HERPC

Hull & East Riding Prescribing Committee

Prescribing Framework for The Treatment and Management of Dementia

Patient's Name:…….. NHS Number: ……

Patient's Address:……..……(Use addressograph sticker)

GP's Name:……..

Communication

We agree to treat this patient within this Prescribing Framework

Specialist Prescriber's Name…… Prof Reg. No. ……

Specialist Prescriber's Signature…… Date:…….

Where prescriber is not a consultant:

Consultant's Name: …… GMC No ……..

Consultant's Signature ……... ……. Date:…….

GP's Signature:…… Date:……..

GP's Name (if different from listed above)……..

The front page of this form should be **completed by the specialist** and the form sent to the patient's general practitioner.

The patient's GP should sign and **send back to specialist**, to confirm agreement to enter into shared care arrangement. If the General Practitioner is unwilling to accept prescribing responsibility for the above patient the specialist should be informed within two weeks of receipt of this framework and specialist's letter.

Full copy of framework can also be found at: http://www.hey.nhs.uk/amber.htm

1. Background

There are three acetylcholinesterase inhibitors (ACHEIs), licensed for the treatment of people with mild to moderate Alzheimer's Disease, namely Donepezil, Galantamine and Rivastigmine, and also a glutamine receptor antagonist Memantine, which is licensed for treating moderate to severe Alzheimer's disease.

Evidence is also beginning to emerge that ACHEIs have some benefit in patients with mixed Alzheimer's/ vascular dementia (i.e. Alzheimer's Disease with concomitant vascular dementia), as well as in patients with mild, moderate or severe Alzheimer's Disease, dementia associated with Parkinson's Disease and Lewy Body Dementia with non-cognitive symptoms and/or behaviour that challenges.

NICE Clinical Guideline 42, published in November 2006, clarified the use of ACHEI's in mild, moderate and **severe** Alzheimer's Disease (AD), as well as Lewy Body Dementia (DLB) in patients who have non cognitive symptoms causing significant distress or behaviour that challenges. This advice has become increasingly pertinent as the evidence base surrounding the risks associated with the use of antipsychotic drugs in such patients, has strengthened. *N.B. The evidence base for dementia in Parkinson's disease (PDD) was not examined specifically in NICE CG 42. However, the guideline suggested that the recommendations for DLB may be useful when considering treatments for dementia in Parkinson's disease.*

The National Institute of Clinical Excellence (NICE)TA 217 (updated May16) recommends that cholinesterase inhibitors should be used in the management of people with Alzheimer's disease of mild to moderate severity also gives guidance for the use of Memantine, recommending it as an option for managing moderate Alzheimer's disease for people who cannot take AChE inhibitors, and as an option for managing severe Alzheimer's disease.

Additionally, since the publication of the NICE Clinical Guideline 42 on dementia, in November 2006, evidence has emerged for the effectiveness of Memantine in the following areas:

a) Patients with moderate stage Alzheimer's Disease or mixed dementia (Alzheimer's disease associated with concomitant vascular dementia) as an alternative to Acetyl Cholinesterase Inhibitors (ACHEIs), when there has been a loss of treatment effect from ACHEIs
b) Patients with Alzheimer's Disease (AD), mixed dementia (Alzheimer's disease with concomitant vascular dementia), dementia associated with Parkinson's disease or Lewy Body Dementia (DLB) with non-cognitive symptoms and behaviour that challenges causing significant distress or potential harm to the individual or others if
    a. A non-pharmacological approach is inappropriate or has been ineffective **AND**
    b. Antipsychotic drugs are inappropriate or have been ineffective and
    c. ACHEIs are inappropriate or have been ineffective.

This framework aims to provide guidelines for the initiation of dementia drugs by specialists for the management of people with Alzheimer's disease, mixed dementia (Alzheimer's disease with concomitant vascular dementia), dementia associated with Parkinson's Disease and Lewy Body Dementia and subsequent management by GPs. It sets out the associated responsibilities of GPs and hospital specialists who enter into the shared care arrangements.

The framework does not outline the circumstances by which GPs with a special interest can initiate cholinesterase inhibitors or memantine. Such GPs should refer to any separate guidance on this, as and when such services are commissioned.

This document should be read in conjunction with the guidance "Responsibility for prescribing between Primary & Secondary/Tertiary Care" https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

2. Indication

The Acetylcholinesterase inhibitors (ACHEIs) are indicated in the treatment of Alzheimer 's disease of mild to moderate severity, as well as for use in the treatment of patients with mild to moderate in Alzheimer's Disease. Rivastigmine is also indicated for mild to moderate dementia in Parkinson's disease. They are additionally used in mixed Alzheimer's disease/vascular dementia (i.e. Alzheimer's Disease with concomitant vascular dementia associated with Parkinson's Disease or Lewy Body Dementia with non-cognitive symptoms causing significant distress or leading to behaviour that challenges).

Memantine is indicated in the treatment of moderate and severe stage Alzheimer's Disease. It is additionally used in mixed dementia (Alzheimer's disease with concomitant vascular dementia), Parkinson's disease dementia and Lewy Body Dementia, in the following circumstances;-

a) Patients with moderate stage Alzheimer's Disease , or mixed dementia (Alzheimer's disease with concomitant vascular dementia) as an alternative to Acetyl Cholinesterase Inhibitors (ACHEIs), in any of the following circumstances;-
   - Patients appropriate for drug treatment are unable to tolerate an ACHEI
   - When there are medical contraindications to the prescription of ACHEIs
   - There has been a loss of treatment effect from ACHEIs

b) Patients with Alzheimer's Disease (AD), mixed dementia (Alzheimer's disease with concomitant vascular dementia),Parkinson's disease dementia or Lewy Body Dementia (DLB) with non-cognitive symptoms and behaviour that challenges causing significant distress or potential harm to the individual or others if a non-pharmacological approach is inappropriate or has been ineffective in patients where:
   - A non-pharmacological approach is inappropriate or has been ineffective and;-
   - Antipsychotic drugs are inappropriate or have been ineffective
   - ACHEIs are inappropriate or have been ineffective

3. Dose

	Dose	Renal Impairment	Hepatic impairment
Donepezil Tablet and orodispersible	5mg OD increasing to 10mg OD after one month Maintenance- 5 to 10mg OD	No adjustment	No adjustment. Caution on titration
Galantamine Tablet and oral solution	4mg BD for 4 weeks then 8mg BD for 4 weeks then 12mg BD Maintenance- 8 to12mg BD	Avoid if eGFR less than 9 mL/minute/1.73m2	Initiation: 4mg OM for at least one week. 4 mg twice daily for at least 4 weeks. Max: 16mg
Galantamine MR Capsule	8mg OD for 4 weeks then 16mg OD for 4 weeks then 24mg OD Maintenance- 16 to 24mg OD		
Rivastigmine Capsule and oral solution	1.5mg BD for 2 weeks then 3mg BD for 2 weeks then 4.5mg BD for 2 weeks then 6mg BD Maintenance- 3 to 6mg BD	No adjustment required, but closer monitoring for side effects is advised	No adjustment required, but closer monitoring for side effects is advised
Rivastigmine Patch (for poor adherence)	4.6mg/24h for 4 weeks then 9.5mg/24hr for six months then 13.3mg/24 hr Maintenance- 9.5 to 13.3mg/24hr		
Memantine Tablets and oral Solution	5mg OD for 7 days then 10mg OD for 7 days then 15mg OD for 7 days then 20mg OD Maintenance- 20mg OD	• eGFR30-49ml/ minute/1.73m2: if 10mg tolerated for 1 week, ok to increase to 20mg • eGFR 5-29ml/minute /1.73m2: Max 10mg. • eGFR below 5: Contraindicated	• Mild to moderate impairment: No adjustment required • Severe impairment: not recommended.

Donepezil: Doses above 10mg daily may be clinically appropriate in individual patients under specific circumstances, but would be 'off licence' and should only be undertaken under the direct supervision of a specialist team for the management of dementia, after a thorough consideration of the possible benefits and risks of such a course of action.

Rivastigmine: If treatment is interrupted for more than three days, it should be re-initiated either orally at 1.5 mg twice daily or at 4.6mg/24h and dose re-titrated.

Rivastigmine oral to transdermal switch: The first patch should be applied on the day following the last oral dose as follows:

- Patients taking 3-6mg by mouth daily should initially switch to 4.6mg/24hour patch, and then titrate as above.
- Patients taking 9mg daily by mouth should switch to 9.5mg/24hour patch if the oral dose is stable and well tolerated; if oral dose is not stable or well tolerated then patient should be switched to 4.6mg/24hour patch and titrate as above.
- Patients taking 12mg by mouth daily should switch to the 9.5mg/24hour patch.

4. Duration of treatment

<table>
<tr><th>Donepezil</th><th>Galantamine</th><th>Rivastigmine</th><th>Memantine</th></tr>
<tr><td colspan="3">Treatment should be continued while it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms, or where it is clinically judged that the withdrawal of treatment would not be in the patient's best interests (for example due to the risk of an adverse clinical outcome, such as triggering behaviour that challenges) .</td><td rowspan="2">Examples of appropriate treatment end points include the development of significant side effects, the development of a significant physical illness, marked deterioration in the patients cognitive state or level of functioning etc.

Treatment should not be stopped on the basis of a score on the MMSE,MMSE; rather it should be a clinical decision, taking into account the patient's mental, cognitive and behavioural state, physical health, and prognosis</td></tr>
<tr><td colspan="3">In circumstances where there is a loss of treatment effect, after several months or years of treatment, the following options should be considered by the specialist team on an individual patient basis when clinically appropriate;-
1. Increasing the dose to the BNF maximum recommended dose
2. Considering prescribing an alternative ACHEI
3. Considering the appropriateness of the addition of memantine</td></tr>
<tr><td colspan="4">Sudden withdrawal of treatment should be avoided if possible, as this can precipitate a withdrawal reaction which can lead to an increased level of confusion</td></tr>
<tr><td colspan="4">The specialist team should provide the GP with clear directions about treatment end points, together with the offer of support and advice when necessary.</td></tr>
</table>

5. Contraindications and cautions

<table>
<tr><th>Donepezil</th><th>Galantamine</th><th>Rivastigmine</th><th>Memantine</th></tr>
<tr><td colspan="3">Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergic effects and should be started at a low dose and the dose increased according to response and tolerability.</td><td>Caution is recommended in patients with epilepsy, former history of convulsions or patients with predisposing factors for epilepsy</td></tr>
<tr><td>• Donepezil may exacerbate or induce extrapyramidal symptoms
• Neuroleptic malignant syndrome (NMS) has been reported to occur very rarely in association with Donepezil, particularly in patients also receiving concomitant antipsychotics.</td><td>• Bioavailability of galantamine may be increased with potent inhibitors of CYP2D6 (such as Quinidine, Paroxetine or Fluoxetine) or CYP3A4 (such as Ketoconazole or Ritonavir): may lead to an increase in cholinergic adverse effects.
• In these circumstances a reduction of the Galantamine maintenance dose may be necessary</td><td>• There is a risk of fatal overdose with patch administration errors, hence patients and carers should be advised of the patch administration instructions, particularly to remove the previous days patch before applying a new patch.
• History of seizures
• Body weight less than 50kg (may experience more adverse reactions and may be more likely to discontinue)</td><td>Concomitant use of N-methyl-D-aspartate (NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds act at the same receptor system as memantine, and therefore adverse reactions (mainly central nervous system (CNS)-related) may be more frequent or more pronounced (see also section 4.5).</td></tr>
<tr><td colspan="3">• Asthma or Chronic Obstructive Pulmonary Disease(COPD)
• Susceptibility to peptic ulcers
• History of falls/syncope
• Sick sinus syndrome or cardiac conduction disorders, including bradycardia
• Electrolyte disturbances
• Urinary retention or bladder outflow obstruction
• Gastro-intestinal obstruction</td><td>In most clinical trials, patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), or uncontrolled hypertension were excluded. As a consequence, only limited data are available and patients with these conditions should be closely supervised.</td></tr>
<tr><td colspan="4">Known hypersensitivity to active ingredient, or any other component of the product</td></tr>
<tr><td colspan="4">Pregnancy & Breastfeeding</td></tr>
<tr><td colspan="4">Hepatic impairment or Renal impairment
(Patients with clinically significant renal or hepatic impairment might experience more adverse reactions) See dosing table (4) for specific instructions with each medication.</td></tr>
</table>

Absolute contraindication to acetylcholinesterase inhibitors:

- Second or third-degree heart block in an unpaced patient– DO NOT prescribe AChEIs
- QT prolongation – Avoid prescribing AChEIs and seek advice
- Bradycardia of < 50 bpm - DO NOT prescribe AChEIs

Use of acetylcholinesterase inhibitors with caution:

AChEIs are potentially contraindicated in the following groups. Seek specialist advice and prescribe cautiously, if used, with ongoing monitoring:

- Left Bundle Branch block
- Patients on concomitant rate limiting drugs such as those listed belwo may be prescribed acetylcholinesterase inhibitors cautiously if pulse is between 50-60 bpm and asymptomatic
    - beta-blockers
    - amiodarone
    - digoxin
    - non-dihydropyradine calcium-channel blockers (e.g. diltiazem, verapamil) -.
- If rate limiting calcium channel blockers or beta-blockers are being used to treat hypertension, alternative anti-hypertensive agents might be considered to facilitate the introduction of acetylcholinesterase inhibitors

6. Adverse effects

Donepezil	Galantamine	Rivastigmine	Memantine
Very common and Common adverse effects			
Headaches & Dizziness			
Nausea, Diarrhoea, Vomiting, Anorexia & Weight Loss			
Fatigue, Syncope, Falls, hallucinations			
○Common cold ○Agitation ○Aggression ○Abnormal dreams or nightmares ○Insomnia ○Abdominal disturbances ○Rash, pruritus ○Muscle cramps ○Urinary incontinence ○Pain	○Decreased appetite ○Depression ○Tremor ○Somnolence or Lethargy ○Bradycardia ○Hypertension ○Abdominal pain ○Dyspepsia ○Hyperhidrosis ○Muscle spasms ○Asthenia ○Malaise	○Anxiety ○Sweating ○Heartburn ○Stomach pain ○Feeling agitated ○Feeling tired or weak ○Generally feeling unwell ○Trembling or feeling confused	○ Drug hypersensitivity ○ Somnolence, ○ Balance disorders, ○ Hypertension, ○ Dyspnoea, ○ Constipation, ○ Elevated liver function test.
Uncommon adverse effects			
Seizures, Bradycardia, Sinus bradycardia			
○Gastrointestinal haemorrhage ○Gastric/duodenal ulcers	○ Hypersensitivity Dehydration ○ Paraesthesia ○ Dysgeusia ○ Hypersomnia ○ Blurred vision ○ Tinnitus ○ Supraventricular extrasystoles ○ Atrioventricular block first degree ○ Palpitations ○ Hypotension ○ Flushing ○ Retching ○ Muscular weakness	○ Depression ○ Difficulty in sleeping ○ Fainting or accidentally falling ○ Changes in how well your liver is working	○ Fungal infections ○ Confusion ○ Hallucinations ○ Abnormal gait ○ Cardiac failure ○ Venous thrombosis / thromboembolism ○ Vomiting ○ Fatigue
Rare and very Rare adverse effects			
○Extrapyramidal symptoms ○Sino-atrial block ○Atrioventricular block ○Liver dysfunction including hepatitis	○Hepatitis	○Chest pain ○Rash, itching ○Fits (seizures) ○ Ulcers in your stomach or intestine	○Pancreatitis ○Psychotic reactions ○Hepatitis Seizures

Specific information should be sought from the current BNF (electronically www.bnf.org/bnf/) or Data Sheet (electronically www.medicines.org.uk)

7. Interactions

Refer to BNF Online to check for potential interactions with the medication/s of choice.

Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF www.bnf.org.uk or SPC (www.medicines.org.uk).

8. Monitoring

a. Drug Monitoring for Acetylcholinesterase Inhibitors

There is no requirement or need to monitor any additional biochemical or other markers during treatment with any of the drugs for dementia. Routine pulse checks should be carried out for patients taking acetylcholinesterase inhibitors at **baseline and during initiation** in accordance with the Rowland algorithm (Page10)

1. Pulse under 50 bpm
    - Withhold treatment with cholinesterase inhibitor
    - Review to identify any underlying cause/consider withdrawal of co-prescribed β –blockers and reassessment
    - If cause found unrelated to drug, or if pacemaker fitted, consider initiation (Patients fitted with cardiac pacemakers do not need pulse checks as pacemakers safeguard from developing bradycardia)
2. Pulse between 50 and 60 bpm and **asymptomatic**
    - Start/continue treatment
    - Review pulse and symptoms after one week
    - If patient remains asymptomatic
        - continue drug
        - check pulse one week after each dose increase
3. Pulse 50-60 bpm and **symptomatic** (e.g. syncope or 'funny turns')
    - Withhold or stop treatment with cholinesterase inhibitor
    - Review to identify any underlying cause/consider withdrawal of co-prescribed β –blockers and reassessment
    - If cause found unrelated to drug, or if pacemaker fitted, consider retrial of medication, with monitoring of pulse
4. Pulse over 60bpm
    - Start/continue treatment
    - Routine pulse checks at baseline, after each dose increase during titration

Routine baseline ECG is only recommended prior to initiating treatment with acetylcholinesterase inhibitors in patients with:

Unexplained syncope, bradycardia and patients taking concomitant cardiac rate-limiting medication e.g. beta-blockers, amiodarone

Cardiac monitoring for patients established on acetylcholinesterase inhibitors

- After initiation the pulse rate and symptoms should be monitored at 1 month.
- After any upwards titration of dose the pulse rate and symptoms should be reviewed after a further month.
- Any abnormal pulse rate or cardiac symptoms should be managed under the "Rowland algorithm" (Page 11)
- Asymptomatic patients with pulse rate above 60 bpm should be rechecked at 6 months.
- Patients with satisfactory pulse who are asymptomatic should be monitored annually e.g. as part of the General Practice dementia Quality Outcomes Framework (QOF) check.
- If the patient becomes unwell or develops symptoms they would need a full assessment including a check of their pulse and blood pressure

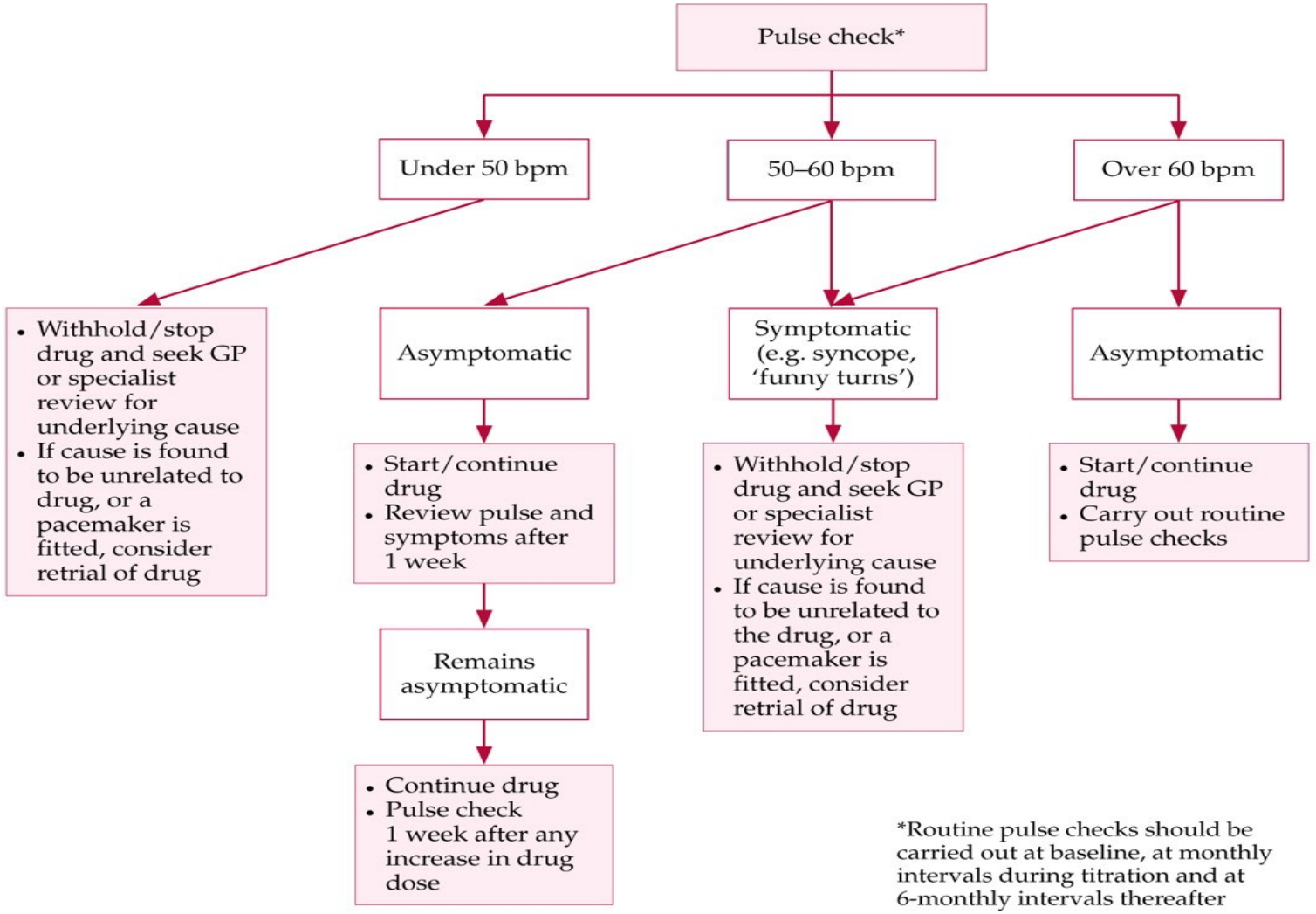

Fig. 1 Suggested guidelines for managing cardiovascular risk prior to and during treatment with acetylcholinesterase inhibitors in Alzheimer's disease. bpm, heartbeats per minute; the 'drug' means the chosen AChE inhibitor.

Courtesy of Rowland et al

b. Disease Monitoring for All Anti-dementia Medications

Routine compliance and side effects should be monitored by patients, carers, members of the specialist team (when appropriate) and the prescriber.

This may be provided by either the primary care team or specialist team, depending on individual patient and carer needs.

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 clinical judgement, taking into account information provided by the patient and carers and after conducting a Mental State Examination (including appropriate assessment of cognition).

The management of patients with dementia should involve partnership working to provide psycho-social and pharmacological interventions as outlined in the locally developed stepped care model for patients with dementia, based on the recommendations of the national Dementia Strategy.

9. Information to patient

The prescriber initiating treatment will be responsible for informing the patient and their carer about likely benefits and risks (including possible side effects) from the treatment prior to starting the drug. In situations where the patient is unable to give informed consent due to a lack of mental capacity, the patient's 'best interests' should be determined as outlined in the Capacity Act, by liaising with the patients relatives and carers, as well as other professionals involved in their care, prior to starting any possible treatment.

10. Responsibilities of clinicians involved in shared care

Stage of Treatment	Specialist	General Practitioner

Initiation	• Selection of suitable patients
	• To develop and co-ordinate the implementation of a comprehensive care plan for the patient and their carer
	• To initiate treatment, assess the patient 2 to 4 months after reaching the maintenance dose and determine whether treatment should be continued or not at this assessment.
	• Undertake monitoring as outlined in section 8a and 8b
	• Undertake and interpret routine baseline ECG prior to initiation **only** in patients with:
	  • Unexplained syncope
	  • Bradycardia
	  • Patients taking concomitant cardiac rate-limiting medication e.g. beta-blockers, amiodarone
	• Provide verbal and written treatment information to patient and their carer
	• To provide appropriate monitoring of the patient for treatment and side effects during the initiation phase, in liaison with the patient's GP
		• Liaise and seek advice from the specialist team, when appropriate
		• Monitoring of pulse prior to or at the point of referral
		• Take over prescribing of medication after the first month of treatment and provide ongoing clinical care

Maintenance	• Liaise and provide support to GP • Ensure clear guidance is provided to the General Practitioner about treatment end points	• Seek advice from specialist if necessary • Carry out routine pulse check and cardiac review 6 months after initiation and then annually as per Fig 1
Discontinuation	• Advising the GP when medication should be discontinued • Provide any necessary supervision, support or advice during the discontinuation phase • To initiate alternative treatment, should this be clinically appropriate	• Co-operate with the specialist during discontinuation

Contact Details:
Humber Teaching NHS Foundation Trust: contact as advised in clinic letter.
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APPROVAL PROCESS

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Consultation process:	***HTFT DTC, HEY Neurology***
Approved by:	***HTFT DTC, HERPC 2015***
Ratified by:	***HERPC April 2018***
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