Berkshire Healthcare NHS
NHS Foundation Trust

ACETYLCHOLINESTERASE INHIBITORS (ChEIs)

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1. Introduction

Berkshire Healthcare NHS Foundation Trust clearly supports the use of acetyl cholinesterase inhibitors (ChEIs) for the treatment of Alzheimer's dementia in accordance with NICE guidance.
The use of ChEIs in dementias not supported by NICE guidance is currently not commissioned by the PCT.

2. Referral

GPs should continue to refer patients with possible Alzheimer's disease to memory clinics in accordance with the NSF for older adults and NICE guidelines on dementia, CG42.
The referring GP will be asked to carry out physical examination, blood screen & ECG if indicated. Other causes of suspected dementia should be considered before referral.
These results will be reviewed by the memory clinic at the point of referral.

3. When treatment with a ChEI should be considered

a. Patients with a diagnosis of predominant Alzheimer Type Dementia of moderate severity, defined by an MMSE score of 10 – 20.
When assessing this score the following should be taken into account:

- There is a variability of MMSE scores in individuals (± 3points) as highlighted by the RCPsych.
- This score should be interpreted for each individual patient as advised by NICE CG42.

b. Treatment may also be considered in patients with a diagnosis of mild, moderate or severe dementia of Alzheimer Type if:

- a non-pharmacological approach is inappropriate or has been ineffective
- antipsychotic drugs are inappropriate or have been ineffective. (NICE CG42)
- people who score less than 10 because of low premorbid attainment or ability or linguistic difficulties, but who have moderate dementia as judged by an assessment tool sensitive to their level of competence
- people are not fluent in the language in which the MMSE is given
- people have learning disabilities, who should be assessed using LD tools and protocol
- people have language difficulties such as dysphasia

4. When treatment with a ChEI should not be considered

- Patients with severe dementia (MMSE< 10, where this appears to be accurate)
- Patients with MMSE above 20 where this appears to be accurate and other criteria (see above) are not met
- Patients with Vascular Dementia
- Patients with Fronto-Temporal Dementia
- Patients with Lewy body dementias*
- Dementia which does not fit the criteria for diagnosis of Alzheimers
- Myocardial Infarction

* services for these patients are not yet commissioned by the PCTs

5. Patients not eligible for treatment with a ChEI

Where patients are not eligible for treatment under NICE guidance (or Berkshire/MOBB Priorities Committee statement) (see below) it will be necessary for the memory clinic to refer the patient back to the GP. This would include those patients with Alzheimer's disease whose MMSE scores fall outside NICE recommendations.

Referrals should include:
- the reasons for the referral
- information for the patient and carer on the reason for the referral
- provision of a suggested date for review by the memory clinic
- suggested treatment options

6. Private patients
The trust is currently investigating the legal aspects of whether patients who are outside NICE guidance can obtain their prescribed medication on a private prescription facilitated by the trust.

7. Treatment

The choice of drug may vary according to the patient's clinical presentation. Where there are no other variables, treatment should be considered with the most cost-effective drug available.
Prescribers must maintain an up to date awareness of the financial differences between brands.

8. Investigations & Initiation of Treatment

All prescribers will be expected to provide the required monitoring and financial data on a quarterly basis. This may need to be collated manually.

a) Assessment, initiation and monitoring of response will be carried out by the Specialist Memory Team (SMT) or Learning Disabilities services (LD). This may include medical and non-medical prescribers, nursing and psychological therapy support and occupational therapists.

b) **Baseline assessment will include:**
- Clinical assessment
- Diagnosis
- Carer interview
- Cognitive assessment- MMSE & other relevant screening tools
- Activities of Daily Living Scale (BADLS)
- Assessment of non-cognitive & behavioural symptoms
- Where clinically indicated, neuroradiology (CT/MRI/SPECT scan)
- Where clinically indicated, neuropsychological Assessment
- Where clinically indicated in LD, the DLD (Dementia in Learning Disability – Evenhuis et al).
- Where clinically indicated in LD, the CAMCOG or DSDS (Dementia Screening in Downs Syndrome)

c) The SMT must be satisfied that the patient will be able to comply with treatment and monitoring.

This will usually mean a carer or care-worker is able to monitor medication. The care worker or relative must be advised by the SMT as to the expectations of the team in this area and provided with information regarding the use of ChEI within NICE guidance.

d) Trust procedures (Care and Control of Medicines Policy - latest version) must be consulted and adhered to.

e) Pre-treatment counselling supported by written information will be given by the SMT or LD. (see attached). There must be specific discussion about cessation of therapy when there is evidence of non-response and discussion about the effects of treatment at different stages of illness, where relevant, to inform choice.

f) The referring GP will be asked to carry out physical examination, blood screen & ECG if indicated.

g) If unacceptable side effects are experienced (as determined by the patient and carer) it may be appropriate to switch to an alternative ChEI for a specified trial period.

9. Recommendations for the use of Cholinesterase Inhibitors (ChEIs) for the management of Moderate Alzheimer's disease

- All three cholinesterase inhibitors (ChEIs); rivastigmine (Exelon®), galantamine (Reminyl ®) and donepezil (Aricept®) are available on the Trust formulary for prescribing as part of a larger management care package for patients with moderate Alzheimer's disease, usually diagnosed by an MMSE score of 10-20, in line with NICE guidance[1],[2]
- Memantine will not be initiated as a treatment option in people with moderately severe to severe Alzheimer's disease except as part of a well designed clinical trial. In exceptional cases, it may be prescribed for named patients with behavioural disturbances unsuitable for alternative treatments. Memantine costs are charged to the ChEI budget.
- Prescribing of ChEIs will remain the responsibility of the initiating consultant within the trust as currently there are no shared care arrangements in place with primary care.
- All things being equal, the choice of ChEI is based on cost grounds. Clinicians are kept informed by the Chief Pharmacist which ChEI is the most cost effective as prices can change at short notice. Whilst there is no evidence to suggest that switching between ChEIs is unsafe, there is no evidence to support this process in situations other than where there are tolerance issues.
- ChEIs prescribed by BHFT clinicians are dispensed by the Pharmacy at Prospect Park Hospital.
- Budgets for ChEIs are allocated on a locality basis and individual consultants, are expected to manage their prescribing budget to ensure that only those patients who fit within the NICE guidance or the Berkshire/MOBB Priorities Committee

[1] NICE/SCIE clinical guidance no. 42 – Dementia: Supporting people with dementia and their carers in health and social care
http://www.nice.org.uk/guidance/CG42

[2] NICE technical appraisal no. TA111 Alzheimer's Disease – donepezil, galantamine, rivastigmine (review) and memantine
http://guidance.nice.org.uk/TA111

statements on ChEIs are being prescribed these drugs. (see below). There are currently over 1300 patients in Berkshire being treated with ChEIs.
- The Berkshire PCTs only commission BHFT to prescribe for patients within this guidance.
- This means that there are difficult choices to be made by all prescribers on who should be started and when they should be stopped.

10. ChEI Dosing Recommendations

- Galantamine 16mg daily is a recognised maintenance dose and many patients will be treated successfully on this dose without further increase. The 24mg daily maintenance dose should only be considered on an individual basis and if used should be carefully monitored and assessed for any additional benefit it provides. If none is apparent the dose should be reduced back to 16mg daily. This also applies to patients already in treatment.
- Donepezil 5mg daily is a recognised maintenance dose and many patients will be treated successfully on this dose without further increase. A Cochrane review reported that benefits of the 10mg dose are marginal at best, and advised that the 5mg dose may be a better option when taking cost and tolerability into account[3]. If 10mg daily is used, it should be carefully monitored and assessed for any additional benefit it provides. If none is apparent the dose should be reduced back to 5mg daily. This also applies to patients already in treatment.
- Rivastigmine 3mg twice a day is a recognised maintenance dose and may patients will be treated successfully on this dose without further increase. A Cochraine review[4] showed no increased benefit from 6mg twice a day then 3mg twice a day, but did find increased side effects. If 6mg twice a day is used, it should be carefully monitored and assessed for any additional benefit it provides. If none is apparent the dose should be reduced back to 5mg daily. This also applies to patients already in treatment.
- Rivastigmine is also available as patches (4.6mg/day and 9.5mg/day) which have been show to be as effective as the equivalent oral dose, but with less nausea, vomiting, weight loss and dizziness. The patches are available for patients either who need to minimise these specific side effects, or those who can not swallow the capsules.
- Regular assessments of maintenance therapy must be carried out at least every 6 months. Treatment should normally only continue if the MMSE score remains at or above 10 points and the treatment is considered to still have worthwhile effect on the global, functional and behavioural condition.

- Consideration should be given to the use of a trial discontinuation during which time deterioration of condition or continued benefits can be more clearly assessed.

[3] Birks J and Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane database of Systematic reviews, 2006

[4] Birks J et al. Rivastigmine for Alzheimer's disease (Review). Cochrane database of Systematic reviews, 2009

11. Recommendations for patients with special problems eg poor compliance; where drug interactions may be a problem; Gastro-intestinal side effects; swallowing difficulties:

- For patients in whom compliance with medication is poor, or is likely to be poor, once-daily oral preparations or rivastigmine patches would be treatment of choice[5].
- For patients in whom concurrent medication regime includes, or is likely to include cytochrome P450 inducers (eg carbamazepine, phenytoin) or inhibitors (eg fluoxetine, paroxetine) – rivastigmine is least likely to interact[6],[7]
- For patients in whom gastro-intestinal side-effects of ChEIs have previously been intolerable – donepezil may be better tolerated than either rivastigmine or galantamine[8], [9]
- For patients who have swallowing difficulties or those with severe BPSD who cannot tolerate oral medicines, rivastigmine patches are the formulation of choice. Alternatively donepezil is available as an orodispersible tablet. Rivastigmine and galantamine are available as liquid preparations but both are very expensive and should be avoided.
- A ChEi should not be taken concurrently with either another ChEi or with anyother medication which acts to increase (e.g. carbachol) or decrease (e.g. dicycloverine, toldterodine, oxybutynin, and ipratropium) the cholinergic neurotransmission.

12. Interruptions in drug treatment

The following guidance is suggested:
a) Rivastigmine patch and capsules - should be retitrated if there is a gap in treatment of 3 days or more.

b) Donepezil - if the patient has only taken this for up to 3 weeks, then any treatment break would have to be discussed with clinician. Although, the 5mg dose is usually prescribed for four weeks before reviewing dose.

If the patient has taken donepezil for more than three weeks then a break of <7 days would not significantly affect plasma levels. Breaks of more than 7 days would need to be retitrated. With donepezil, however, it should be noted that 5mg is a treatment dose in itself.

c) Galantamine (ordinary and 'XL') - Although there is no formal guidance, the manufacturers state that for treatment breaks longer than 7 days, the dose should be retitrated.

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[5] Bullock, R. "A cost-effectiveness model can be useful when selecting cholinesterase inhibitors for AD" The Clinician (3) march 2004

[6] Stockley, I. Stockley's Drug Interactions 2008. Pharmaceutical press.

[7] Bentue-Ferrer, D. at al. clinically significant drug interactions with cholinesterase inhibitors: a guide for neurologists. CNS Drugs. 2003;17 (13): 947-63.

[8] Jones, RW. Et al. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. Int. J. Geriat. Psy. 2004 (19); 58-67.

[9] Wilkinson, DG. Et al. A multinational, randomised 12 week comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. Int.J.Clin.Prac.2002 (56). No. 6; 441-446.

d) Memantine - this is only on the Trust formulary in a limited capacity (for patients with significant behavioural disturbances associated with dementia - only 30 patients allowed). It is not routinely prescribed within this Trust. (See section 9 above)
The manufacturers state that:

- Break of 1-2 days - the patient can restart at their original dose.
- Break of 3-7 days - dose would be titrated from 10mg daily.
- Break of more than 7 days - retitrate from 5mg daily.

13. Berkshire/MOBB Priorities Committee statements

BHFT prescribers are required to comply with Berkshire Priorities Committee statements.(Note: from April 1st 2010, the Berkshire Priorities committee merged with those of Milton-Keynes, Oxfordshire and Buckinghamshire to form the MOBB Priorities Committee). The South Central (includes Berkshire) Priorities Committee has made the following policy statements with regard to prescribing of: Donepezil, galantamine, rivastigmine and memantine:

- For the treatment of Alzheimer's disease (January 2001, updated February 2009) recommending that the NICE technology appraisal 111 (amended) should be endorsed as they have found no evidence to recommend deviating from these guidelines.

http://www.berkshire.nhs.uk/priorities/_policies/BPC-policy-11b-AChEIS-for-Alzheimers-disease.pdf

- For the treatment of dementia associated with Parkinson's disease or Lewy bodies (February 2009) recommending that the ChEIs donepezil, galantamine, rivastigmine should be available as an option to treat patients with dementia associated with Parkinson's disease or dementia with Lewy bodies if they have non-cognitive symptoms causing significant distress to the individual (for example visual hallucinations), or leading to behaviour that challenges. Other uses of ChEIs donepezil, galantamine, rivastigmine in patients with PDD or LBD are low priority (and therefore should not be prescribed).

http://www.berkshire.nhs.uk/priorities/_policies/BPC-policy-146-AChEIS-for-PDD-LBD.pdf

14) Patients with language difficulties, Learning Disability patients, and patients judged to have moderate dementia but are outside MMSE 10-20 range

Though it is recommended that ChEIs should be prescribed only to people with Alzheimer's disease of moderate severity, healthcare professionals should not just rely on the MMSE score in people who:

- Score greater than 20, but who have moderate dementia as judged by significant impairments in functional ability and personal and social function compared with premorbid ability
- Score less than 10 because of low premorbid attainment or ability or linguistic difficulties (or other communication difficulties) or other disabilities (for example sensory impairments) but who have moderate dementia as judged by an assessment tool sensitive to their level of competence
- Are not fluent in the language in which MMSE is given
- Have learning disabilities; according to the level of competence, consider alternative tests: eg CAMCOG; CAMDEX;DMR;DSDS; DLD
- There are similarly exceptional reasons why use of MMSE would be an inappropriate assessment tool.
- If patients assessed as having moderate Alzheimer's disease are initiated on or continue on ChEIs who have MMSE scores outside of the range 10-20, a record of

the reason will be made in the notes and information on why the decision has been made supplied in the quarterly reporting to the Chief Pharmacist. Each specialist will keep a simple database of all patients being treated with MMSE scores outside the range 10 – 20. This will include a reason to justify its use (see appendix 1)

15) Prescribing for Learning Disability patients

- LD consultants can prescribe ChEIs, (provided the patient fulfils NICE criteria), and will be responsible for the monitoring of patients.
- Funding for the ChEIs will be charged to the relevant locality memory clinic budget. This will mean the pharmacy will need to know the locality of the patient before the drugs can be dispensed. Pharmacy will record the spend in each locality on LD patients.
- Choice of drug is based on price – Contact the Chief Pharmacist for the current most cost-effective ChEI.
- To prescribe the drugs, the LD consultant must write a prescription using the BHFT out-patient prescription chart which can be obtained by contacting the memory clinic pharmacy technician or dispensary manager on 0118 960 5080
- The prescription will be dispensed by the pharmacy Prospect Park Hospital – usually the drugs are posted out to the patient at monthly intervals, the pharmacy will advise how this is best organised.

16) Patients from out of area (and/or prescribed by a non-BHFT prescriber)

- Patients arriving from out of area (and/or prescribed by a non-BHFT prescriber) and already established on a ChEI will be reviewed with regard to continuing benefit and whether the drug should be discontinued.
- BHFT will not be able to continue prescribing until an assessment of the patient has been made – the patient should be asked to obtain at least 3 months supply from their previous (eg out of area) prescriber to ensure sufficient time for an appointment and assessment to be made.
- If a patient is unable to obtain a supply from their previous prescriber, then it will be the responsibility of the patient's new GP to decide whether to continue prescribing the ChEI until such time as the patient can be assessed by BHFT.
- In cases where a patient is unable to obtain a three month supply then, on a case by case basis, a BHFT prescriber may consider it appropriate to prescribe a supply until able to fully review the patient, however this is not standard practice.
- Patients already established on memantine, including those from out of area will be reviewed with regard to continuing benefit and whether the drug should be discontinued.
- Patients from out of area (or prescribed by a non-BHFT prescriber), already established on a ChEI, who are assessed and found to be outside current NICE guidelines, should be referred to the GP and/or original prescriber and the PCT case review committee. In such cases BHFT will not initiate prescribing and the current prescriber will be asked to maintain the current prescription.
- Where the PCT case review committee agree on ethical grounds that the prescribing should continue, the trust will agree with the PCT whether the GP or other non-BHFT prescriber will take over the prescribing or whether BHFT will prescribe and invoice the PCT.
- In such cases, the prescribing team must inform the pharmacy department of the names of such patients so that correct invoicing can occur.
- Once the patient's state is within NICE guidelines then the trust will take on prescribing for the patient.

17) Patients admitted to hospital

a) Patients admitted to a BHFT in-patient ward:

- Patients already established on a ChEI should be advised, where possible, to bring in their own supply of all prescribed medications including their ChEI when they come into hospital (or their carer's asked to bring in their medication)
- pharmacy staff will check:
    - the "Patient's own drugs" are suitable for re-use
    - Complete the medicines reconciliation process to ensure prescribed medication corresponds to that prescribed prior to admission
    - The patient is currently prescribed the ChEI by BHFT
- If the patient is not known to BHFT, then the admitting consultant will need to liaise with the relevant locality memory clinic consultant to check whether treatment can be continued (see above "Patients from out of area (and/or prescribed by a non-BHFT prescriber).
- If the patient is from out of area then arrangements will need to be made depending on whether the patient will remain in Berkshire following discharge.

b) Patients admitted to the Royal Berkshire hospital or Heatherwood and Wexham Park hospitals

- For patients who are prescribed ChEI by BHFT, these patients will have been given a supply of the ChEI which will have (usually) been posted to the patient's or carer's home. The Acute hospital should be asked to obtain the already dispensed supply via a family member/carer and administer this supply to the patient while in hospital. Where this supply cannot be obtained, the acute trust should be asked to procure and dispense a supply to the patient as they would for any in-patient prescribed treatment.
- On discharge, checks should be made by the acute trust to confirm that the patient has a supply (which should have been dispensed by Prospect Park hospital pharmacy) and any of the patient's own remaining ChEI on the ward should be given to the patient (unless a decision has been made in conjunction with the memory clinic team to discontinue the ChEI).
- For patients who are not under the BHFT memory clinic, the acute trust should supply in the usual way.

18) Monitoring

- Patients taking ChEI should have their weight monitored during treatment. Weight loss is thought to be due to the disease state rather than the ChEI.
- Patients should be observed for extrapyramidal symptoms, which could be exacerbated, or even initiated by ChEI therapy.

19) Initial Evaluations

a) Patients will be reviewed by the SMT 12 weeks after reaching the optimum dose. The assessment will include

- clinical review
- MMSE, Carer interview
- BADLS
- Assessment of non-cognitive symptoms.

b) The drug will be continued where there has been significant demonstration of:

- improvement or stabilisation in cognition and/or
- evidence of stability or improvement in functional ability and/or

- improvement in behaviour or non-cognitive symptoms where this has been the main indication for use.

c) Where there is doubt it may be appropriate to further increase dose to the recommended BNF daily maximum, or consider a trial discontinuation.

d) The drug should be discontinued if there is no significant demonstrated benefit.

e) Patients who continue on the drug will have a full review as above every 6 months.

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9 SPC for Aricept, last updated 28/05/2009. Accessed 17/03/10 via www.emc.medicines.org.uk
10 SPC for Reminyl Tablets, last updated 16/10/2009. Accessed 17/03/10 via www.emc.medicines.org.uk
11 SPC for Exelon, last updated 27/11/2009. Accessed 17/03/10 via www.emc.medicines.org.uk

20) Ongoing Evaluation and Audit

The use of the drugs and memory clinic activity will be audited every two months as part of the function of the Medicines Management Committee.

A 6-monthly report on levels of prescribing will be prepared by the CHEI working party, and sent to Berkshire Healthcare NHS Trust Board. This will include:

a) Trust participation in nationwide POMH-UK audit

b) Clinic data including:
- Patients referred
- Patients treated with ChEI
- MMSE & BADLS scores at referral, after 3 months of treatment at optimum dose, and every 6 months thereafter
- selection criteria i.e. which patients' MMSE scores were used solely as a selection criteria and which other selection criteria are used
- Scan & neuropsychometric referrals

c) Prescribing data including
- choice of drug
- Length of treatment
- switching data

d) It is anticipated that this data will be collected via the DeNDRoN networks but otherwise must be recorded by locality Clinics

21) Discontinuation of Treatment

Patients/ carers should be told to advise the memory clinic or pharmacy department at Prospect Park Hospital as soon as possible if the prescribed drugs are no longer needed to prevent accumulation of unwanted drugs and to minimise wastage.

As a patient's MMSE falls to around 10 or 11, plans should be made with the patient and family to discontinue the medication.

The drug should not be continued if there is deterioration in the patient's cognitive global, functional and behavioural condition and if the MMSE falls below 10.

The decision to discontinue the ChEI should only be made by the consultant in conjunction with the SMT, and carers' views should be sought. The reasons for discontinuation of the drug should be clearly discussed with the patient and family, and documented in the patient's medical notes.

Where patients are admitted to full time care, the role of the ChEI in treatment should be reconsidered. Where the MMSE remains above 10, discussion with primary care teams around the benefits of continuing the medication should include the increased role of the primary care teams. Where possible, transfer of the prescribing responsibility should pass to primary care, but this must remain a joint agreement.

Any change in medication should always involve a review with the SMT, patient and carer.

22) Memantine

As stated above the trust, and the Berkshire/MOBB Priorities committee support the view taken by NICE that memantine should only be prescribed as part of a well designed clinical trial.

However the trust recognises that very occasionally there will be exceptional patients who have significant behavioural disturbances associated with dementia with an MMSE of less than 14. It has limited these to only a few patients within the trust at a time, and the funding for these will come from each locality's ChEI budget.

Memantine will be prescribed as monotherapy and not in combination with cholinesterase inhibitors or atypical antipsychotics except during a time limited change over a specified period.

Those patients prescribed memantine will be monitored as follows:

Month One
Repeat baseline assessments. Patient or carer supplied with 28 day supply prescribed on hospital prescription every 28 days.

Month Four
The patient will have been on 10mg bd for at least 12 weeks, then repeat baseline assessments. A decision is made to stop or continue Memantine based on the repeat assessments.

Prescribing will only continue after the month 4 assessment if there has been an improvement in any of the 4 standard assessment tools used. Prescribing will cease when all of the 4 assessment scores have declined or the drug is thought generally to be ineffective.

Normally a patient will have a trial off the medication for a month. If there is deterioration in the patient's mental health the memantine therapy can be restarted and reviewed regularly as if it had not been stopped. There is no published data on how or when to stop memantine and these guidelines are aimed primarily at preventing ineffective prescribing

Patient or carer supplied with 28 day supply prescribed on hospital prescription every 28 days if the patient is benefiting from treatment.

Month Six and Six monthly thereafter

Repeat baseline assessments.
Patient or carer supplied with 28 day supply prescribed on hospital prescription every 28 days if the patient is benefiting from treatment. GPs will be advised of the results of the assessment and of further management. The locality Consultant Psychiatrist will retain responsibility for these assessments to ensure the patient continues to benefit from this treatment.
Assessment with the 4 tools above will occur every 6 months during maintenance treatment. This is in line with the way the cholinesterase inhibitors are monitored.

Appendix 1

Berkshire Healthcare NHS
NHS Foundation Trust

CHEI: DATA COLLECTION FORM

CLINIC:		PERIOD:	
Total number of patients prescribed CHEI			
INITIATION	DIAGNOSIS		
	ALZHEIMERS	PDD / LBD	OTHER
Number of new patients diagnosed with dementia			
Number of new patients prescribed CHEI			
Number of new patients with MMSE >20 or <10			
Number of new patients prescribed CHEI with MMSE >20 or <10			
Number of new patients prescribed galantamine			
Number of new patients prescribed rivastigmine			
Number of new patients prescribed donepezil			
Number of new patients prescribed memantine			
Total number of patients started on CHEI			
DISCONTINUATIONS	DIAGNOSIS		
	ALZHEIMERS	PDD / LBD	OTHER
Side effects			
Non-response			
Deterioration			
Death			
Moved away			
Patient choice			
Other			
Total number of patients discontinued medication			

Treatment with a Cholinesterase Inhibitor (ChEI)