



Care
Compassion
Understanding

Adapting Prescribing for Symptom Management in Dementia

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Outline



- Context & prevalence
- Why adapt prescribing in dementia?
- The brainy bits
- Prescribing pitfalls & principles
- Anticipated symptoms & adapting prescribing

Context (Alheimers Society)



- 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 (Alz Soc) & symptom clusters (McKeith & Cummings 2005)



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- Alzheimers 67%
- Vascular 17%
- Mixed 10%
- Lewy body 4%
- Parkinson's 2%
- Frontotemporal 2%
- Apathy, agitation, anxiety, depression
- Behavioural disturbance (delusions & hallucinations less common)
- Apathy, depression, delusions, emotional lability. BPSD higher than AD. Increased dyspraxia and falls
- Visual hallucinations, delusions, depression, sleep disturbance (REM sleep-behaviour disorder)
- Apathy, disinhibition

Prevalence of BPSD in advanced dementia



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

- Agitation / aggression 50%
- Depression 45%
- Withdrawal / lethargy 41%

Dementia associated with other conditions



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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 arrhythmias 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



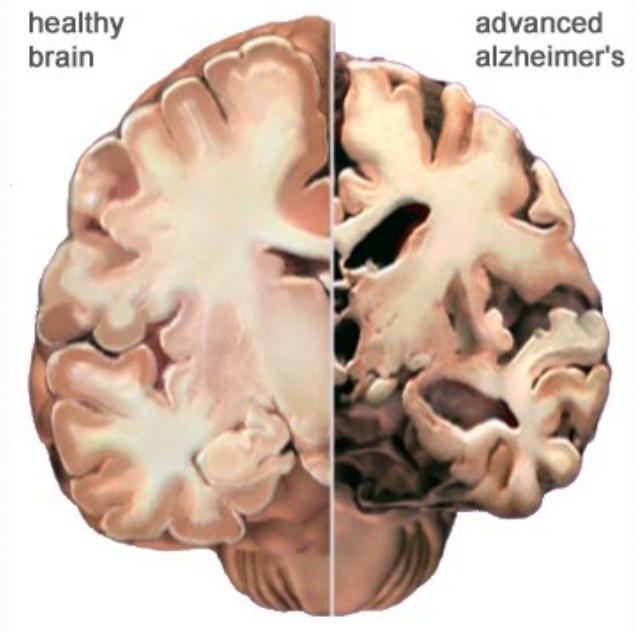
- Vulnerability to adverse drug effects:
 - Frailty & falls risk
 - Cognitive impairment lowers threshold for sedation & delirium
 - Impaired baroreceptor response > greater risk of postural hypotension
- Polypharmacy (>5 drugs) and adverse drug events
- Guidelines written assuming single disease states & therefore need adjusting for multi-morbidities

Brief neurochemistry next...

To make sense of the drugs



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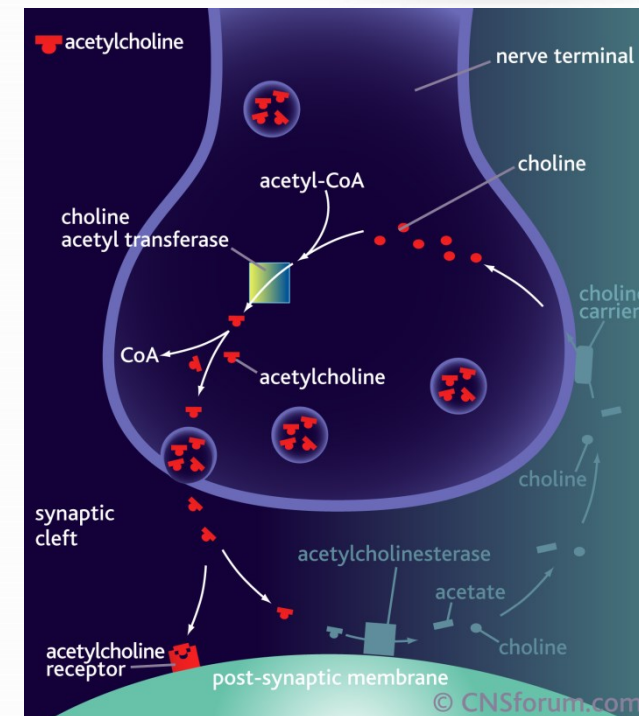
Brief neurochemistry of dementia



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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 stroke may cause impaired function in VascD
- DLB – Ach loss > AD
- Treatments: Cholinesterase inhibitors increase Ach available at receptors



Brief neurochemistry of dementia



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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

Brief neurochemistry of dementia



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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)

Prescribing hazards – common scenario



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?



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Medication

Bisprolol

Warfarin

Ramipril

Statin

Baclofen

Trazodone

Lactulose

Tramadol

Zopiclone



PRN: Paracetamol, Oramorph,
Lorazepam, Haloperidol

Which drugs might cause problems?



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The Good guys

Bisoprolol
Paracetamol

Needs
improving

Lactulose,
Oramorph,

why am I
here?

Statin

Trouble

Warfarin
Ramipril
Baclofen
Trazodone
Lorazepam
Haloperidol
Tramadol
Zopiclone

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

<u>Medication class</u>	<u>Odds Ratio</u>
Opioids	2.5
Benzodiazepines	3
Calcium channel blocker	2.4
Antihistamines	1.8

Davies & Mahoney, Br J Clin Pharmacol / 80:4 / 799

Prescribing hazards

Anticholinergic burden



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- 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

the effects of the anticholinergic medicine may be magnified.¹²

Table 1: Commonly used medicines with anticholinergic effects in older veterans^{12, 16}

	Antipsychotics	Antidepressants	Bladder antispasmodics	Antihistamines	Opioids	Inhaled medicines	Other medicines
Higher anticholinergic effects	chlorpromazine clozapine trifluoperazine	amitriptyline clomipramine dothiepin doxepin imipramine nortriptyline	darifenacin* oxybutynin propantheline solifenacin* tolterodine*	cyproheptadine promethazine	tapentadol	aclidinium glycopyrronium ipratropium tiotropium	benztropine homatropine
Lower anticholinergic effects	haloperidol lithium carbonate olanzapine prochlorperazine quetiapine risperidone	citalopram fluoxetine fluvoxamine mirtazapine paroxetine		cetirizine fexofenadine loratadine	codeine fentanyl methadone morphine oxycodone tramadol		alprazolam amantadine baclofen carbamazepine clonazepam colchicine diazepam digoxin disopyramide domperidone entacapone frusemide loperamide metoclopramide ranitidine temazepam theophylline

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)

ACB Score 1 (mild)	ACB Score 2 (moderate)	ACB Score 3 (severe)
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Belladonna alkaloids	Amoxapine
Alverine	Carbamazepine	Atropine
Atenolol	Cyclobenzaprine	Benztropine
Beclometasone dipropionate	Cyproheptadine	Chlorpheniramine
Bupropion hydrochloride	Loxapine	Chlorpromazine
Captopril	Meperidine	Clemastine
Chlorthalidone	Methotrimeprazine	Clomipramine
Cimetidine hydrochloride	Molindone	Clozapine
Clorazepate	Oxcarbazepine	Darifenacin
Codeine	Pethidine hydrochloride	Desipramine
Colchicine	Pimozide	Dicyclomine
Dextropropoxyphene		Diphenhydramine
Diazepam		Doxepin
Digoxin		Flavoxate
Dipyridamole		Hydroxyzine
Disopyramide phosphate		Hyoscyamine
Fentanyl		Imipramine
Fluvoxamine		Meclizine
Furosemide		Nortriptyline
Haloperidol		Orphenadrine
Hydralazine		Oxybutynin
Hydrocortisone		Paroxetine
Isosorbide preparations		Perphenazine
Loperamide		Procyclidine
Metoprolol		Promazine
Morphine		Promethazine
Nifedipine		Propentheline
Prednisone/Prednisolone		Pyrilamine
Quinidine		Scopolamine
Ranitidine		Thioridazine (withdrawn)
Theophylline		Tolterodine
Timolol maleate		Trifluoperazine
Trazodone		Trihexyphenidyl
Triamterene		Trimipramine
Warfarin		

Prescribing hazards

Neuroleptics



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- 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



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- 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)

Principles for prioritising medication



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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)

Stopping meds – how quickly

(Polypharmacy Guidance 2015)



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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

Stopping meds – how quickly

(Polypharmacy Guidance 2015)



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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)



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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



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- 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



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Opioids

- Start lower doses (eg 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



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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



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- Look for triggers and causes
- Prioritise non drug measures

Agitation

- + Depression – consider SSRI (Escitalopram lower s/e) or Mirtazepine
- + Anxiety – non drug measures
- + paranoid features – atypical neuroleptic. Review after 6 & 12 weeks.
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



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

- Best approach is non-drug measures

Seizures



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 & Vajjala 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



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Any questions?

References



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- Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research and medical education: a cross sectional study. *Lancet* 2012; 380:37
- McLean G, Gunn J, Wyke S, Guthrie B, Watt GC, Blane DN, Mercer SW. The influence of socioeconomic deprivation on multimorbidity at different ages: a cross-sectional study. *Br J Gen Pract* 2014; 64: 440-7
- 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
- Scottish Intercollegiate Guidelines network, Management of people with Dementia, 86. <http://www.sign.ac.uk/pdf/sign86.pdf>

References



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- Ballard CG, Waite J, Birks J. Atypical antipsychotics for aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev 2006; (1): CD003476.
- Banerjee S. The use of antipsychotic medication for people with dementia: time for action. A Report for the Minister of State for Care Services by Professor Sube Banerjee. London: Stationary Office, 2009
- National Dementia and anti-psychotic prescribing audit 2012. www.ic.nhs.uk/dementiaaudit
- Polypharmacy Guidance 2015, NHS Scotland
http://www.sign.ac.uk/pdf/polypharmacy_guidance.pdf
- Veterans' Medicines Advice and Therapeutics Education Services; Topic 39 Thinking clearly about anti-cholinergic burden 2014
- Kirsty TM Rodger et al, Expert opinion on the management of pain in hospitalised older patients with cognitive impairment: mixed method analysis of a national survey. BMC Geriatr. 2015; 15:56
- Sivaraaman K, Vajjala VS, Seizures in setting of dementia. Curr Treat Options Neurol. 2015 Apr;17(4):342