Prescribing for dementia

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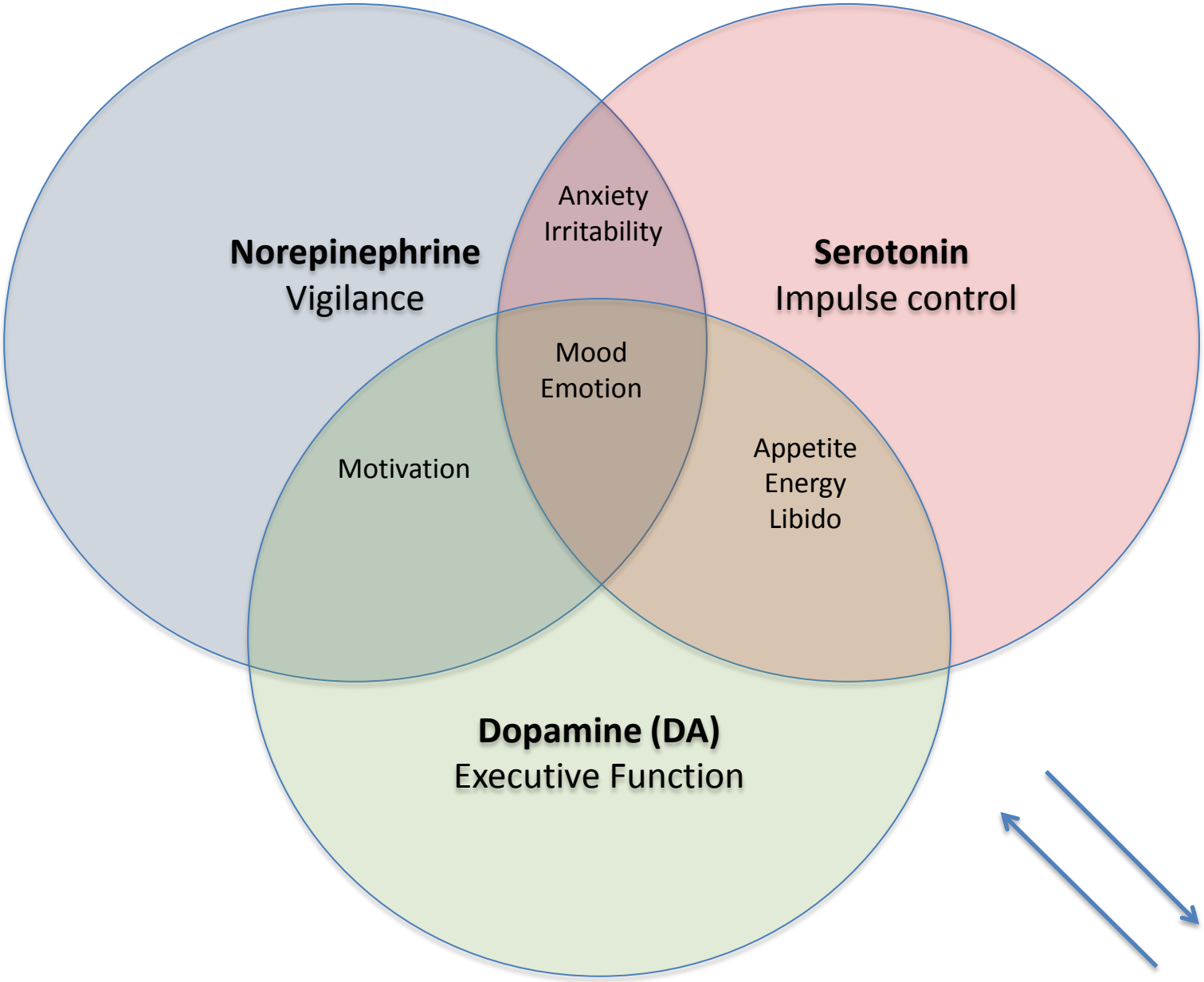
Overview

- Licenced medications: indications and monitoring
- Anticholinergic drug burden and implications
- Vascular dementia
- Deprescribing/ Rational polypharmacy
- Non-cognitive symptoms
- Serotonin syndrome
- Modifiable dementias

Medical management of Dementia

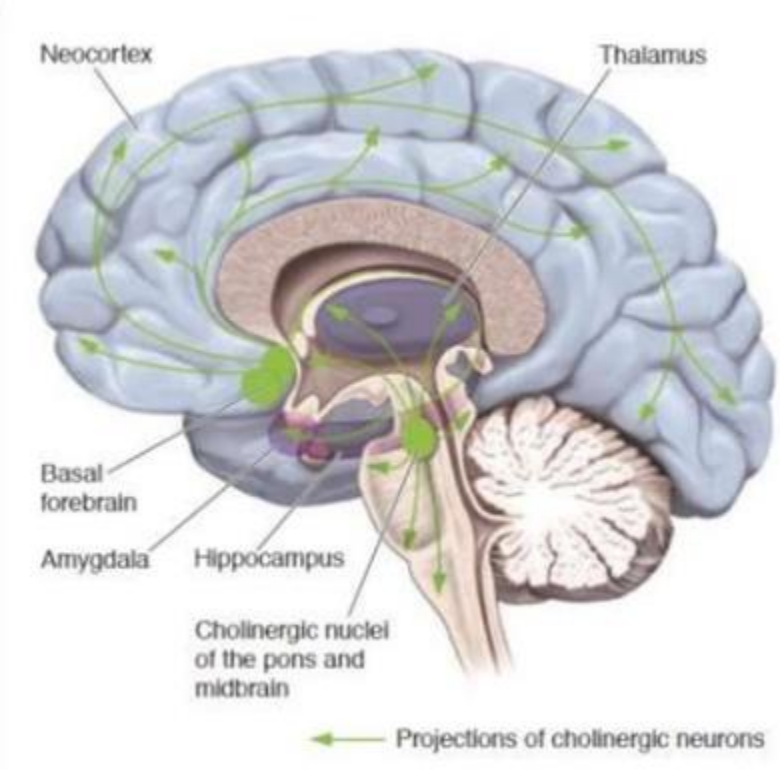
- Non-pharmacologic
  - ❑ Cognitive enrichment
  - ❑ Cognitive rehabilitation
  - ❑ Vocational support
  - ❑ Safety and security
  - ❑ Social support
  - ❑ Care-giver support
- Pharmacotherapy for behavioural and personality symptoms (BPSD) – generic approach
- Disease-specific pharmacotherapy
  - ❑ Disease-modifying *[none currently available]*
  - ❑ Palliative *['cognitive-enhancing therapy']*

Monoamine modulation



Acetylcholine (Ach)

Cholinergic systems



- Cortical excitability
- REM sleep
- Attention
- Selective attention
- Arousal (alertness)
- Declarative memory

- Deficiency/inhibition:

disorientation, cognitive decline, falls, impaired reality monitoring

Licensed medications: UK

	Donepezil	Rivastigmine	Galantamine	Memantine
Mild Alzheimer's disease	Yes	Yes	Yes	No
Moderate Alzheimer's disease	Yes	Yes	Yes	Yes
Severe Alzheimer's disease	No	No	No	Yes
Mild to moderate Parkinson's disease dementia	No	Yes	No	No ★
Vascular dementia	No	No	No	No
Mild cognitive impairment	No	No	No	No
Dementia with Lewy bodies ★	No	No	No	No
Frontotemporal dementia	No	No	No	No

Mild-Moderate Dementia due to either AD or PD

Use in DLB is expert consensus

Grading dementia due to AD

Grade	MMSE cut-offs (/30)
Mild	21-26
Moderate	10-20
Severe	< 10

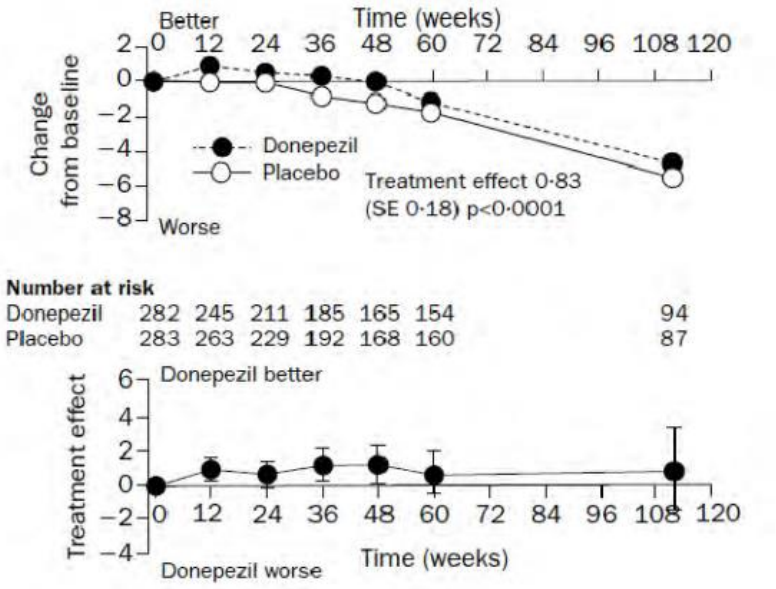
Limitations of MMSE-based grading

- Validity of the MMSE
- Security of AD diagnosis
- Confounded by level of education
- Atypical AD
- Ignores level of assistance required by patient

Dosing, adverse effects and monitoring

Drug	Maintenance Dose	Common AEs	Monitoring
Donepezil	5-10mg od	GI (20%; nausea, vomiting, diarrhoea), insomnia, vivid dreams	ECG, if needed Syncope (1.5-2*) *Gait freezing*
Galantamine	8mg bd	GI + headache	ECG, if needed Syncope *Gait freezing*
Rivastigmine	3-6mg bd Patch: 4.6 to 9.5mg	GI ***(less with patch)*** + headache + somnolence	ECG, if needed Syncope *Gait freezing*
Memantine	10mg bd	Constipation, headache, somatic pain	Polypharmacy-related disequilibrium

Cholinesterase inhibitors (ChEIs)



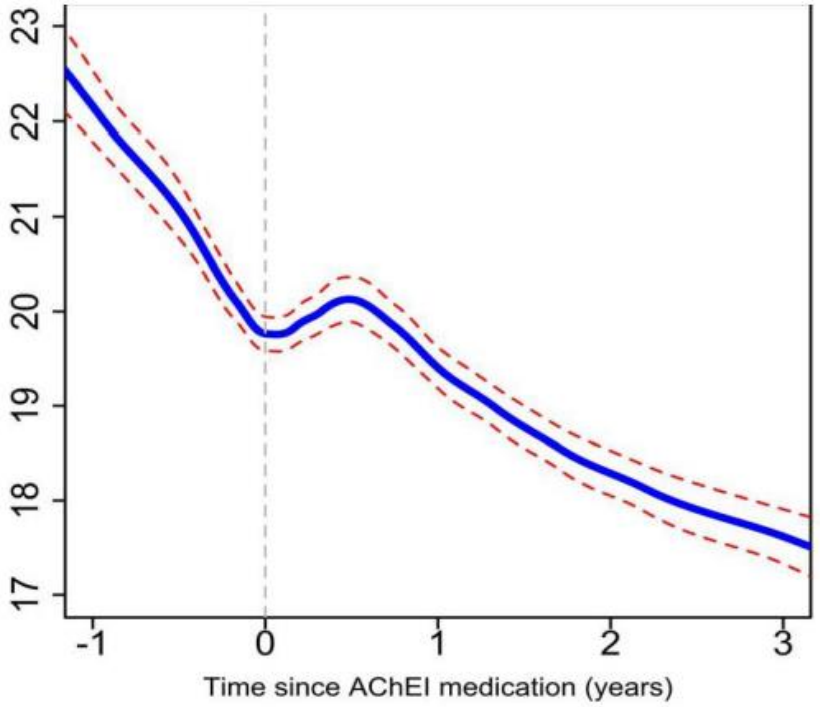
Change in MMSE (upper)
Effect of Donepezil (lower)

- Donepezil, galantamine: rapidly reversible ChEIs
- Rivastigmine: slowly reversible ChEI
- Similar efficacy for AD
- No long-term benefit
- Risks:
  - ❑Bradycardia (1.3-2*)
  - ❑PPM-insertion (1.1-2*)
  - ❑Hip # (1.0-1.34*)

Lancet 2004; 363:2105-2115

Arch Intern Med 2009; 169:867-873

ChEIs



Factors Associated with Response to Acetylcholinesterase Inhibition in Dementia: A Cohort Study from a Secondary Mental Health Care Case Register in London

Gayan Perera[1]*, Mizanur Khondoker[1], Matthew Broadbent[2], Gerome Breen[1], Robert Stewart[1]

1 King's College London (Institute of Psychiatry), London, United Kingdom, **2** South London and Maudsley NHS Foundation Trust, London, United Kingdom

Clinical benefit highest if:

- Early treatment initiation
- No vascular comorbidity
- No antipsychotic use

N=2460

ChEIs and ECGs

- ChEIs: sinus brady, SA-block, sinus pauses
- 10%: ‘dizziness’ without ECG change
- Up to 1%: severe bradyarrhythmia
- Consider pre-Rx ECG if:
  - ❑HR < 50 bpm
  - ❑Syncope
  - ❑Irregular heart rate
  - ❑Negative chronotrope polypharmacy
- Pulse checks before, at one month, 3 months and 6 months. ECG if clinically indicated.

Memantine

- Non-competitive NMDAR antagonist
- No significant drug interactions
- Usually in addition to ChEI
- Monotherapy if ChEI contra-indicated

NICE: moderate-severe AD

- Bd regime was used in most trials (10 bd max)
- Dose adjustment needed if eGFR < 50

NICE: non-AD dementia

Pharmacological management of non-Alzheimer's dementia

1.5.10 Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies.[1]

1.5.11 Only consider galantamine[2] for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine[1] are not tolerated.

1.5.12 Consider donepezil or rivastigmine for people with severe dementia with Lewy bodies[1].

1.5.13 Consider memantine[3] for people with dementia with Lewy bodies if AChE inhibitors[4] are not tolerated or are contraindicated.

1.5.14 Only consider AChE inhibitors[4] or memantine[3] for people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies.

1.5.15 Do not offer AChE inhibitors or memantine to people with frontotemporal dementia[5].

1.5.16 Do not offer AChE inhibitors or memantine to people with cognitive impairment caused by multiple sclerosis.

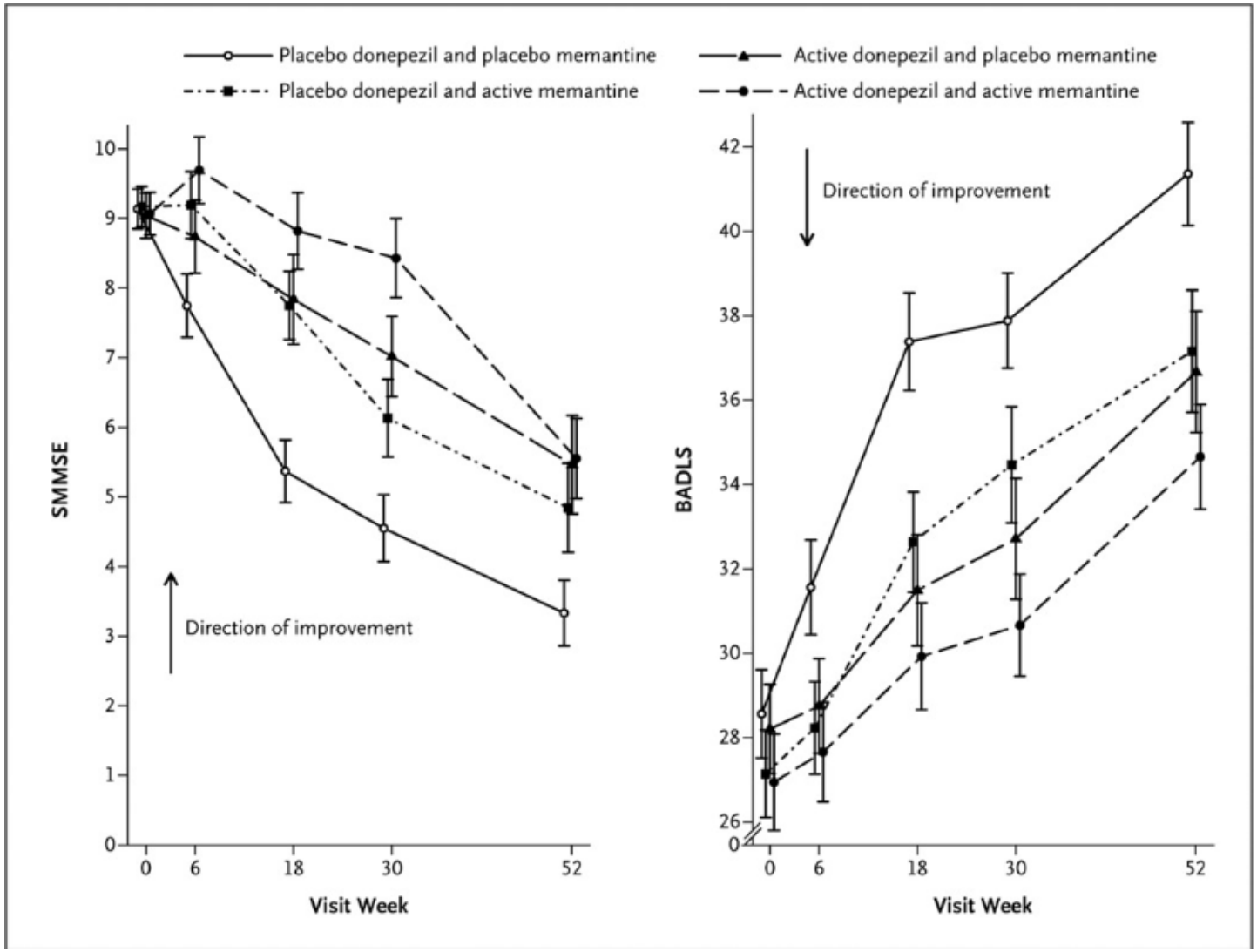
1.5.17 For guidance on pharmacological management of Parkinson's disease dementia, see Parkinson's disease dementia in the NICE guideline on Parkinson's disease.

NICE 2018: prescribing guideline

1.5.5 Treatment should be under the following conditions:

- For people who are not taking an AChE inhibitor or memantine, prescribers should only start treatment with these on the advice of a clinician who has the necessary knowledge and skills. This could include:
  - secondary care medical specialists such as psychiatrists, geriatricians and neurologists
  - other healthcare professionals (such as GPs, nurse consultants and advanced nurse practitioners), if they have specialist expertise in diagnosing and treating Alzheimer's disease.
- Once a decision has been made to start an AChE inhibitor or memantine, the first prescription may be made in primary care.
- For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, primary care prescribers may start treatment with memantine (see recommendation 1.5.4) without taking advice from a specialist clinician.
- Ensure that local arrangements for prescribing, supply and treatment review follow the NICE guideline on medicines optimisation.
- Do not stop AChE inhibitors in people with Alzheimer's disease because of disease severity alone.

ChEIs: Try not to stop



NEJM 2012; 366:893-903

Monitoring

1.5.7 When using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate. Healthcare professionals should also be mindful of the need to secure equality of access to treatment for patients from different ethnic groups, in particular those from different cultural backgrounds.

This recommendation is from NICE technology appraisal guidance on donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease.

1.5.8 When assessing the severity of Alzheimer's disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. These include:

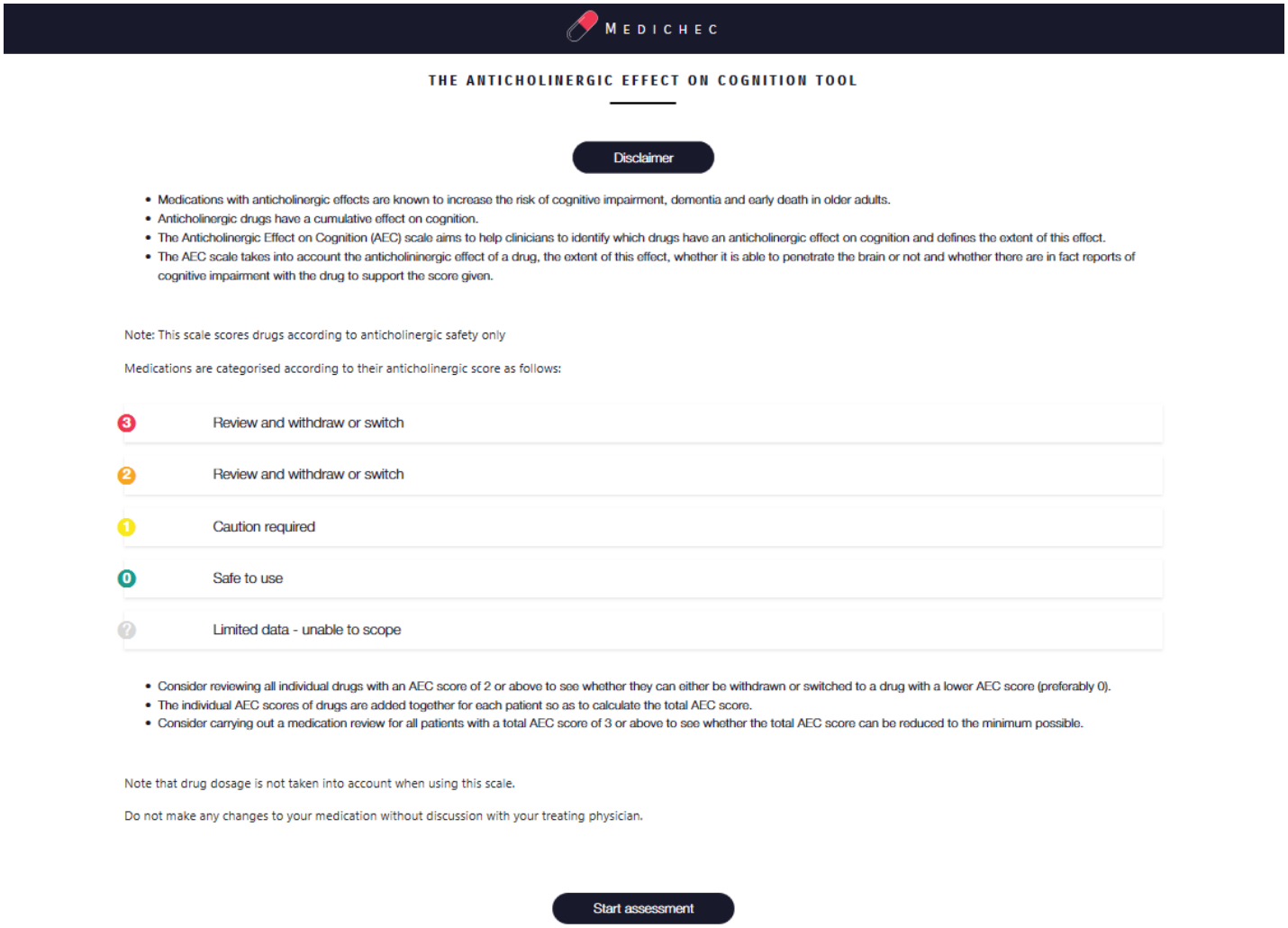
- if the cognition score is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning difficulties or other disabilities (for example, sensory impairments), linguistic or other communication difficulties or level of education **or**
- if it is not possible to apply the tool in a language in which the patient is sufficiently fluent for it to be appropriate for assessing the severity of dementia **or**
- if there are other similar reasons why using a cognition score, or the score alone, would be inappropriate for assessing the severity of dementia.

In such cases healthcare professionals should determine the need for initiation or continuation of treatment by using another appropriate method of assessment.

What can you ask about in five mins?

- Use of telephone
- Independent travel via car or public transport
- Shopping for clothes and food
- Preparation of meals + change in complexity
- Housework
- Medication adherence
- Managing bills
- *What does the carer help them with and why*

Anticholinergic burden



MEDICHEC

THE ANTICHOLINERGIC EFFECT ON COGNITION TOOL

Disclaimer

- Medications with anticholinergic effects are known to increase the risk of cognitive impairment, dementia and early death in older adults.
- Anticholinergic drugs have a cumulative effect on cognition.
- The Anticholinergic Effect on Cognition (AEC) scale aims to help clinicians to identify which drugs have an anticholinergic effect on cognition and defines the extent of this effect.
- The AEC scale takes into account the anticholininergic effect of a drug, the extent of this effect, whether it is able to penetrate the brain or not and whether there are in fact reports of cognitive impairment with the drug to support the score given.

Note: This scale scores drugs according to anticholinergic safety only

Medications are categorised according to their anticholinergic score as follows:

3	Review and withdraw or switch
2	Review and withdraw or switch
1	Caution required
0	Safe to use
?	Limited data - unable to scope

- Consider reviewing all individual drugs with an AEC score of 2 or above to see whether they can either be withdrawn or switched to a drug with a lower AEC score (preferably 0).
- The individual AEC scores of drugs are added together for each patient so as to calculate the total AEC score.
- Consider carrying out a medication review for all patients with a total AEC score of 3 or above to see whether the total AEC score can be reduced to the minimum possible.

Note that drug dosage is not taken into account when using this scale.

Do not make any changes to your medication without discussion with your treating physician.

Start assessment

www.Medichec.com

Anticholinergic burden

- Orange (review/switch)

Amantadine

Chlorpheniramine

Olanzapine

Paroxetine

Propantheline

Tolteridone

Pethidine…..

- Red (review/switch)

Amitriptyline

Atropine/Hyoscine

Clomipramine

Dothiepin

Cyproheptadine

Oxybutinin

Trihexyphenidyl…

Note: darifenacin, fesoteridone and trospium least cogno-toxic bladder anticholinergics

Note: avoid first generation anti-histamines (this includes cyclizine)

Vascular dementia

Identifying Lesions	Clinical presentation	Risk factors
Multiple† cortical and subcortical infarcts in the distribution of major cerebral vessels (MCA, ACA, PCA)	-Abrupt onset in association with clinically-diagnosed stroke -Stepwise progression -Focal neurologic signs including visual field defect, hemiparesis	-CHF, CAD -atrial fibrillation -hypertension -diabetes mellitus
Multiple small-to-medium sized infarcts of subcortical gray and white matter (lacunar state)	-Abrupt onset and stepwise progression‡ -Pseudobulbar palsy -Early incontinence without urologic cause -Gait disorder characterized as "magnetic", parkinsonian or apractic	-hypertension -diabetes mellitus
Lobar hemorrhages or infarcts due to cerebral amyloid angiopathy	-Abrupt onset and stepwise progression -Neuroimaging showing multiple lobar cerebral hemorrhages	-age over 70 years -concomitant AD

- Control risk factors
- Anti-platelet vs anticoagulant vs. neither
- Strongly consider mixed pathology and offer ChEIs if appropriate
- Cognitive rehab for strategic strokes

Deprescribing in dementia

- Avoid anticholinergics
- Avoid first generation anti-histamines
- Review anti-arrhythmic medication
- Terminal illness
- Drugs associated with falling:
  - ❑**Antipsychotics**
  - ❑Antidepressants
  - ❑**Hypnotics**
  - ❑**Antihypertensives**
  - ❑NSAIDS
  - ❑**Diuretics**
  - ❑Opiates

Agitation, aggression, distress and psychosis

Triggers	Investigate	Manage	Engage
Severe illness	*FBC, U&Es, CRP, LFTs, Glucose, Mg, Ca, PO_4 urinalysis Consider ABG*	*First and foremost treat underlying causes*	*Families and carers can give you a history of change. Always speak to them to obtain history and baseline function.*
Trauma/surgery	*Culture, urine, sputum, wounds. Consider blood culture (Sepsis Six), CXR*	*Manage sepsis*	*Families and friends can help reorientate.*
Pain	*Always carry out routine observations (EWS) including AVPU and Think Glucose*	*Refer to delirium management: comprehensive pathway on page 6 for complete care guidance*	*Always document delirium diagnosis.*
Infection/sepsis	*Start fluid balance*	*DO NOT USE RESTRAINT*	*Reassure families and carers.*
Dehydration	*Think about hydration status*	*AVOID ANTIPSYCHOTIC MEDICATIONS – these may worsen delirium or contribute to the risk of falls and immobility (see delirium management: comprehensive pathway on page 6)*	
Hypoxia			
Hypoglycaemia			
Medications			
Alcohol and drugs withdrawal			
Urinary retention/ constipation			

Memory aid for delirium precipitants – think DELIRIUM

Drugs (withdrawal/toxicity, anticholinergics)/**D**ehydration
Electrolyte imbalance
Level of pain
Infection/**I**nflammation (post surgery)
Respiratory failure (hypoxia, hypercapnia)
Impaction of faeces
Urine retention
Metabolic disorder (liver/renal failure, hypoglycaemia)/**M**yocardial infarction

Before pharmacotherapy:

- Environmental factors
- Patient factors
- Caregiver factors

Only offer antipsychotics if:

- at risk of harming themselves or others **or**
- experiencing agitation, hallucinations or delusions that are causing them severe distress.

If an antipsychotic is prescribed:

- Remember, there is a NICE guideline
- use the lowest effective dose
- for the shortest possible time
- reassess the indication at least every 6 weeks
- Medication review, rationalise polypharmacy
- Stop treatment with antipsychotics:
  - ❑ if the person is not getting a clear ongoing benefit from taking them **and**
  - ❑ after discussion with the person taking them and their family members or carers (as appropriate)

Depression, anxiety and sleep

- Avoid pharmacotherapy in mild to moderate depression. Consider psychological treatments.
- Avoid melatonin or hypnotics
- Sleep hygiene
- Increase levels of physical/social activity

- If an antidepressant/anxiolytic is started, be cautious with rapid up-titration.

Serotonin syndrome (SS)

- Recent introduction or dose increase of serotonergic agent
- Three of: agitation, cognitive change, myoclonus, hyper-reflexia, diaphoresis, shivering, tremor, diarrhoea, fever
- Not recently started on an antipsychotic agent
- SS may cause CK increases, hyperpyrexia
- Strongly consider if one of: myoclonus, dilated pupils, shivering tremor

Sternbach H. *Am J Psychiarty* 1991; 148:705-713

SS: causes

- SSRIs/SSRI-like: **TCAs**, Amphetamine, Cocaine, MDMA, **St John's Wort**
- Inhibitors of serotonin metabolism: **MAO-B inhibitors** (selegeline/rasagiline), linezolid
- Increased serotonin synthesis: L-tryptophan
- Enhanced serotonin release: DOAs, Fenfluramine
- Serotonin agonists: Triptans, Buspirone
- Lithium

Polypharmacy is biggest RF

Modifiable Dementias… pointers

- Rapid decline
- Early-onset age
- Prominent fluctuations
- High-risk exposures
- Abnormal neurological signs

- B12/TSH/HIV/syphilis/GGT/INR
- Cardiac/liver/renal