- Review if being used for BPSD as limited benefit—use non-drug measures
- Continue if co-morbid psychosis, psychotic depression or bipolar disorder—seek specialist advice

- Low dose—stop without tapering
- Otherwise slow reduction by 25%, review after 1 wk for withdrawal symptoms (N&V, anxiety, agitation, insomnia). If occur consider tapering by 10% steps
- After 4 weeks further 25% reduction etc
Benzodiazepines
Slow taper to avoid withdrawal – 10% reduction every 1-2 wk
Consider switch to Diazepam to manage tapering if:
• Dose/preparation doesn’t enable small reductions
• Short-acting BZD (Lorazepam, Alprazolam)

Seek specialist advice if
• History of alcohol or other drug dependence, severe mental health illness
• Previous withdrawal seizures
• Significant hepatic dysfunction
Medicine ‘Sick day Rules’ (Polypharmacy Guidance 2015)

Medicines to stop temporarily if sickness causing dehydration (vomiting, sweating, fever) to avoid acute kidney injury

- ACE inhibitors, ARB
- NSAID
- Diuretics
- Metformin
- Stop while symptoms troublesome (24-72 hrs) and then re-start if appropriate

How often do we do this or advise care homes to do so?
Review patients with deteriorating oral intake from dementia
Pain management in dementia

- Pain common (~50%), due to co-morbidities, impaired mobility and frailty (Rodger et al 2015)
- Under-diagnosed and under-treated due to staff awareness, assessment skills and patient inability to communicate effectively
- Common cause of aggression & agitation

**Consensus**

Paracetamol safe
Codeine & compounds – avoid (cognitive s/e, constipation)
NSAIDs – avoid if possible otherwise caution +++
Tramadol – avoid > delirium
Pain management in dementia

**Opioids**
- Start lower doses (e.g., Morphine 1.25-2.5mg) & titrate with caution
- General prescribing principles same for Morphine & Oxycodone depending on renal function
- Watch for s/e & anticholinergic burden
- Butrans TD – advantage due to lower dose & administration
- Fentanyl TD – generally too high to start with

**Neuropathic pain**
Lidocaine TD – generally well tolerated
TCA – avoid due to ACB
Pregabalin generally prescribed > Gabapentin - caution due to sedation & confusion
Nausea

Nightmare!!
Eliminate potential causes
Consider metabolic, drug related, physical causes

Domperidone
or
Hobson’s choice of least worst option & constraints of administration.
Keep lower doses eg metoclopramide 30mg max
BPSD- Agitation and aggression

- Look for triggers and causes
- Prioritise non drug measures

**Agitation**
- Depression – consider SSRI (Escitalopram lower s/e) or Mirtazepine
- Anxiety – non drug measures
  At least 30% can stop without relapse

**Aggression**
- Weak evidence of benefit with atypicals in AD.
- Risperidone 2mg od is only licensed atypical for BPSD
- Haloperidol NNT 4-5 so caution due to ADR

- Avoid neuroleptics in DLB (less response & greater ADR) – seek advice
Sleep disorder

- Very little evidence for medication being effective in dementia
- Melatonin – no evidence
- Benzo & ‘z’ drugs – avoid
  (Case reports of Clonazepam low dose)
- Mirtazapine may help but insufficient evidence

- Best approach is non-drug measures
Seizures relatively common in advanced dementia
Tend to respond well to pharmacological management

Acute management – as usual (Lorazepam or Midazolam)

Preventative
• Some evidence that newer agents better tolerated (eg levotiracetam oral / sc preps)
• Avoid valproate, phenytoin and carbamazepine due to ADR, interactions and pharmaco-kinetics

(Sivaraaman & Vajiala 2015)
In summary

- Principles of assessment and tailored prescribing the same
- Caution required due to complex pharmacology and co-morbidities
- Use non-drug measures wherever possible

In essence
- Don’t prescribe unless essential
- Stop more drugs than you start
- Avoid Benzodiazepines, neuroleptics and anticholinergics as far as possible
Any questions?


Davies EA, O'Mahoney, MS. Adverse Drug Reactions in special populations – the elderly. Br J Clin Pharmacol 2015; 80:4 796-807

Mate, K et al Impact of multiple low-level anticholinergic medications on anticholinergic load of community-dwelling elderly with and without dementia. Drugs Aging. 2015 Feb;32(2):159-67. doi: 10.1007/s40266-014-0230-0

• National Dementia and anti-psychotic prescribing audit 2012. [www.ic.nhs.uk/dementiaaudit](http://www.ic.nhs.uk/dementiaaudit)
• Veterans’ Medicines Advice and Therapeutics Education Services; Topic 39 Thinking clearly about anti-cholinergic burden 2014
• Sivaraaman K, Vajiala VS, Seizures in setting of dementia. Curr Treat Options Neurol. 2015 Apr;17(4):342