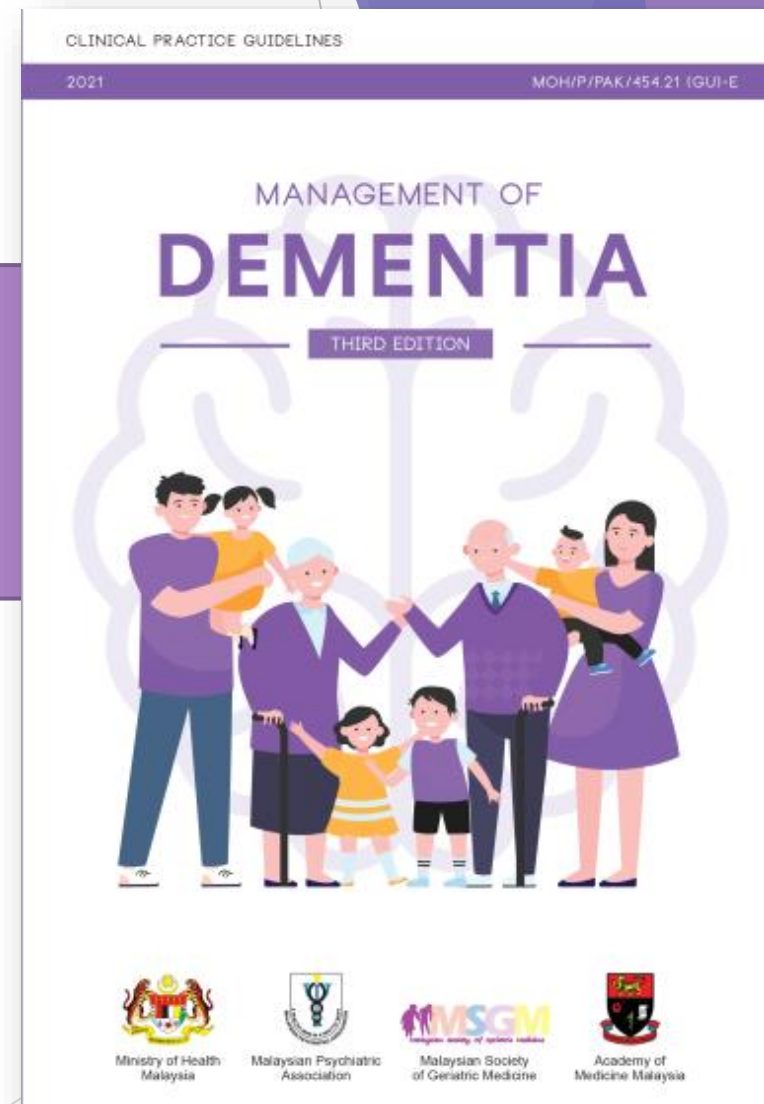


Training of Core Trainers CPG Management of Dementia (Third Edition)

Pharmacological Treatment

By:
Mr. Rajeswaran A/L Ramalingam
Pegawai Farmasi
Hospital Kuala Lumpur

Dr. Chan Yee Fai
Geriatric Psychiatrist
Hospital Kuala Lumpur



Learning Objectives

1. To understand the efficacy & tolerability of various pharmacological agents in the management of people with dementia (PWD)



Introduction

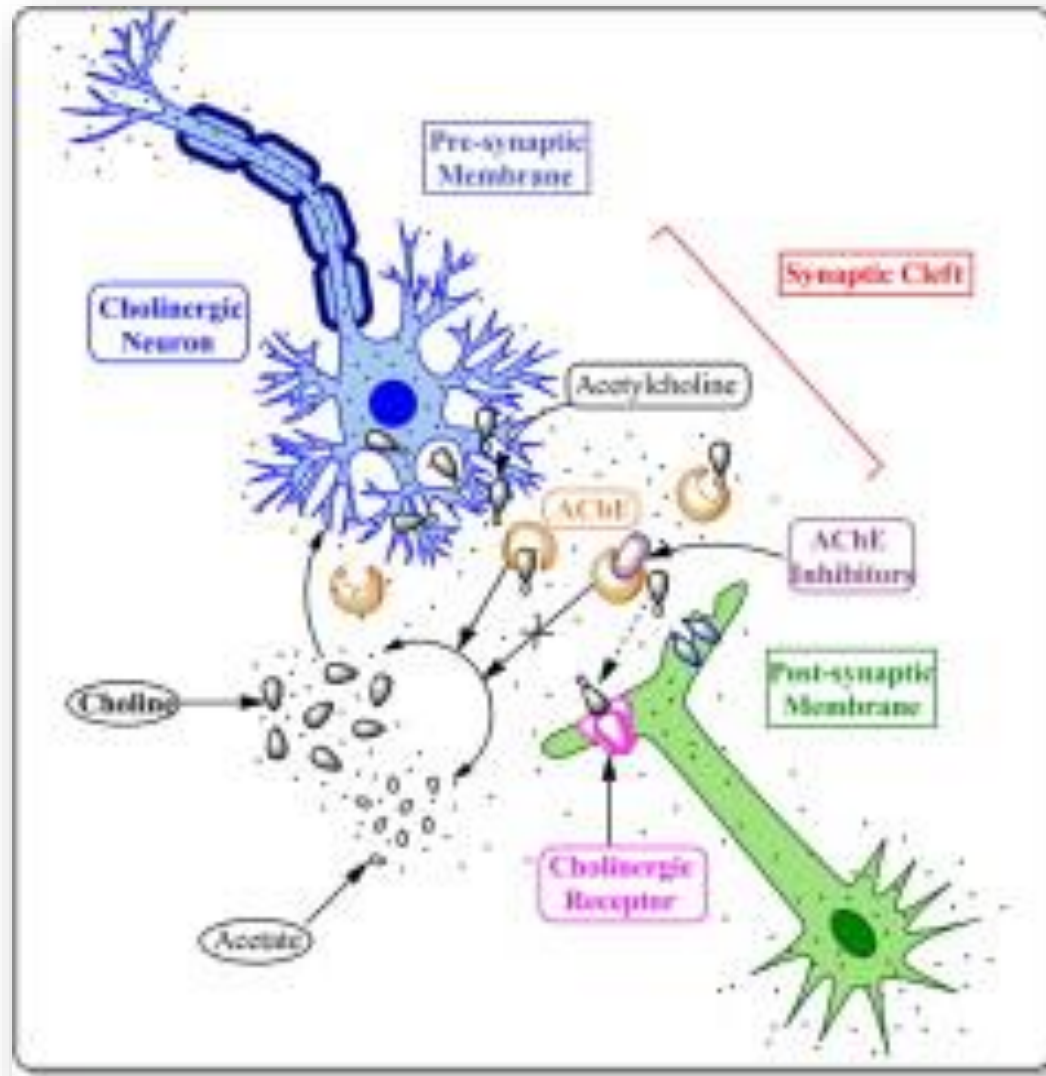
- ▶ No new drug licensed since CPG Dementia 2nd ED. 2009
- ▶ Acetylcholinesterase Inhibitors (AChEI) (**donepezil**, galantamine **and rivastigmine**)
- ▶ N-methyl-D-aspartate (NMDA) receptor antagonist (**memantine**)



Glimpse at MOH Formulary

- ▶ Donepezil
 - Alzheimer's Dementia
- ▶ Rivastigmine
 - Alzheimer's Dementia
 - Parkinson's Disease Dementia
- ▶ Memantine
 - Alzheimer's Dementia





Source: Singh M, Kaur M, Kukreja H, et al. Acetylcholinesterase inhibitors as Alzheimer therapy: from nerve toxins to neuroprotection. *Eur J Med Chem.* 2013;70:165-88. Available at: <https://www.sciencedirect.com/science/article/pii/S0223523413006314>



Considerations

- ▶ Available pharmacological treatment for dementia is not curative; however, they are aimed at managing symptoms (cognitive, noncognitive and behavioral), improve independence and preserve function.⁴²
- ▶ For those who require regular medication, the '3T' approach is a good practice
 - Specific target symptom
 - Start low and titrate
 - Time limited

42. National Institute for Health and Care Excellence (NICE). Dementia: assessment, management and support for people living with dementia and their carers. London: NICE; 2018.



Alzheimer's Disease - Donepezil

- ▶ All severity⁷⁵, level I
 - 10mg > placebo at 24 - 26 weeks on MMSE (MD=1.05, 95% CI 0.73 to 1.37)
- ▶ Mild to moderate⁷⁵, level I
 - 10mg > placebo 24 - 26 weeks on ADAS-Cog (MD= -2.67, 95% CI -3.31 to -2.02)
 - 5mg > placebo 12 - 24 weeks on MMSE (MD=1.22, 95% CI 0.54 to 1.90)
- ▶ Severe⁷⁵, level I
 - 10mg > placebo on SIB (MD=5.92, 95% CI 4.53 to 7.31)
 - 5mg = 10mg at 24 weeks on MMSE and SIB
 - 10mg > 5mg at 24 weeks on ADAS-cog (MD=-1.05, 95% CI -1.80 to -0.30)

75. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. The Cochrane database of systematic reviews. 2018;6(6):CD001190.



Alzheimer's Disease - Donepezil-2

► Safety⁷⁵, level I

- Donepezil 5mg = placebo at 24 weeks
- Donepezil 10mg > 5mg 26 weeks (OR=1.56, 95% CI 1.07 to 2.28) & placebo 24 weeks (OR=1.59, 95% CI 1.23 to 2.05)
- mild AEs namely nausea, vomiting and diarrhea



Alzheimer's Disease - Rivastigmine

- ▶ Mild to moderate^{76, level I}
 - 6 to 12 mg/day twice daily or 9.5 mg/day patch > placebo at 26 weeks on MMSE (WMD=0.74, 95% CI 0.52 to 0.97)
 - ADAS-Cog test score (WMD= -1.79, 95%CI -2.21 to -1.37)
- ▶ Capsules (given BD) > placebo at 26 weeks on MMSE for:^{76, level I}
 - 1 - 4 mg/day (WMD=0.43, 95% CI 0.08 to 0.78)
 - 6 - 12 mg/day (WMD=0.82, 95% CI 0.56 to 1.08)
- ▶ Rivastigmine patch > placebo at 24 weeks on MMSE for:^{76, level I}
 - 20 cm² (17.4 mg/day) patch (MD=0.90, 95% CI 0.32 to 1.48)
 - 10 cm² (9.5 mg/day) patch (WMD=0.64, 95% CI 0.26 to 1.02)
- ▶ Rivastigmine 5 cm² (4.6 mg/day) patch = placebo at 24 weeks^{76, level I}



Alzheimer's Disease - Rivastigmine-2

- ▶ Rivastigmine 10 cm² (9.5 mg/day) patch = 6 to 12 mg/day twice daily capsules showed in MMSE at 24 weeks⁷⁶, level I
- ▶ An RCT found Rivastigmine 13.3 mg/24h patch >4.6 mg/24h patch in severe AD on SIB at 24weeks and ADAS-CGIC but no difference in NPI⁷⁷

76. Birks JS, Grimley Evans J. Rivastigmine for Alzheimer's disease. The Cochrane database of systematic reviews. 2015(4):CD001191.

77. Farlow MR, Grossberg GT, Sadowsky CH, et al. A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia. CNS neuroscience & therapeutics. 2013;19(10):745-52.



Alzheimer's Disease - Rivastigmine-3

► Safety⁷⁶, level I

- 6 to 12mg/day and 9.5mg/day patch > placebo by at least ONE AE at 26 weeks (OR=2.16, 95% CI 1.82 to 2.57)
- Patch may have fewer AE vs capsules
- 17.4mg/24h (OR=2.28, 95% CI 1.64, 3.16) > 9.5mg/24h (OR=1.63, 95% CI 1.29 to 2.06) > placebo in at least one AE
- AE in 13.3 mg/24 h > 9.5 mg/24 h (75.0% vs 68.2% respectively) but most were mild and decreased over time



Alzheimer's Disease - Galantamine

- ▶ HTA of variable quality evidence found galantamine > placebo:⁷⁴, level I
 - ADAS-Cog 12 - 16 weeks (WMD= -2.39, 95% CI -2.80 to -1.97)
 - ADAS-Cog 21 - 26 weeks (WMD= -2.96, 95% CI -3.41 to -2.51)
 - NPI at 21 - 26 weeks (WMD= -1.46, 95% CI -2.59 to -0.34)
 - Higher AE (mainly GI)
- ▶ Network meta-analysis of moderate quality studies found galantamine 24mg daily > placebo in mild to moderate severity⁷⁹

74. Bond M, Rogers G, Peters J, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. Health technology assessment (Winchester, England). 2012;16(21):1-4
75. Dou KX, Tan MS, Tan CC, et al. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. Alzheimer's research & therapy. 2018;10(1):126.



Alzheimer's Disease - AChEI

- ▶ NICE 2018 recommends AChEI as monotherapy options for mild to moderate severity⁴²



Alzheimer's Disease - Memantine

► Mild

- Cochrane SR found Memantine = placebo based on ADAS-Cog (SMD= -0.03, 95% CI -0.19 to 0.13) and CIBIC+ (SMD=-0.08, 95% CI -0.27 to 0.12)⁸⁰, level I

► Moderate to Severe

- Memantine > placebo on SIB (SMD= -0.27, 95% CI -0.34 to -0.21) and CIBIC+ (SMD= -0.20, 95% CI -0.28 to -0.13)⁸⁰, level I

► NICE recommends monotherapy in

- Moderate disease: if intolerant or Contraindicated to AChEi
- Severe disease

80. McShane R, Westby MJ, Roberts E, et al. Memantine for dementia. The Cochrane database of systematic reviews. 2019;3(3):CD003154



Alzheimer's Disease - Memantine-2

- ▶ Moderate to Severe +/- AChEI ⁸⁰, level I
 - SIB
 - with AChEI (SMD= -0.24, 95% CI -0.33 to -0.14)
 - without AChEI (SMD= -0.33, 95% CI -0.43 to -0.23)
 - CIBIC+
 - with AChEI (SMD= -0.21, 95% CI -0.32 to -0.09)
 - without AChEI (SMD= -0.20, 95% CI -0.30 to -0.10)
- ▶ Safety
 - Memantine = placebo with at least one AE (RR=1.03, 95% CI 1.00 to 1.06)⁸⁰
 - In a meta-analysis, memantine = placebo in: ⁸¹, level I
 - AEs (OR=1.05, 95% CI 0.88 to 1.25)
 - serious AEs (OR=0.89, 95% CI 0.70 to 1.13)
 - mortality (OR=1.03, 95% CI 0.74 to 1.44)

81. Blanco-Silvente L, Capellà D, Garre-Olmo J, et al. Predictors of discontinuation, efficacy, and safety of memantine treatment for Alzheimer's disease: meta-analysis and meta-regression of 18 randomized clinical trials involving 5004 patients. BMC geriatrics. 2018;18(1):168.



Alzheimer's Disease - RECOMMENDATION

Recommendation 7

- Donepezil should be offered in Alzheimer's Disease (AD) of all severity.
 - Rivastigmine is an option in mild to moderate AD.
- Memantine may be considered in moderate to severe AD as monotherapy or in combination with acetylcholinesterase inhibitors.



Vascular Dementia - Donepezil

- ▶ Cognition⁸², level I
 - Donepezil > placebo
 - V-ADAS-cog at 12, 18 and 24 weeks ($p < 0.05$)
 - MMSE at 24 weeks ($p = 0.0301$)
- ▶ Safety⁸², level I
 - Well tolerated; most AE are transient and mild to moderate in severity

82. Román GC, Salloway S, Black SE, et al. Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: differential effects by hippocampal size. Stroke. 2010;41(6):1213-21.



Vascular Dementia - Rivastigmine

► Cognition:⁸³, level I

- Probable VD: Rivastigmine 3 to 12 mg/day > placebo at 24 weeks in MMSE (MD=0.60, 95% CI 0.11 to 1.09)
- Subcortical VD: Rivastigmine 6mg/day = placebo on MMSE
- MCI and CIND: Rivastigmine 3-9mg/day = placebo on ADAS-Cog

► Safety⁸³, level I

- Significantly higher rates of nausea, vomiting, diarrhoea and anorexia in rivastigmine vs placebo

83. Birks J, McGuinness B, Craig D. Rivastigmine for vascular cognitive impairment The Cochrane database of systematic reviews. 2013(5):CD004744.



Vascular Dementia - Memantine

- ▶ Cognition ^{80, level I}
 - Memantine > placebo on ADAS-Cog (MD= -2.15, 95% CI -3.25 to -1.05)
- ▶ Behavioural ^{80, level I}
 - Memantine > placebo on NOSGER (SMD= -0.20, 95% CI -0.37 to -0.03)



Vascular Dementia - All meds

- ▶ Cognition ⁸⁴, level I
 - Donepezil 10 mg/day and rivastigmine 6 mg/day > placebo based on MMSE with MD of 0.84 (95% CI 0.14 to 1.57) and 1.37 (95% CI 0.22 to 2.53)
- ▶ Safety ⁸⁴, level I
 - Derived hierarchy of risk of total AEs
 - donepezil 10 mg > galantamine > donepezil 5 mg > memantine > placebo > rivastigmine

84. Jin BR, Liu HY. Comparative efficacy and safety of cognitive enhancers for treating vascular cognitive impairment: systematic review and Bayesian network meta-analysis. Neural regeneration research. 2019;14(5):805-16



Vascular Dementia - RECOMMENDATIONS

- Patients with vascular dementia with concurrent vascular risk factors should be treated with recommended drugs for the management of the medical problems.¹⁰

Recommendation 8

- Acetylcholinesterase inhibitors or memantine may be considered in vascular dementia.



Lewy Body Disease (Dementia with Lewy Body/Parkinson's Disease Dementia)

► Cognition

- DLB, PDD and CIND-PD: AChEI (rivastigmine and donepezil) > placebo on MMSE (WMD=1.08, 95% CI 0.50 to 1.66)⁸⁵, level I
- DLB, PDD: AChEI (rivastigmine and donepezil) and memantine > placebo on MoCA and MMSE (SMD=0.46, 95% CI 0.36 to 0.55)⁸⁶, level I
- Memantine = placebo on MMSE⁸⁰, level I

► Safety

- Treatment group < control in tolerability (OR=1.64, 95% CI 1.26 to 2.15)⁸⁵, level I and (RR=1.09, 95% CI 1.04 to 1.16)⁸⁶, level I
- Rivastigmine < donepezil and memantine in tolerability

85. Rolinski M, Fox C, Maidment I, et al. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. The Cochrane database of systematic reviews. 2012(3):CD006504.

86. Meng YH, Wang PP, Song YX, et al. Cholinesterase inhibitors and memantine for Parkinson's disease dementia and Lewy body dementia: A meta-analysis. Experimental and therapeutic medicine. 2019;17(3):1611-24.



Lewy Body Disease (Dementia with Lewy Body/Parkinson's Disease Dementia) - RECOMMENDATIONS

Recommendation 9

- Rivastigmine or donepezil may be considered for dementia with Lewy body and Parkinson's disease dementia.



Frontotemporal Dementia

- ▶ Donepezil⁸⁷, level I
 - Low level evidence that discontinuation resulted in reduction in NPI and ZBI scores after 2 weeks
- ▶ Rivastigmine⁸⁷, level I
 - Open label study demonstrated amelioration of behavioural changes after 12 months of treatment in probable FTD
- ▶ Galantamine
 - SR found to be not effective based on FBI, WAB, CGI-S, CGI-I in bvFTD⁸⁸, level I
 - Not associated with improvements in psychiatric symptoms in FTD⁸⁷, level I
- ▶ Memantine
 - Memantine = placebo based on CGI, MMSE, NPI, ZBI, CGIC, CIBIC+, MDRS and DAD^{80, 87, 88, 89}, level I

87. Buoli M, Serati M, Caldiroli A, et al. Pharmacological Management of Psychiatric Symptoms in Frontotemporal Dementia: A Systematic Review. *Journal of geriatric psychiatry and neurology*. 2017;30(3):162-9.

88. Nardell M, Tampi RR. Pharmacological treatments for frontotemporal dementias: a systematic review of randomized controlled trials. *American journal of Alzheimer's disease and other dementias*. 2014;29(2):123-32.

89. Kishi T, Matsunaga S, Iwata N. Memantine for the treatment of frontotemporal dementia: a meta-analysis. *Neuropsychiatric disease and treatment*. 2015;11:2883-5.



Frontotemporal Dementia - SAFETY

► Safety

- Galantamine was well tolerated⁸⁸, level I
- Memantine was well tolerated⁸⁰, level I; ⁸⁸, level I; ⁸⁹, level I



Frontotemporal Dementia

- There is insufficient evidence to support the use of AChEI or memantine to patients with FTD.



Behavioural and Psychological Symptoms (BPSD) - Antipsychotics

- ▶ Network Meta Analysis⁹¹, level I
 - Risperidone > placebo in PWD based on CMAI, NPI-A, BEHAVE-AD-A and NBRSA (OR=1.96, 95% CI 1.49 to 2.59)
 - Haloperidol less effective vs all comparators
- ▶ Network Meta Analysis⁹², level I
 - Aripiprazole > placebo in reducing BPSD in PWD on NPI (SMD= -0.17, 95% CI -0.31 to -0.02)
 - Risperidone > placebo in reducing BPSD in PWD on CMAI (SMD= -0.26, 95% CI -0.37 to -0.15)
 - No significant difference between APs

91. Kongpakwattana K, Sawangjit R, Tawankanjanachot I, et al. Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis. British journal of clinical pharmacology. 2018;84(7):1445-56.

92. Yunusa I, Alsumali A, Garba AE, et al. Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis. JAMA network open. 2019;2(3):e190828.



Behavioural and Psychological Symptoms (BPSD) - Antipsychotics

- ▶ AP > placebo in reducing BPSD (small but significant) in PWD(SMD= -0.13, 95% CI -0.21 to -0.06)⁹⁰, level I
- ▶ Based on TWO RCT⁹³, level I
 - Brexpiprazole 2mg/day > placebo at 12 weeks on CMAI (adjusted MD= -3.77, 95% CI -7.38 to -0.17)
 - Brexpiprazole 0.5mg to 2mg/day = placebo at 12 weeks on CMAI >>> post hoc analysis on 2mg showed improvement at week 12 (adjusted MD= -5.06, 95% CI -8.99 to -1.13)

90. Dyer SM, Harrison SL, Laver K, et al. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. *International psychogeriatrics*. 2018;30(3):295-309.

93. Grossberg GT, Kohegyi E, Mergel V, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2020;28(4):383-400.



Behavioural and Psychological Symptoms (BPSD) - Antidepressants

- ▶ Systematic Review⁹⁰, level I
 - Sertraline = placebo based on NPI for global BPSD in PWD and concomitant depression
- ▶ Network Meta Analysis⁹¹, level I
 - SSRI > placebo for based on CMAI, NPI-A, BEHAVE-AD-A, NBRS-A (OR=1.61, 95% CI 1.02 to 2.53)
- ▶ NICE 2018
 - not to offer antidepressants in mild to moderate depression for people with mild to moderate dementia



Behavioural and Psychological Symptoms (BPSD) - Mood Stabilizers

- ▶ Placebo > valproate on NPI (WMD=3.71, 95% CIs 0.15 to 7.26)⁹⁴, level I
- ▶ Valproate = placebo at 6 weeks on BPRS⁹⁵, level I

94. Xiao H, Su Y, Cao X, Sun S, Liang Z. A meta-analysis of mood stabilizers for Alzheimer's disease. J Huazhong Univ Sci Technolog Med Sci. 2010 Oct;30(5):652-8.
95. Baillon SF, Narayana U, Luxenberg JS, et al. Valproate preparations for agitation in dementia. The Cochrane database of systematic reviews. 2018;10(10):Cd003945.



Behavioural and Psychological Symptoms (BPSD) - Others

- ▶ Analgesics reduced global BPRS (SMD= -0.24, 95% CI -0.47 to -0.01)⁹⁰, level I
- ▶ some beneficial effects on sleep from trazodone and orexin antagonists with no harmful effects⁹⁶, level I
- ▶ benzodiazepine use to be **avoided** in the elderly based on results from a meta-analysis of 45 RCTs and review of 24 RCTs⁹⁷, level I

96. McCleery J, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. The Cochrane database of systematic reviews. 2020;11(11):CD009178.

97. Schroeck JL, Ford J, Conway EL, et al. Review of Safety and Efficacy of Sleep Medicines in Older Adults. Clinical therapeutics. 2016;38(11):2340-72.



Behavioural and Psychological Symptoms (BPSD) - Safety

- ▶ Treatment acceptability vs placebo is Non-significant except for oxcarbazepine ^{91, level I}
- ▶ A Network meta analysis found that:^{92, level I}
 - Somnolence: Placebo > risperidone > aripiprazole > olanzapine > quetiapine
 - EPS: quetiapine and aripiprazole > olanzapine and risperidone
 - CV AE: aripiprazole > quetiapine > risperidone > olanzapine
 - Falls, fracture or injury: risperidone, quetiapine > aripiprazole, placebo, olanzapine



Behavioural and Psychological Symptoms (BPSD) - Safety-2

- ▶ Cochrane meta-analysis of low quality evidence showed higher AE rate in valproate vs control (OR=2.02, 95% CI 1.30 to 3.14).^{95, level I}
- ▶ Two RCT found no notable difference in treatment emergent AE between brexpiprazole and placebo.^{93, level I}



Behavioural and Psychological Symptoms (BPSD)

- United States Food and Drug Administration (US FDA) issued a warning regarding increased mortality associated with the use of AP in elderly patients with dementia-related psychosis in response to emerging evidence since 2005.^{98, level III}
- NICE recommends AP to be offered to PWD who are either at risk of harming themselves or others, or experiencing symptoms that are causing them severe distress.⁴²
- NICE recommends on AP in PWD:⁴²
 - the lowest effective dose should be used and for the shortest possible duration
 - should be reassessed regularly and wean off if it is not needed



Behavioural and Psychological Symptoms (BPSD) - RECOMMENDATIONS

Recommendation 10

- Antipsychotics may be considered for behavioural and psychological symptoms in people with dementia (PWD) where there is a risk of harming themselves or others.
 - Antidepressants:
 - may be considered for PWD who have agitation
 - may be prescribed for PWD with pre-existing severe mental health problem
-
- There is insufficient evidence to support the use of mood stabilisers to treat agitation in PWD



Potentially Inappropriate Prescription (PIP)

- ▶ Medications with high anticholinergic burden (ACB) which cause negative outcomes in patients.
- ▶ American Geriatric Society on Beer's criteria consider PIPs as best avoided by older adults in most circumstances or under specific situations e.g., in certain diseases or conditions.⁹⁹, level III

99. American Geriatrics Society. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society. 2019;67(4):674-94.



ANTICHOLINERGIC BURDEN SCORE

Drugs with ACB Score of 1			
Alimemazine	Clidinium	Fluvoxamine	Nifedipine
Alverine	Clorazepate	Haloperidol	Paliperidone
Alprazolam	Codeine	Hydralazine	Prednisone
Aripiprazole	Colchicine	Hydrocortisone	Quinidine
Asenapine	Desloratadine	Iloperidone	Ranitidine
Atenolol	Diazepam	Isosorbide	Risperidone
Bupropion	Digoxin	Levocetirizine	Theophylline
Captopril	Dipyridamole	Loperamide	Trazodone
Cetirizine	Disopyramide	Loratadine	Triamterene
Chlorthalidone	Fentanyl	Metoprolol	Venlafaxine
Cimetidine	Furosemide	Morphine	Warfarin
Drugs with ACB Score of 2			
Amantadine	Cyclobenzaprine	Meperidine	Nefopam
Belladonna	Cyproheptadine	Methotrimeprazine	Oxcarbazepine
Carbamazepine	Loxapine	Molindone	Pimozide
Drugs with ACB Score of 3			
Amitriptyline	Darifenacin	Imipramine	Propiverine
Amoxapine	Desipramine	Meclizine	Quetiapine
Atropine	Dicyclomine	Methocarbamol	Scopolamine
Benzotropine	Dimenhydrinate	Nortriptyline	Solifenacin
Brompheniramine	Diphenhydramine	Olanzapine	Thioridazine
Carbinoxamine	Doxepin	Orphenadrine	Tolterodine
Chlorpheniramine	Doxylamine	Oxybutynin	Trifluoperazine
Chlorpromazine	Fesoterodine	Paroxetine	Trihexyphenidyl
Clemastine	Flavoxate	Perphenazine	Trimipramine
Clomipramine	Hydroxyzine	Promethazine	Trospium
Clozapine	Hyoscyamine	Propantheline	



Potentially Inappropriate Prescription (PIP)-2

► Prevalence

- A SR of 26 studies found >>> range of 13 - 74% for PWD.¹⁰⁰, level II-2
- meta-analysis, lower prevalence in PWD living in the community compared with those in nursing homes and specialized care homes¹⁰¹, level II-2

100. Hukins D, Macleod U, Boland JW. Identifying potentially inappropriate prescribing in older people with dementia: a systematic review. *European journal of clinical pharmacology*. 2019;75(4):467-81.

101. Delgado J, Bowman K, Clare L. Potentially inappropriate prescribing in dementia: a state-of-the-art review since 2007. *BMJ open*. 2020;10:e029172.



Potentially Inappropriate Prescription (PIP)-3

- ▶ A cross sectional study showed average ACB score of >3 in the first three months of AChEI initiation led to increased risk of:^{101, level III}
 - treatment modification at one year (HR=1.12, 95% CI 1.02 to 1.24)
 - delirium at one year (HR=1.52, CI 1.17 to 1.96)
 - mortality at two years (HR=1.23, CI 1.06 to 1.41)



Potentially Inappropriate Prescription (PIP)

- RECOMMENDATIONS

- ▶ NICE recommends minimizing use of high ACB related medications and to look for alternatives whenever possible.⁴²

Recommendation 11

- The use of anticholinergic medications in dementia should be done cautiously with regular review of indication and deprescribed whenever possible.



Appendix 10

SUGGESTED GUIDE TO REVIEW AND DEPRESCRIBE (POTENTIALLY INAPPROPRIATE PRESCRIPTION/PSYCHOTROPIC) IN DEMENTIA

Step 1: Evaluation

Does the patient have more than one (PIP/psychotropic)?	<input type="checkbox"/> No <input type="checkbox"/> Yes
Has the patient been on (PIP/psychotropic) >3 months?	<input type="checkbox"/> No <input type="checkbox"/> Yes

- If **YES** for at least one of the above, kindly proceed to **Step 2**.

Step 2: PIP/Psychotropic Review

Parameter	Description	Review
Indication	Is there a justified reason?	<input type="checkbox"/> No <input type="checkbox"/> Yes
Effectiveness	Has it been effective for the indication?	<input type="checkbox"/> No <input type="checkbox"/> Yes
	Is it the recommended choice for the indication?	<input type="checkbox"/> No <input type="checkbox"/> Yes
Safety	Is there therapeutic duplication?	<input type="checkbox"/> No <input type="checkbox"/> Yes
	Is there any contraindication(s) to the patient?	<input type="checkbox"/> No <input type="checkbox"/> Yes
	Is there a potential or actual and significant drug interaction?	<input type="checkbox"/> No <input type="checkbox"/> Yes
	Is this regime a result of prescribing cascade?	<input type="checkbox"/> No <input type="checkbox"/> Yes
Pharmacotherapy	Is the dose appropriate?	<input type="checkbox"/> No <input type="checkbox"/> Yes
	Is the frequency appropriate?	<input type="checkbox"/> No <input type="checkbox"/> Yes

- If **YES** for any one of the above, kindly proceed to **Step 3**.

Step 3: PIP/psychotropic Reconciliation

Kindly consider the following actions for this patient:

1. Deprescribing PIP/psychotropic
2. Substituting to a better alternative
3. Modify the regime (dose, frequency and duration, etc.)
4. Consider potential for managing all symptoms with a single PIP/psychotropic



TCM - EGb 761

- ▶ In a meta-analysis on PWD, extract of Ginkgo biloba (EGb761) of 240 mg/day improved:¹⁰³
 - cognitive function (WMD= -3.19, 95% CI -3.56 to -2.83)
 - ADL (SMD= -0.45, 95% CI -0.55 to -0.36)
 - global assessment of change (OR=2.47, 95% CI 1.91 to 3.20)
 - behavioural symptoms (WMD= -4.82, 95% CI -5.44 to -4.20)
- ▶ However, there was significant heterogeneity among the primary papers.

103. Tan MS, Yu JT, Tan CC, et al. Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. Journal of Alzheimer's disease: JAD. 2015;43(2):589-603.



TCM - EGb 761

- ▶ On safety, there were no significant differences between EGb761 and placebo in the proportion of participants experiencing any adverse events or serious adverse events for whole group and subgroup analysis
- ▶ Another meta-analysis did not indicate a higher bleeding risk associated with standardised ginkgo biloba extract compared with placebo. However, the study population was not entirely on dementia and the primary papers were mostly of moderate/high risk of bias.¹⁰⁴

104. Kellermann AJ, Kloft C. Is there a risk of bleeding associated with standardized Ginkgo biloba extract therapy? A systematic review and meta-analysis. *Pharmacotherapy*. 2011;31(5):490-502.



TCM - Melatonin

- ▶ A Cochrane systematic review found low-certainty evidence that melatonin doses up to 10 mg may have little or no effect on any major sleep outcome over eight to 10 weeks in people with AD and sleep disturbances.⁹⁶
- ▶ Another meta-analysis of seven RCTs (mainly moderate quality primary papers) showed melatonin prolonged total sleep time at night (SMD=0.26, 95% CI 0.01 to 0.51) compared with placebo in AD patients
- ▶ However, there was no significant difference in sleep efficacy between melatonin and placebo (SMD= 0.14, 95% CI -0.17 to 0.44).¹⁰⁵

96. McCleery J, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. The Cochrane database of systematic reviews. 2020;11(11):Cd009178.

105. Wang YY, Zheng W, Ng CH, et al. Meta-analysis of randomized, double-blind, placebo-controlled trials of melatonin in Alzheimer's disease. International journal of geriatric psychiatry. 2017;32(1):50-7.



TCM

- ▶ A Cochrane review could not conclude on the effectiveness and safety of traditional Chinese herbal medicine for VaD due to poor reporting and trial methodology of the primary papers.¹⁰⁶
- ▶ There is insufficient evidence to support curcumin supplementation as an effective means of both preventing and treating dementia and symptoms of cognitive decline.¹⁰⁷

- There is insufficient evidence to recommend the use of TCM in the treatment of dementia.

106. Chan ES, Bautista DT, Zhu Y, et al. Traditional Chinese herbal medicine for vascular dementia. The Cochrane database of systematic reviews. 2018;12(12):Cd010284.

107. Seddon N, D'Cunha N, Mellor D, et al. Effects of Curcumin on Cognitive Function—A Systematic Review of Randomized Controlled Trials. 2019;4:1-11.

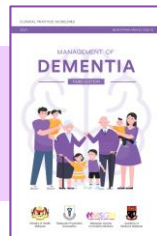


Take Home Message

- For those who require regular medication, the '3T' approach is a good practice:¹⁰
 - treatments should have a specific target symptom
 - the starting dose should be low and then titrated upwards
 - treatments should be time limited



Thank You



**Training of Core Trainers on
CPG Management of Dementia
(Third Edition)**