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Prescribing Pathway - Use of Donepezil, Galantamine, Rivastigmine and Memantine in Dementia

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Trust wide	
Mental Health (Tower Hamlets, City & Hackney, Newham)	✓
Community Health Services	

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Version Control Summary

Version	Date	Author	Status	Comment
2.0	04 February 2010	James Innes	Final	
3.0	13 October 2011	James Innes	Final	Updated to reflect new 2011 NICE guidance on treatment of dementia
4.0	13th September 2017	Lewis Pope		Updated to reflect inclusion of rivastigmine transdermal patches
5.0	March 2021	Kapila Sachdev, Matthew Lines	Final	Change in title from Shared Care Guideline-Use of Donepezil, Galantamine, Rivastigmine and Memantine in Dementia. Updated to reflect recommendations in NICE NG 97

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Abbreviations and definitions

OPCMHT	**Older Person's Community Mental Health Team**
MAS	**Memory Assessment Services**
MHCOP	**Mental Health Care for Older People**
AChE	**Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine)**
CED	**Cognitive enhancer drugs (donepezil, galantamine, rivastigmine and memantine)**
BPSD	**Behavioural & psychological symptoms of Dementia.**
MMSE	**Mini Mental State Examination**

Severity of Dementia

ICD-10	**Clinical trial definition**
Mild – New learning mainly affected. Impaired performance in daily living but not to a degree it makes the individual dependent on others.	MMSE score >18 (max score 30)
Moderate – Degree of memory loss represents a serious handicap to independent living. Unable to function without assistance of another in daily living.	MMSE score 10-18
Severe – Complete inability to retain new information, failure to recognise close relatives. Absence of intelligible ideation.	MMSE score <10

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Introduction

This document has been published with the intention to update the existing “Shared Care Guideline-Use of Donepezil, Galantamine, Rivastigmine and Memantine in Dementia”, which has guided prescribing in Tower Hamlets, Hackney & Newham since 2011, to reflect recommendations from NICE Guideline 97: Dementia: assessment, management and support for people living with dementia and their carers, itself published in 2018. This guidance relates to the prescribing of the cognitive-enhancer drugs (CEDs) Donepezil, Galantamine, Rivastigmine and Memantine for patients with Alzheimer’s disease.

Summary of previous shared care protocol

Patients are referred to the single point of entry for assessment for dementia, where they will then be assessed by Memory Assessment services (MAS) within Mental Health Care for Older People (MHCOP). If diagnosed with dementia and deemed to be a candidate for a trial of a CED, a month’s supply is provided. For the first 12 weeks of treatment the patient is reviewed by MHCOP for tolerability and efficacy at monthly intervals. At this point the shared care guideline is sent to the GP, if accepted, prescribing of CEDs are taken over by the GP. A consultant psychiatrist continues to review the patient at 6-12 month intervals for response to treatment. The SCG is terminated if the consultant adjudges the therapy is no longer beneficial for the patient.

NICE Guideline 97: Dementia: assessment, management and support for people living with dementia and their carers

The new guideline replaces one of the recommendations in the NICE technology appraisal guidance (TA217) on donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer’s disease. In the new guidance, prescribers should only start treatment with a cholinesterase inhibitor or memantine on the advice of a clinician who has the necessary knowledge and skills. This could include a psychiatrist, geriatrician, neurologist, nurse consultant, advanced nurse practitioners or a GP with specialist expertise in diagnosing and treating Alzheimer’s disease. Once a decision has been made to start treatment, the first prescription may be made in primary care.

Memantine monotherapy is recommended as an option for managing Alzheimer’s disease for people with:

- Moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors or
- Severe Alzheimer's disease.

For people with an established diagnosis of Alzheimer's disease already taking a cholinesterase inhibitor, primary care prescribers may start treatment with memantine without taking advice from a specialist clinician in moderate to severe disease. NICE adds that a cholinesterase inhibitor should not be stopped on the basis of disease severity alone.

For dementia with Lewy bodies, the NICE guideline states:

- Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies
- Only consider galantamine for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated
- Consider donepezil or rivastigmine for people with severe dementia with Lewy bodies
- Consider memantine for people with dementia with Lewy bodies if AChE inhibitors are not tolerated or are contraindicated

For Parkinson's disease dementia the NICE Parkinson's disease guideline states:

- Offer a cholinesterase inhibitor for people with mild or moderate Parkinson's disease dementia
- Consider a cholinesterase inhibitor for people with severe Parkinson's disease dementia
- Consider memantine for people with Parkinson's disease dementia, only if cholinesterase inhibitors are not tolerated or are contraindicated

Roles of primary and secondary care in initiation of acetylcholinesterase inhibitors and memantine (in patients who are not already prescribed an AChE inhibitor)

The decision to initiate an AChE inhibitor, or memantine in patients who are not already prescribed an AChE inhibitor, should be made by a dementia specialist (psychiatrist, neurologist, geriatrician, nurse prescriber, GP with special interest). There is no requirement for the specialist to issue the first prescription.

It is recommended that the first prescription should be provided by primary care (on the advice of a specialist) for the following reasons:

- Commencing medication is not urgent
- New medications should be integrated with current medications to support adherence and to ensure integration with a patient's dossette box/blister pack
- It is more convenient and safer for a patient to have all prescriptions issued by the same prescriber

Prescribing recommendation from the specialist to primary care must be clearly communicated and include:

- Indication for the medication
- Absence of contra-indications or cautions (e.g. pulse check findings)
- Medication, formulation and dose
- Titration plan
- How to seek advice from a specialist

Prescribing memantine for patients who are already established on an acetylcholinesterase inhibitor

For patients with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, primary care prescribers can initiate memantine without advice from a specialist. eGFR needs to be checked prior to prescribing memantine and should be avoided if eGFR is less than 5 mL/minute/1.73 m2 (see appendix 1 for further details).

Memantine (in addition to an AChE inhibitor) should be considered in people with moderate dementia and offered to people with severe dementia. A good opportunity to consider the suitability of memantine is during an annual care plan review.

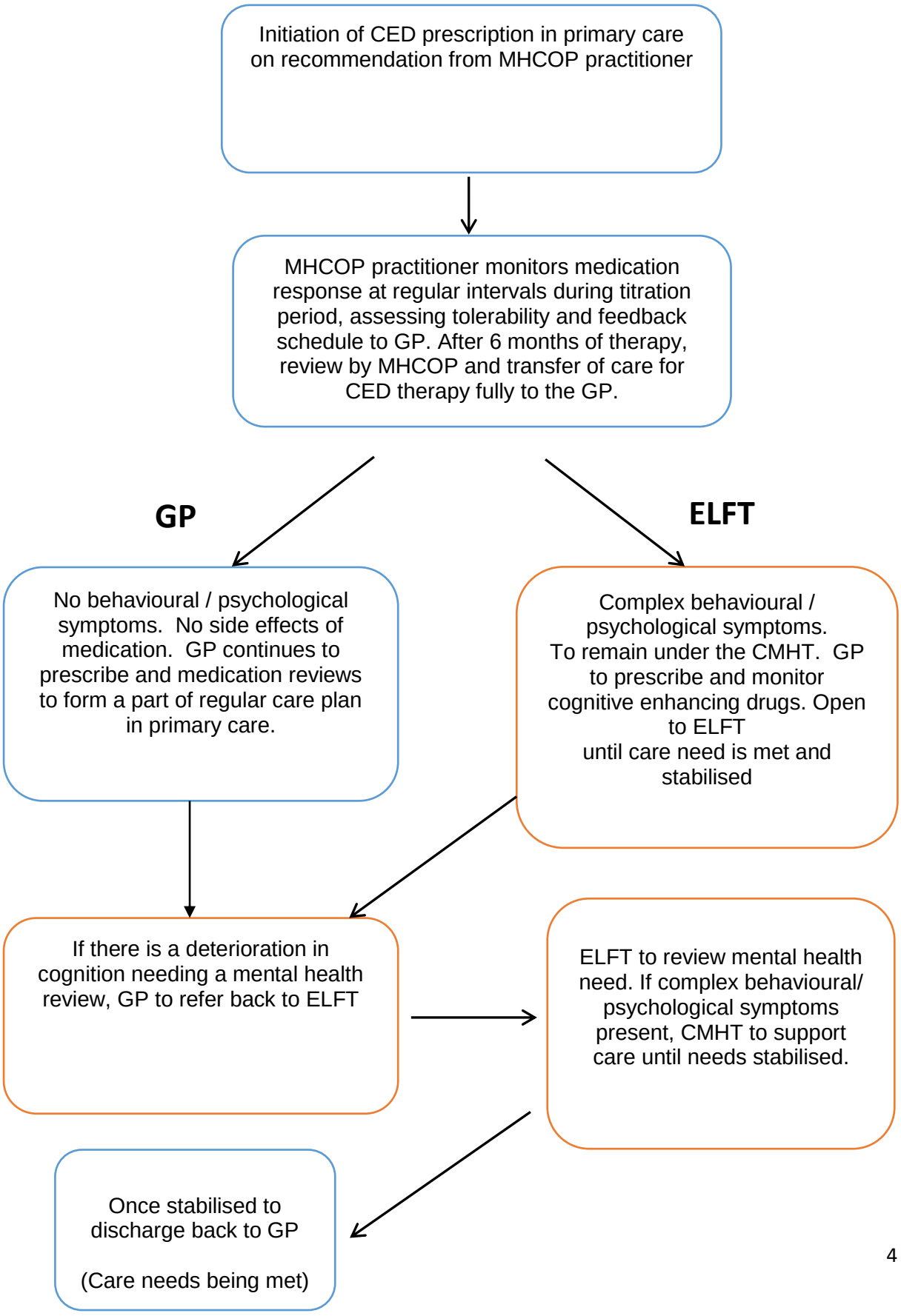
Do not rely solely on a score on a cognitive test to decide if a patient has mild, moderate or severe dementia. Consider any physical, sensory or learning disabilities or communication difficulties in your assessment of the stage of dementia. The descriptions below are a guide to what to expect at the different stages of dementia:

Mild Dementia – a person with mild dementia will be able to continue most of their normal activities independently. Friends and family close to the person may be aware of increased difficulties, in for example making plans or finding the right word.

Moderate Dementia –usually people will require support and a greater level of care to carry out their activities of daily living. They may need support with shopping, meal planning, managing household finances and getting washed and dressed and they may sometimes get lost. They may show increased frustration when they are aware they cannot do things they previously used to do. They may lack insight into their increasing difficulties and develop apathy and less interest in joining social activities.

Severe Dementia – in this final stage of dementia, a person requires significant support, around the clock, for basic activities of daily living like bathing, dressing, and eating. Their communication is likely to be significantly impaired. They may have impaired swallowing ability, increasing difficulty with continence and increasing physical frailty. Most people living with dementia in care homes have severe dementia.

Updated Patient Care Pathway for Use of Drugs for Dementia in Mild to Severe Alzheimer's Disease



Summary of specialist Mental Health Care for Older People team responsibilities

1. Confirm the diagnosis of Dementia, including subtype.

2. If a diagnosis of Alzheimer's disease is confirmed, consider whether the patient fits the criteria for and would benefit from a trial with a CED in accordance with NICE Guideline 97.

3. Assess the likelihood of patient/carer compliance.

4. Counsel patients/carers as to the likely benefits and risks of treatment, including the consequence of poor compliance. Offer advice as to the limited effectiveness of treatment over time as the illness progresses. A pulse check should be performed before advising primary care to prescribe AChE.inhibitors (please see Appendix 3 for further guidance).

5. Provide clear documentation of mental capacity assessments/power of attorney in patient notes

6. Offer an initial trial period of treatment of CEDs for 6 months whilst assessing response during and at the end of the trial period. The dose should be titrated according to response and tolerance. Explain that prescription will be issued by GP.

7. Submit a written request to the service user's GP for prescribing of CED with a detailed report, outlining information relating to the initial assessment. MHCOP will monitor the patient and inform the GP of progress with dose titration at regular intervals.

8. On initiation, MHCOP to provide the GP and patient (±carer) with information about treatment; particularly with regard to stopping treatment, the circumstances when treatment may be stopped and the benefits that might be expected from a successful trial period for that patient in accordance with NICE Guideline 97.

9. Assess and manage any behavioural/psychological difficulties experienced by the patient, including those arising from the use of CEDs and any other adverse events reported by the GP relating to the treatment of this condition. Share this information with the GP.

10. MHCOP to review the patient if further mental health input is warranted or if the GP has any clinical concerns, e.g. problematic behavioural and psychological disturbances, adverse events, discontinuation of treatment, etc.

11. On discontinuing/adjusting treatment, consider restarting/switching treatment if the patient experiences a dramatic deterioration of cognitive function or unacceptable side effects. Inform GP and patient/carer of rationale.

Summary of GP responsibilities

1. Provide a full drug/medical history (preferably as recorded on the GP computerised records) to the MAS as per referral pathway.

2. Prior to referral to MAS, perform an initial blood screen to rule out possible causes for cognitive impairment (FBC, ESR, U&E, LFT, calcium profile, blood glucose, TFT, B12 and red cell folate). Also provide a 12-lead ECG if practically possible for those likely to start treatment.

3. At the time of referral, inform the specialist clinician regarding the availability of a carer or care-worker in order to ensure compliance with treatment.

4. Once the specialist recommendation for initiation of CED therapy has been received, the GP will continue prescribing in the community.

5. Monitor the patients overall health and wellbeing during the normal consultation process, noting that MHCOP will carry out mental health reviews of patients on CED's for the first 6 months of therapy.

6. Highlight any concerns (which may arise at any time), that you consider warrant further investigation by the OPCMHT e.g. emergence of problematic behavioural and psychological symptoms (BPSD), emergence of adverse effects etc.

7. Undertake minor dosage adjustments if necessary in accordance with specialist advice.

8. Check for possible drug interactions when newly prescribing or stopping concurrent medication.

9. Report any suspected adverse event to the specialist clinician and, if appropriate, to the MHRA.

10. Deal with any concomitant illness, with specialist clinic support if appropriate.

11. Refer the patient to the OPCMHT upon admission to a nursing home to evaluate treatment efficacy if any problems are envisaged.

12. Inform the specialist clinic of life situation changes which may require revaluation in the suitability of CEDs for the patient.

13. On discontinuation/amendment of treatment by secondary care, refer back to OPCMHT if the patient is observed to experience a dramatic deterioration in cognitive function.

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Appendices

1. Titration and monitoring of acetylcholinesterase inhibitors and memantine

Once medication is titrated to optimum dose no further specific review is required other than general medication review appropriate to age and comorbidities. Medication should be continued lifelong if tolerated. It may be appropriate to withdraw medication during the last phase of life in discussion with a GP or palliative care team.

Titration guideline: (BNF online https://bnf.nice.org.uk/ last updated 11 January 2021)

Donepezil: The starting dose is 5 mg once daily (taken at bedtime). Review after one month and if tolerated offer to increase to 10 mg. Donepezil is also available in orodispersible tablets and oral solution; due to cost this is only recommended for people who have difficulties swallowing tablets

Rivastigmine (oral): The starting does is 1.5 mg twice daily, review after two weeks and increase in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to response and tolerance. Maximum dose is 6 mg twice daily.

Rivastigmine (transdermal): Apply 4.6 mg/24 hours daily, review at 4 weeks, if tolerated increased to 9.5 mg/24 hours daily for a further 6 months. After 6 months if well tolerated and cognitive deterioration or functional decline is demonstrated then it can be increased to 13.3 mg/24 hours daily. Rivastigmine is also available in an oral solution, however this is currently more costly then transdermal patches, therefore transdermal patch is recommended for people with swallowing difficulties.

Galantamine modified release: The starting does is 8 mg daily increasing by 8mg at four weekly intervals to a maximum dose of 24 mg. (Non-modified release tablets are soon to be withdrawn, therefore not recommended.)

If an oral AChE inhibitor is not tolerated due to gastrointestinal side effects, consider transdermal rivastigmine.

Memantine: The starting dose is 5 mg once daily; if tolerated increase in steps of 5 mg every week to a maximum 20 mg per day (this is the usual maintenance dose). Memantine is available in a titration pack with one week (7 tablets) of 5 mg,10 mg, 15 mg and 20 mg. Memantine 5 mg tablets are not readily available, 10 mg tablets are scored and should be split in half give a 5mg dose. Memantine should be avoided if eGFR is less than 5 mL/minute/1.73 m2. Reduce dose to 10 mg daily if eGFR 5–29 mL/minute/1.73 m2. Reduce dose to 10 mg daily if eGFR 30-49 mL/minute/1.73 m2; if well tolerated after at least 7 days dose can be increased to 20 mg daily in 5 mg steps.

Cautions

Donepezil: Asthma; chronic obstructive pulmonary disease; sick sinus syndrome; supraventricular conduction abnormalities; susceptibility to peptic ulcers

Galantamine: Avoid in gastro-intestinal obstruction; avoid in urinary outflow obstruction; avoid whilst recovering from bladder surgery; avoid whilst recovering from gastro-intestinal surgery; cardiac disease; chronic obstructive pulmonary disease; congestive heart failure; electrolyte disturbances; history of seizures; history of severe asthma; pulmonary infection; sick sinus syndrome; supraventricular conduction abnormalities; susceptibility to peptic ulcers; unstable angina

Rivastigmine: Bladder outflow obstruction; conduction abnormalities; duodenal ulcers; gastric ulcers; history of asthma; history of chronic obstructive pulmonary disease; history of seizures; risk of fatal overdose with patch administration errors; sick sinus syndrome; susceptibility to ulcers

Memantine: Epilepsy; history of convulsions; risk factors for epilepsy

Drug interactions

Cardiac

For patients prescribed an AChE inhibitor there is a possible interaction with agents that can cause bradycardia e.g. digoxin, β blockers, certain calcium-channel blockers and amiodarone. Caution with concomitant use of medications known to induce QT prolongation and/or torsade de pointes; an ECG is recommended by the manufacture when prescribing galantamine and these medications. A full list of interactions can be found in appendix four

Anticholinergics

The combination of AChE inhibitors and anticholinergic medications such as amitriptyline or oxybutynin can lead to pharmacological antagonism. The Anticholinergic Effect on Cognition (AEC) scale can be used to establish which medications have an anticholinergic effect on cognition, the online tool can be accessed here. A full list of interactions can be found in the BNF

2. Medication review guidance for Primary Care

Monitor for adverse effects including:

- Exacerbation of asthma and COPD
- Anorexia and weight loss
- GI ulcer or bleed
- AV node block as a possible cause of collapse.
- Additive interactions can occur with other drugs that share similar adverse effects (e.g. bradycardia and digoxin, beta-blockers, verapamil) or anorexia (e.g. SSRIs).

Monitor for compliance and consider strategies to promote improved concordance (e.g. blister pack, large print labels).

Physical Health Monitoring	**Rationale for Required Monitoring**
Weight	If weight loss has started or accelerated after starting AChE inhibitor medication, this may be the cause. If concerns then refer to secondary care.
Pulse	If <60, or irregular carry out an ECG. If PR interval > 200ms, stop drug or discuss with mental health specialist.
LFTs	All CEDs should be avoided in severe hepatic impairment. Caution in mild to moderate impairment. Clinical benefit needs to be weighed before plan is made to continue anti dementia medications in patients with mild to moderate hepatic impairment. If concerns then refer to secondary care. **For further information – see summary of product characteristics (SPC) for each medication**
U+Es with eGFR	Galantamine- avoid if eGFR is less than 9ml/min/1.73 m2 Rivastigmine- titrates according to individual tolerability. Memantine- Reduce dose to 10mg if eGFR 30-49 ml/min/1.73 m2. If well tolerated after at least 7 days dose than can be increased in steps of 5mg up to 20mg daily. Reduce dose to 10mg if eGFR 5-29 ML/min/1.73 m2, avoid if e GFR less than 5ml/min/1.73 m2.
Overall tolerance to medication	GI symptoms - anorexia, nausea, vomiting and diarrhoea

	Neurological symptoms – headaches, dizziness, drowsiness, syncope

Impact on global functioning

Functional and behavioural assessment is best made via a discussion with both patient and carer. It may be important to see the carer alone to elicit behavioural problems.

Functional assessment	Impact on daily living
Carer impact	Does the carer value the effect of the medication?
Behavioural assessment	New behavioural problems? Is the patient displaying behavioural and psychological symptoms of dementia? (BPSD)
Cognitive assessment • Some patients are distressed by repeated formal cognitive scoring tests. Cognition can be assessed through patient and carer interview instead of repeatedly using a formal scale. • When judged to be appropriate (e.g. significant reduction in global functioning), consider using either either of the following open access primary care validated scales, 6CIT (six item cognitive impairment test) or GPCOG (the General Practitioner assessment of Cognition).	

Discontinuation of CED therapy

Medication should be stopped if:

- There is no cognitive, behavioural, functional or global benefit.
- Patient cannot tolerate side effects of CED therapy – it is advised to discontinue with reducing doses rather than stopping abruptly.

Other factors to consider:

- Patient/carer views and expectations
- Frailty – Extent of CED contribution to quality of life if they are increasingly physically frail.

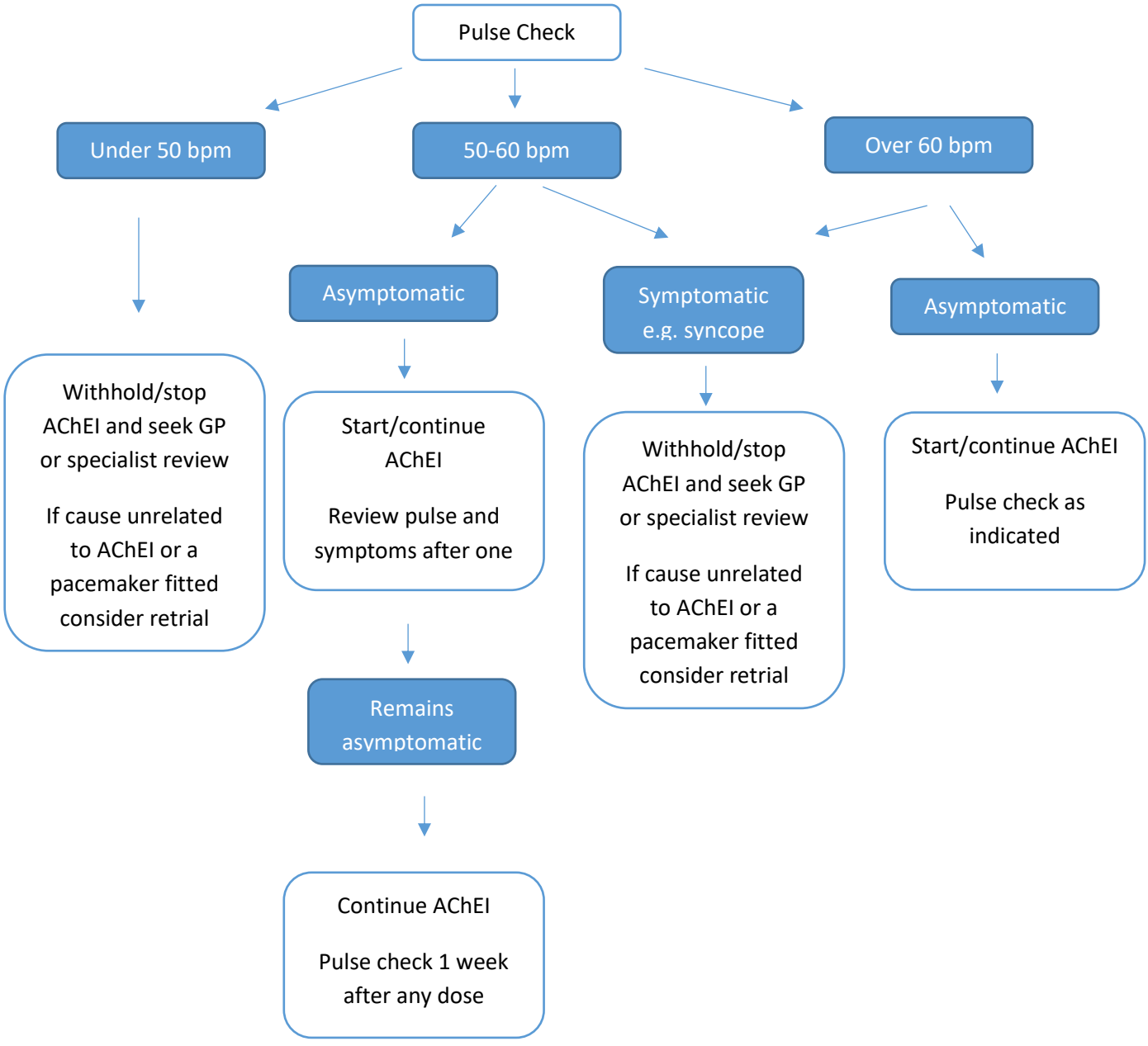
- Medical complications - For patients with increasing physical problems, the risks of stopping CEDs need to be weighed against the likelihood of developing new complications on continuing treatment.
- A subacute decline in cognitive performance, in the absence of other causes, may indicate that the CED is no longer effective.
- For patients at risk of entering care home, stopping a ChEI may disrupt care and hasten admission
- Once a patient is in a care home individual patient factors need to be taken into account when deciding if memory-enhancing medication is right for them.

There is a lack of robust evidence on how to stop AChE inhibitors and memantine, however it is recommended discontinuation should be by gradual dose reduction, see table below:

Stopping CEDs

Donepezil	Long half-life, so can be stopped without the need for tapering, however it may be advisable to reduce to 5 mg daily for a month and monitor for deterioration before stopping altogether.
Rivastigmine	Short half-life, reverse titration recommended – i.e. a reduction of 1.5 to 3 mg every 2 to 4 weeks.
Galantamine	Long half-life, so can be stopped without the need for tapering, however it may be advisable to gradually reduce the dose over a month and monitor for deterioration before stopping altogether.
Memantine	Gradual reduction recommended, e.g. half dose for a month and monitor for deterioration before stopping.

3. **Pulse check pathway** (adapted from Rowland et al 2007)



4. Contact details for MHCOP

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