National Institute for Health and Care Excellence

Draft for consultation

Addendum to clinical guideline 42, Dementia: supporting people with dementia and their carers in health and social care

Clinical Guideline Addendum 42.1

Methods, evidence and recommendations

February 2016

Draft for Consultation

Developed by the National Institute for Health and Care Excellence

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

Internal clinical guidelines

The Internal Clinical Guidelines team develops clinical guidelines that address key aspects of diagnosis or management for specific diseases and conditions.

These guidelines are developed using a Committee whose members are topic experts recruited based on their clinical experience and expertise in the condition under consideration. The Committee have specialist knowledge of the topic and may include providers, commissioners and practitioners, and should include at least 1 lay member.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on Dementia (NICE clinical guideline CG42) was reviewed in 2015 as part of NICE's surveillance programme.

The surveillance report acknowledged that an update of the guideline should include an update of recommendation 1.3 from TA217 regarding the systems for prescribing and reviewing treatment with donepezil, galantamine, rivastigmine and memantine in people living with Alzheimer's disease. This had previously been agreed following the 2014 review recommendation proposal consultation of the TA guidance. The full surveillance report can be found here.

1.2 Making recommendations

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Person-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Information for consultation

You are invited to comment on the new recommendations in this update. These are marked as **[new 2016]** if the evidence has been reviewed and the recommendation has been added or updated.

Where recommendations are shaded in grey and end **[2011]**, the evidence has not been reviewed since the publication of NICE technology appraisal 217. We will not be able to accept comments on these recommendations.

Recommendations

1. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (incorporating TA217)

Incorporated from TA217: **NOT FOR COMMENT**

1.1. The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine are recommended as options for managing mild to moderate Alzheimer's disease under all of the conditions specified in 1.3 and 1.4. [2011]

1.2. Memantine 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.

Treatment should be under the conditions specified in 1.3. [2011]

1.3. Treatment should be under the following conditions:

- Prescribers should only start treatment with donepezil, galantamine, rivastigmine or memantine on the advice of a clinician experienced in diagnosing and treating Alzheimer's disease. **[new 2016]**
- Ensure that local arrangements for prescribing and supply follow the NICE guideline on medicines optimisation (NICE guideline NG5). **[new 2016]**

Incorporated from TA217: **NOT FOR COMMENT**

- Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms. **[2011]**

- Review treatment in line with local shared-care arrangements, and the NICE guideline on medicines optimisation (NICE guideline NG5). **[new 2016]**

Incorporated from TA217: **NOT FOR COMMENT**

1.4. If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles. [2011]

1.5. When using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical,

Incorporated from TA217: **NOT FOR COMMENT**

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. [2011]

1.6. 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. [2011]

1.3 Person-centred care

This guideline offers best practice advice on the care of people aged 40 years and over living with dementia.

Individuals and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

NICE has also produced guidance on the components of good service user experience. All healthcare professionals and social care practitioners working with people using adult NHS mental health services should follow the recommendations in Service user experience in adult mental health.

1.4 Methods

This update was developed based on the process and methods described in The Manual 2014

2 Evidence review and recommendations

2.1 Introduction

The aim of this review question was to determine which clinicians should prescribe and review donepezil, galantamine, rivastigmine or memantine for the cognitive symptoms of dementia in people diagnosed with Alzheimer's disease.

This review question updated the issues around initiation and review of the acetylcholinesterase inhibitors (AChEIs; donepezil, galantamine and rivastigmine) and the NMDA receptor antagonist (memantine), relating to the first and third bullet points of recommendation 1.3 of the existing NICE technology appraisal guidance TA217 (Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease). The second bullet point of recommendation 1.3, which considers continuation of these drugs, will be considered as part of a full update of the existing NICE Clinical Guideline on Dementia (which is due for publication in September 2017).

2.2 Review question

Who should start and review the following pharmacological interventions:

- donepezil
- galantamine
- rivastigmine
- memantine

for people with Alzheimer's disease and how should a review be carried out?

2.3 Clinical evidence review

A systematic evidence search was conducted (see appendix D) which identified 6344 articles. The titles and abstracts were screened and 66 full-text papers were identified for inclusion. Sixty three papers were subsequently excluded because they did not fit the inclusion criteria. Two studies described in 3 papers were presented to the Committee (Aupperle et al., 2000; Aupperle et al., 2003; Watanabe et al., 2012).

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.3.1 Methods

The review focused on identifying studies that were specified in the PICO framework described in Table 1.

Table 1: PICO

Population	• People aged 40 years and over with a diagnosis of Alzheimer's disease
Intervention	• The initiation and review of donepezil, galantamine, rivastigmine, memantine by non-specialists in any setting (for example secondary care; mental health services; community mental health services, including memory clinics; GP outreach clinics; primary care) • Shared-care prescribing protocols
Comparator	• The initiation and review of donepezil, galantamine, rivastigmine, memantine by psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of older people
Outcome	• Clinical outcome including cognitive functional and behavioural ability • Over-prescribing/under-prescribing and potentially avoidable adverse effects (including hospital admission) • Medication errors • Access to health and social care support • Adherence • Patient and carer experience and satisfaction • Resource use and cost

For full details of the review protocol please see appendix C.

There was no restriction on study design for inclusion in the evidence review. However, it was anticipated that the most useful study types would be observational designs including prospective/ retrospective cohort studies. It was expected that the most appropriate design would be a study that compares non-specialist prescribing of these interventions with specialist prescribing.

The Committee was interested in identifying evidence relating to both the prescribing and reviewing of AChEIs and memantine. This is because it was expected that the prescribing of these medications for people living with Alzheimer's disease may be carried out by a different health professional to the person undertaking the review. Evidence associated with these practices was identified independently.

Two observational studies were included in the evidence review. One study presented in 2 papers provided evidence on the prescribing of donepezil for people living with Alzheimer's disease and 1 paper was identified as evidence for reviewing treatment with donepezil.

The quality of evidence for each outcome was considered using the approach recommended by the Grading Recommendations, Assessment, Development and Evaluation (GRADE) working group. Due to variations in the way the outcome data were reported by each study, the evidence statements were presented by intervention/study rather than by outcome.

For a summary of included studies please see Table 2 (for the full evidence tables and full GRADE profiles please see Appendix G: and Appendix I:).

Table 2: Summary of included studies

Author (year)	Study type	Participant details	Comparisons	Outcomes of interest	Length of follow up	Study location
Prescribing donepezil						
Aupperle et al. (2000); Aupperle et al. (2003)	Retrospective cohort	**Patient characteristics:** All patients had received an initial evaluation and diagnosis of Alzheimer's disease from a university diagnostic clinic **Evaluable total:** Original population receiving diagnosis (N=80) **Participants with 1-year follow up data** (N= 58) mean age 78.8 years MED (n=31); mean age = 82.9 years GERO (n=27); mean age = 80.4 years **Participants with 2-year follow up data:** (N= 39) mean age 78.4 years MED (n=22); mean age = not reported GERO (n=17); mean age = not reported	• Participants being seen by a primary care physician Compared with: • Participants being seen by a member of a geriatric psychiatry facility	• Clinical outcome (including cognitive, functional, behavioural ability) • Access to health care and social care support • Concordance and compliance • Patient and carer experience and satisfaction	1 year (2000) 2 year (2003)	USA
Reviewing donepezil						
Watanabe et al. (2012)	Observational before-and-after study	**Patient characteristics:** The records of patients diagnosed with AD or mixed AD/VaD were followed up with the GP	• Participants enrolled into a donepezil outpatient advisory service after it was established (DOCS) Compared with:	• Concordance and compliance • Patient and carer experience and satisfaction	4 weeks	Japan

Author (year)	Study type	Participant details	Comparisons	Outcomes of interest	Length of follow up	Study location
		Evaluable total: Total sample (N=111) Non DOCS (n=59); mean age = 79.0 years DOCS (n=52); mean age = 77.2 years	• Participants enrolled before a donepezil outpatient advisory service was established (non DOCS)			

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2.4 Health economic evidence review

A literature review was undertaken by applying standard health economic filters to the clinical literature searches. 1049 records were returned; 0 were retained as cost–utility analyses that addressed the review question.

2.5 Clinical evidence statements

2.5.1 Evidence statement

2.5.1.1 Prescribing donepezil (speciality versus non-speciality prescribing)

One very low-quality observational study conducted in the USA in the 1990s with 57 participants found at 1 year follow up the number of people receiving a prescription of donepezil was significantly lower for people being seen by a primary care physician compared with those seen by a geriatric psychiatrist.

At 1 year follow up, the study reported a mean Clinical Dementia Rating significantly higher (indicating more severe dementia) for people being seen by a primary care physician compared with those being seen by a geriatric psychiatrist. The use of health and social care support (including number of hospitalisations, use of home health aides and dementia day care programs), and the mean carer distress rating were not significantly different for people being seen by a primary care physician compared with those being seen by a geriatric psychiatrist.

In the same study, at 2 year follow up , (39 participants), the number of people receiving a prescription of donepezil and the use of health and social care support (including number of hospitalisations, use of assisted living and residence in nursing homes) were not significantly different for people being seen by a primary care physician compared with those being seen by a geriatric psychiatrist.

2.5.1.2 Reviewing donepezil (advisory service versus no advisory service)

One very low-quality before-and-after study conducted in Japan with 111 participants reported the number of people living with Alzheimer's disease who were continuing to use donepezil after 1 year was significantly greater for people using an advisory consultation service compared with those who had not used this service. The mean duration of donepezil treatment and mean level of understanding for patients and carers was also significantly higher for people using the advisory consultation service compared with those who had not used the service.

2.6 Evidence to recommendations

Relative value of different outcomes	The Guideline Committee agreed it was important that included outcomes considered the impact of medication changes on access to health and social care support and also reflected outcomes for both people living with dementia and their carers. The Committee recognised that the outcomes presented in the evidence review were limited and felt this was consistent with the very low quality of the evidence (see 'Quality of evidence' below). The Committee noted that the processes for issuing and dispensing prescriptions differ across primary and secondary care settings. For example, it was perceived that the issuing of repeat prescriptions in primary care is likely to be more reactive to requests from the person living with dementia, whereas the issuing of prescriptions in specialist services is perceived to be more proactive when treatment is initiated.

	The Committee noted that the number of prescriptions dispensed may not necessarily equate to adherence with prescribed medication, as it does not indicate whether people take the medicines dispensed. The Committee observed for the outcome concordance and compliance, that the relative risk associated with the number of prescriptions at 2 year follow up did not identify a significant effect; however the primary data indicated a large difference. The Committee considered this magnitude of effect as potentially important regardless of statistical significance. Although, in Aupperle et al. 2003, the authors did not report standard deviation at 2 year follow up the Committee noted that, participants who were seen by a geriatric psychiatrist experienced an overall decline in Clinical Dementia Rating (CDR) over 2 years (suggesting that the average participant's dementia improved over this period). The committee thought this would be very unusual, as Alzheimer's disease is a degenerative condition. The Committee agreed that the outcomes reported were in line with their own clinical experience. It was noted that people with dementia in non-specialist settings may be more likely to stop medications.
Quality of evidence	The Committee agreed that the evidence presented was very low quality and noted the methodological limitations of the identified studies. The Committee agreed that the identified research evidence would not necessarily reflect current practice in the UK for the use of AChEIs. It was noted that the studies were conducted during the 1990s, when clinicians were much less familiar with AChEIs. The included studies were also conducted overseas where healthcare systems and services differ to practice in the UK. For Aupperle et al. (2000) and Aupperle et al. (2003) the Committee noted that the observational design of the studies meant that there was a high risk of selection bias. The Committee further noted that the observational design of Aupperle et al. (2003) meant there was a lack of interpretable findings on reasons for attrition, making it difficult to infer whether attrition was a consequence of adverse effects or lack of efficacy. The Committee acknowledged the limitations of the Watanabe et al. (2012) study. They agreed the observational design, small sample size, short follow up and selective reporting reflected that the study was very low quality.
Trade-off between benefits and harms	The Committee discussed the evidence base and agreed that they would be unable to make recommendations based solely on the reported outcomes. The Committee raised concerns about the lack of evidence identified in relation to the initiation of AChEIs and memantine but agreed that initiation is implicitly linked to diagnosis. It noted that recommendation 1.1 and 1.2 of TA217 imply that a diagnosis is needed before treatment can be initiated. The Committee agreed that the purpose of memory clinics is not solely to prescribe AChEIs and memantine but to provide specialist assessment in diagnosing, treating and supporting people living with dementia. The Committee noted that the current guideline suggests that diagnosis should be made by a specialist (CG42 1.4.3.1), and that this will be subject to a separate evidence review as part of the ongoing update. The Committee acknowledged the practical issues around the mechanisms for prescribing, dispensing and monitoring medication adherence. Committee members raised concerns that people may have to wait for a diagnosis before they can start treatment but the Committee agreed that there should not be an artificial barrier preventing the transfer of care between specialist and non-specialist healthcare settings. The Committee was keen to ensure that AChEIs and memantine were only initiated following a diagnosis and those treatment recommendations are made by a clinician with appropriate specialist expertise. However, it acknowledged the difficulties that sometimes arise where the diagnosing clinician is required to

	issue the first prescription for an AChEI or memantine. The Committee acknowledged that licensing for AChEIs and memantine (as set out in each product's Summary of Product Characteristics; SPC) is clear about initiation and supervision of these drugs and therefore agreed that it was appropriate to reflect this in the recommendations. The Committee noted that the SPCs for each of the AChEIs and memantine make reference to initiation and supervision of treatment by specialist physicians. However, it noted that the wording of these SPCs pre-dates legislative changes, in the early 2000s, which authorised the use of non-medical prescribers. The committee agreed that any interpretation of the recommendations would need to take account of this different prescribing environment. For this reason, the Committee thought it was not necessary to stipulate that treatment should be initiated by physicians (i.e. doctors) alone, and preferred to emphasise that the prescriber starts treatment on advice from a healthcare professional with specialist experience, regardless of professional label. The Committee discussed their concerns over communication of information between specialist and non-specialist settings and agreed that reference to NICE's Medicines Optimisation guideline (NG5) would be helpful. The Committee discussed recommendation 1.2 in the NICE Medicines Optimisation guideline which considers medicines-related communication systems where patients move between care which is of particular relevance. However, following further discussion, it was agreed that reference to all of NG5 would be more appropriate. When considering the monitoring and review of these drugs, the Committee noted and agreed that an annual dementia review is mandated. They agreed that these drugs should be part of the annual dementia review as opposed to a standard medicines review. The Committee noted again that it would be appropriate to refer to the Medicines Optimisation NICE guidance with regard to medication review, and the arrangements that should be in place between different care settings (in this instance, secondary and primary care).
Trade-off between net health benefits and resource use	No published health economic evidence was identified for this review question. The Committee noted that, in the past (including when TA217 was published), the medicines under consideration all had proprietary status, but they are all now available in generic formulations. This change has been accompanied by a significant fall in the acquisition costs of the drugs. The committee felt that, if cost containment had been a motivating factor in restricting prescribing to people with specialist experience of Alzheimer's disease, this was no longer such a substantial concern. However, the Committee emphasised that other reasons for involving specialists remain relevant.
Other considerations	It was noted that the current recommendations make reference to carers' views. The Committee agreed that this is an important consideration. However following discussion it was agreed that it could be adequately addressed by cross-reference to NICE's Medicines Optimisation guideline (NG5), which gives detailed guidance on the need to involve carers in the diagnosis, management and treatment of individuals.

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2.7 Recommendations

Incorporated from TA217: **NOT FOR COMMENT**

1. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (incorporating TA217)

1.1. The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine are recommended as options for managing mild to moderate Alzheimer's disease under all of the conditions specified in 1.3 and 1.4. [2011]

1.2. Memantine 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.

Treatment should be under the conditions specified in 1.3. [2011]

1.3. Treatment should be under the following conditions:

- Prescribers should only start treatment with donepezil, galantamine, rivastigmine or memantine on the advice of a clinician experienced in diagnosing and treating Alzheimer's disease. **[new 2016]**
- Ensure that local arrangements for prescribing and supply follow the NICE guideline on medicines optimisation (NICE guideline NG5). **[new 2016]**

Incorporated from TA217: **NOT FOR COMMENT**

- Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms. **[2011]**

- Review treatment in line with local shared-care arrangements, and the NICE guideline on medicines optimisation (NICE guideline NG5). **[new 2016]**

Incorporated from TA217: **NOT FOR COMMENT**

1.4. If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles. [2011]

1.5. 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. [2011]

1.6. 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

Incorporated from TA217: **NOT FOR COMMENT**

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. [2011]

3 References

Aupperle,P.M., Coyne.A.C., (2000), Primary vs subspecialty care: a structured follow-up of dementia patients and their caregivers, American Journal of Geriatric Psychiatry 8: 167-170

Aupperle,P.M., MacPhee,E.R., Coyne,A.C., Blume,J., Sanchez,B. (2003). Health service utilization by Alzheimer's disease patients: a 2-year follow-up of primary versus subspecialty care, Journal of Geriatric Psychiatry & Neurology 16: 15-17

Watanabe,N., Yamamura,K., Suzuki,Y., Umegaki,H., Shigeno,K., Matsushita,R., Sai,Y., Miyamoto,K., Yamada,K. (2012). Pharmacist-based Donepezil Outpatient Consultation Service to improve medication persistence, Patient preference & adherence 6: 605-611

4 Glossary and abbreviations

Please refer to the NICE glossary.

Additional terms used in this document are listed below.

Acetylcholinesterase inhibitors (AChEIs): A pharmacological treatment for Alzheimer's disease. The generic AChEIs are donepezil, rivastigmine and galantamine.

NMDA receptor antagonist: A pharmacological treatment for Alzheimer's disease. The generic NMDA receptor antagonist is memantine.

Appendices

Appendix A: Guideline Committee members and NICE teams

A.1 Core members

Name	Role
Damien Longson	Chair
Louise Allan	Consultant Geriatrician
Linda Clare	Clinical Psychologist
Richard Clibbens	Older adults Mental Health Nurse
Carol Duff	Occupational Therapist
Paul Dunnery	Lay member
Sandra Evans	Consultant Psychiatrist in older people
Karen Harrison-Dening	Admiral Nurse
Hannah Luff	Speech and Language Therapist
Kevin Minier	Lay member
John O'Brien	Consultant Psychiatrist in older people
Ruth O'Dea	Care Home Manager
Chris Roberts	Lay member
Louise Robinson	GP
Tracey Wright	Social Worker

A.2 Co-opted Committee members

Name	Role
Joanne Brady	Consultant in palliative care
Jeremy Isaacs	Consultant Neurologist
Kate Mitchell	NHS Commissioner
Sarah Partington	Community Matron
Catherine Pascoe	Local Authority Commissioner

A.3 NICE project team

Name	Role
Mark Baker (until Dec 2015)	Clinical advisor
Steven Barnes	Technical lead
Elizabeth Barrett	Information specialist
Rupert Franklin	Guideline commissioning manager
James Hall	Senior editor
Ross Maconachie	Health economics lead
Clifford Middleton (until Nov 2015)	Guideline commissioning manager
Angela Parkin	Senior advisor – medicines evidence
Rebecca Pye (until Nov 2015)	Guideline coordinator

Name	Role
Sharon Summers-Ma	Guideline lead
Trudie Willingham (from Nov 2015)	Guideline coordinator
Jeremy Wright (from Dec 2015)	Clinical advisor

A.4 Internal clinical guidelines team

Name	Role
Sue Ellerby (until Dec 2015)	Consultant clinical advisor
Vicky Gillis	Technical analyst
Holly Irwin (until Feb 2016)	Project manager
Hugh McGuire (until Dec 2015)	Technical advisor
Joshua Pink (from Feb 2016)	Technical advisor
Gabriel Rogers	Technical advisor – health economics
Sue Spiers	Associate director
Steven Ward	Health economist
Sarah Mills (from Feb 2016)	Project manager

Appendix B: Declarations of interest

Name	Job title, organisation	Declarations of Interest, date declared	Type of interest	Decision taken
Damien Longson	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust	Director of R&I for Manchester Mental Health & Social Care Trust Jul 2015	Non-specific, personal, non-financial	Declare and participate
Linda Clare	Professor of Clinical Psychology of Ageing and Dementia, University of Kent	Chair of British Psychological Society advisory group on dementia Aug 2015	Specific, personal, non-financial	Declare and participate
Paul Dunnery	Lay member	Employed as Operations Director with the Alzheimer's Society Aug 2015	Specific, personal, non-financial	Declare and participate
Sandra Evans	Consultant Psychiatrist and Lecturer in Psychiatry, St Bartholomew's Hospital, London	Author of several articles on the psychoanalytic aspects of dementia Oct 2015	Specific, personal, non-financial	Declare and participate
Sandra Evans	Consultant Psychiatrist and Lecturer in Psychiatry, St Bartholomew's Hospital, London	Part owner of a lavender farm producing essential lavender oil. Majority used to make soap and toiletries sold in the UK and Italy. Oct 2015	Specific, personal financial	Excluded from meetings considering use of essential oils
Karen Harrison-Dening	Admiral Nurse, Dementia UK	Twice yearly 'dementia & end of life care' lecturer for NAPP Education Foundation Aug 2015	Specific, personal, non-financial	Declare and participate
Hannah Luff	Lead Speech and Language Therapist, South London and Maudsley NHS Foundation Trust	Writing a chapter of a book on speech therapy and the Mental Capacity Act	Specific, personal, non-financial	Declare and participate
John O'Brien	Professor of Old Age Psychiatry, University of Cambridge	Symposia speaker (GE Healthcare) and advisory group member (Lilly). Consultancy work relating predominantly to imaging technology used in dementia. Aug 2015	Specific, personal financial	Excluded from future meetings relating to imaging technologies
John O'Brien	Professor of Old Age Psychiatry, University of Cambridge	Data safety & Monitoring Board Member (both Axona and TauRx). Remuneration is paid to the University of Cambridge. Aug 2015	Specific, personal non-financial	Declare and participate

Name	Job title, organisation	Declarations of Interest, date declared	Type of interest	Decision taken
John O'Brien	Professor of Old Age Psychiatry, University of Cambridge	Active research grant from Lilly, paid directly to Newcastle University, for the AMPLE study. Research co-funded and led by NIHR. Membership of the British Association of Psychopharmacology (BAP) Guidelines Group for anti-dementia drugs Aug 2015	Specific, personal non-financial	Declare and participate
Louise Robinson	GP and Professor in primary Care, Newcastle University	Paid member of Government Office: 'science foresight ageing expert review group' & lead author for 'Future health care for older people review' (due to publish 2015). Professorship with NIHR (funding paid to employing University) Aug 2015	Specific, personal, non-financial	Declare and participate
Jeremy Isaacs	Consultant Neurologist and Dementia Lead, St George's University Hospitals NHS Foundation Trust	Principle investigator on clinical trials of two new Alzheimer's disease drugs (Lupin Pharmaceuticals and AC Immune). Funding paid directly to employing hospital in-line with standard NHS R&D template. Aug 2015	Specific non-personal financial	Declare and participate
Jeremy Isaacs	Consultant Neurologist and Dementia Lead, St George's University Hospitals NHS Foundation Trust	Remunerated market research interview (with GfK Market Access) on future, currently unlicensed, treatments for Alzheimer's Disease and Dementia with Lewy Bodies. For the purposes of the market research participants were blinded from knowing which pharmaceutical company produced the unlicensed drugs. Oct 2015	Non-specific, personal-financial	Declare and participate
Jeremy Isaacs	Consultant Neurologist and Dementia Lead, St George's University Hospitals NHS Foundation Trust	Member of Young Dementia UK's 'National Young Onset Dementia Network' work stream on pre-diagnosis, diagnosis & post diagnostic support Oct 2015	Specific, personal non-financial	Declare and participate

Name	Job title, organisation	Declarations of Interest, date declared	Type of interest	Decision taken
Kate Mitchell	Commissioner and Programme Lead for Long Term Conditions, NHS Kernow	Paid consultancy work for Point of Care Foundation (POCF) to undertake scoping work focused on training needs for people with dementia and their carers Apr-sept 2014. This was followed up with further consultancy work to support development of peer engagement and support, plus training packages, for people with dementia and their carers Apr15 through into 2017. Sept 2015	Specific, personal, financial	Excluded from meetings focused on peer support and/or training
Catherine Pascoe	Commissioning Manager Adult Services, Hampshire County Council	Produced report on improving domiciliary care whilst working for the DoH south/west (no direct payment for this work) Sept 2015	Specific, personal, non-financial	Declare and participate

1 # Appendix C: Review protocol

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	Details
Review question	**Who should start and review the following pharmacological interventions:** • **donepezil** • **galantamine** • **rivastigmine** • **memantine** **for people with Alzheimer's disease and how should a review be carried out?**
Objective	To determine if it is clinically appropriate for non-specialists to initiate and review donepezil, galantamine, rivastigmine or memantine for the cognitive symptoms of dementia in people diagnosed with Alzheimer's disease
Population	People aged 40 years and over with diagnosis of Alzheimer's disease
Intervention	• The initiation and review of donepezil, galantamine, rivastigmine, memantine by non-specialists in any setting (for example secondary care; mental health services; community mental health services,including memory clinics; GP outreach clinics; primary care) • Shared care prescribing protocols
Comparator	The initiation and review of donepezil, galantamine, rivastigmine, memantine by psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of older people
Outcome	• Clinical outcome including cognitive functional and behavioural ability • Over prescribing/under prescribing and potentially avoidable adverse effects (including hospital admission) • Medication Errors • Access to health and social care support • Concordance and compliance • Patient and carer experience and satisfaction • Resource use and cost
Language	English language only
Study design	No restriction on study design
Other criteria for inclusion/exclusion of studies	Studies will be included if they report on the proportion of patients who experience any of the outcomes listed above
Search overview	• The following databases will be searched: • Medline • Medline in process • Embase • Psycinfo • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • Cochrane Central Register of Controlled Trials (Central) • Health Technology Assessment Database (HTA)
Review strategies	• Appropriate methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables

	• Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Appropriate methods (such as thematic analysis) will be used to identify issues that emerge from qualitative aspects • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements
Background papers	A Comparative Study of Dementia Care in England and the Netherlands Using Neo-Institutionalist Perspectives Living well with dementia: national dementia strategy Memory clinics in context Curing and Caring: The Work of Primary Care Physicians With Dementia Patients English National Memory Clinics Audit Report 2013

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Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in table 1. The Medline search strategy is shown in table 2. The same strategy was translated for the other databases listed.

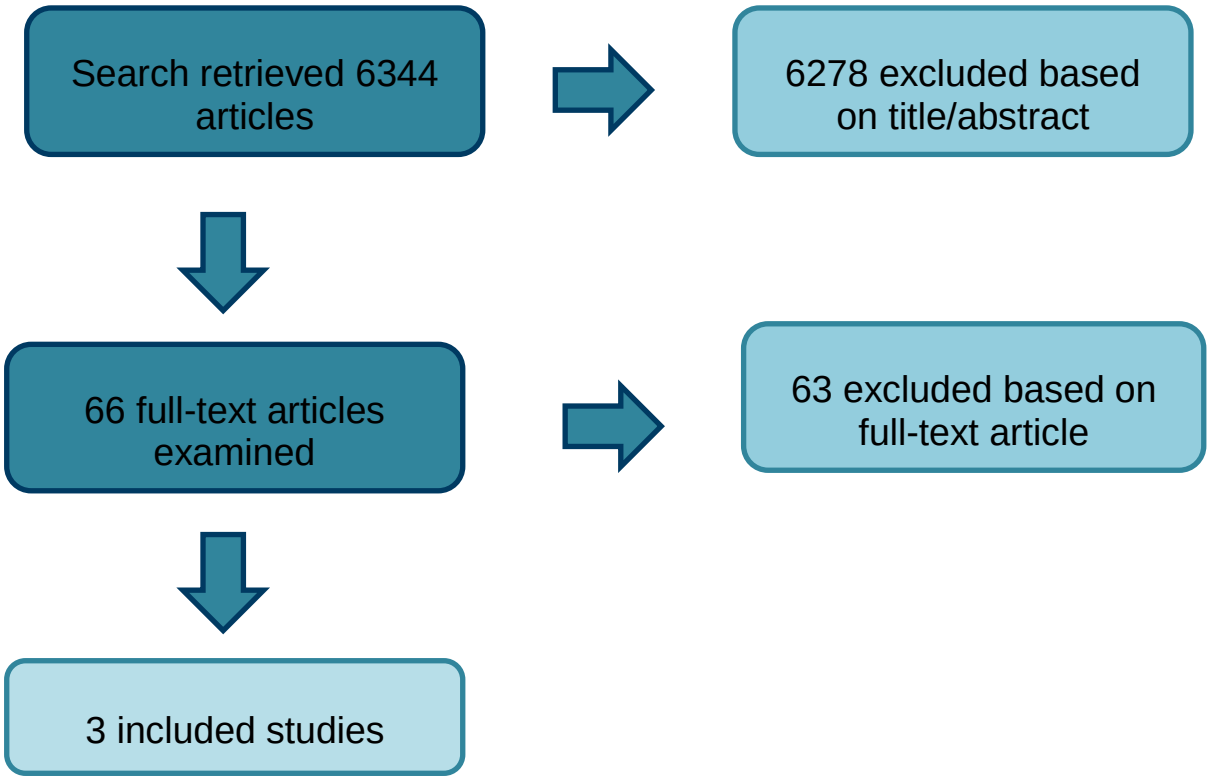
Table 1: Clinical search summary

Database	Date searched	Number retrieved
Medline (Ovid)	23/09/2015	2444
Medline in- process (Ovid)	23/09/2015	372
Embase (Ovid)	23/09/2015	4741
PsycInfo (Ovid)	23/09/2015	1564
Cochrane Central Register of Controlled Trials (CENTRAL)	23/09/2015	1127
Cochrane Database of Systematic Reviews (CDSR)	23/09/2015	18
Database of Abstracts of Reviews of Effect (DARE)	23/09/2015	27
Health Technology Assessment (HTA) Database	23/09/2015	15
Pubmed (supplementary search only)	23/09/2015	85

Table 2: Clinical search terms (Medline)

Line number/Search term/Number retrieved
1 Alzheimer Disease/73878
2 (alzheimer* or alzeimer*).tw.93580
3 (dementia adj2 (senile or presenile)).tw.3240
4 (cortical adj4 sclerosis).tw.421
5 or/1-4 106130
6 (donepezil or aricept* or asenta or eranz or memac or memorit).tw.2239
7 Galantamine/1332
8 (galantamin* or reminyl* or lycoremin* or galanthamine or nivalin* or razadyne or jilkon).tw.1575
9 (rivastigmin* or exelon* or nimvastid or prometax).tw.1130
10 Memantine/1779
11 (memantin* or axura or namenda or ebix* or maruxa* or nemdatine* or akatinol).tw.2172
12 or/6-11 6326
13 5 and 12 3229
14 limit 13 to english language 2901
15 animals/ not humans/4017726
16 14 not 15 2444

Appendix E: Review flowchart



1 # Appendix F:Excluded studies

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Excluded studies - 1. Who should start and review the following pharmacological interventions: donepezil, galantamine, rivastigmine, memantine, for people with Alzheimer's disease and how should a review be carried out?	
Study	Reason for Exclusion
20150408, Prescribing drugs for Alzheimer's disease in primary care: managing cognitive symptoms, Drug & Therapeutics Bulletin, 52, 69-72, 2014	Exclude: Narrative review only
Alander,J., Lonnroos,E., Hartikainen,S., Klaukka,T., 20060425, Nationwide use of medicines for Alzheimer's disease by community-dwelling persons in Finland, Journal of the American Geriatrics SocietyJ.Am.Geriatr.Soc., 54, 557-558, 2006	Exclude: Letter only
Antai-Otong,Deborah, Acetylcholinesterase Inhibitors in Dementia. [References], Perspectives in Psychiatric Care, 39, 83-85, 2003	Exclude: Review article only
Arai,T., 20080221, Practical clinical use of therapeutic agents for Alzheimer's disease. [Review] [34 refs], Nippon Yakurigaku Zasshi - Folia Pharmacologica Japonica, 130, 494-498, 2007	Exclude. Non English language paper
Atri,A., 20120508, Effective pharmacological management of Alzheimer's disease. [Review], American Journal of Managed Care, 17, Suppl-55, 2011	Exclude: Narrative review only
Benbow,S., Jones,R., Jolley,D., 19991021, Prescribing. Short rations, Health Service Journal, 109, 26-27, 1999	Exclude: Narrative review
Bishop,J., Hutchinson,J., Steffen,W.M., Review of Alzheimer's disease treatment at 8 Omnicare long-term care treatment facilities in Minnesota, Formulary, 38, 441-442, 2003	Exclude: Does not report outcomes of interest in prescribing or reviewing
Boustani,M., Hake,A.M., Shah,S., Knoth,R., Wyrwich,K., Oresana,J., Realworld prescribing in the treatment of Alzheimer's disease: Results of an in-depth physician survey, Alzheimer's and DementiaAlzheimer's Dementia, 8, 130-, 2012	Exclude: Narrative review
Bouwmeester,C., Chen,H., Assessment of antidementia medication prescribing patterns in a community setting according to a proposed treatment algorithm in a PACE program, Consultant PharmacistConsult.Pharm., 26, 734-, 2011	Exclude: Abstract only
Brewer,L., Bennett,K., McGreevy,C., Williams,D., 20131106, A population-based study of dosing and persistence with anti-dementia medications, European Journal of Clinical PharmacologyEur.J.Clin.Pharmacol., 69, 1467-1475, 2013	Exclude: Only reports dosing trends
Cameron,I., Curran,S., Newton,P., Petty,D., Wattis,J., 20001122, Use of donepezil for the treatment of mild-moderate Alzheimer's disease: an audit of the assessment and treatment of patients in routine clinical practice, International Journal of Geriatric PsychiatryInt.J.Geriatr.Psychiatry, 15, 887-891, 2000	Exclude: Does not report prescribing practices
Chertkow,H., Diagnosis and treatment of dementia: Introduction - Introducing a series based on the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, CMAJ, 178, 316-321, 2008	Exclude: Narrative review
Costa,A.C., 20120730, Alzheimer disease: Treatment of Alzheimer disease in Down syndrome, Nature Reviews NeurologyNat.Rev.Neurol., 8, 182-184, 2012	Exclude: Narrative summary
Cummings,J.L., Frank,J.C., Cherry,D., Kohatsu,N.D., Kemp,B.,	Exclude:

Excluded studies - 1. Who should start and review the following pharmacological interventions: donepezil, galantamine, rivastigmine, memantine, for people with Alzheimer's disease and how should a review be carried out?	
Hewett,L., Mittman,B., Guidelines for managing Alzheimer's disease: Part II. Treatment, American Family PhysicianAm.Fam.Phys., 65, 2525-2534, 2002	Narrative review only
Cummings,J.L., Isaacson,R.S., Schmitt,F.A., Velting,D.M., 20150327, A practical algorithm for managing Alzheimer's disease: what, when, and why?. [Review], Annals of Clinical & Translational Neurology, 2, 307-323, 2015	Exclude: Narrative summary only
Cummings,J.L., 20030703, Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. [Review] [87 refs], American Journal of Geriatric PsychiatryAm.J.Geriatr.Psychiatry, 11, 131-145, 2003	Exclude: Only reports on efficacy not prescribing/ reviewing practices
Curran,S., Habibi,M., Mitra,L., Stephenson,J., Nagarajan,P., Khan,A., Use of acetylcholinesterase inhibitors in routine clinical practice, European NeuropsychopharmacologyEur.Neuropsychopharmacol., 24, S636-S637, 2014	Exclude: Abstract only
Dimitrov,I., Kaprelyan,A., Usheva,N., Ivanov,B., Alzheimer's disease outpatient referrals to a dementia centre: Diagnostic challenges, Neurodegenerative DiseasesNeurodegenerative Dis., 15, 1116-, 2015	Exclude: Abstract only
Droeschel,D., Kaier,K., Walzer,S., The clinical evidence base of treatment options in alzheimer's disease: A systematic literature search, Value in HealthValue Health, 17, A392-, 2014	Exclude: Abstract only
Dybicz,S.B., Keohane,D.J., Erwin,W.G., McRae,T., Shah,S.N., 20061114, Patterns of cholinesterase-inhibitor use in the nursing home setting: a retrospective analysis, American Journal of Geriatric PharmacotherapyAm.J.Geriatr.Pharmacother., 4, 154-160, 2006	Exclude: Does not provide information relating to speciality status of prescribing physician
Farlow,M.R., Cummings,J.L., 20070522, Effective pharmacologic management of Alzheimer's disease. [Review] [78 refs], American Journal of MedicineAm.J.Med., 120, 388-397, 2007	Exclude: Narrative review only
Ferris,S., Meng,X., Velting,D., Caregiver treatment preference/satisfaction and efficacy among patients in the optimising transdermal exelon in mild-to-moderate alzheimer's disease (optima) study, Neurology, 84, -, 2015	Exclude: Abstract only
Finne-Soveri,U.H., Noro,A., Topinkova,E., Fialovsa,D., Foebel,A.D., Onder,G., Gindin,J., Bernabei,R., Makela,M., Use of anti-dementia drugs in nursing homes, European Geriatric MedicineEur.Geriatr.Med., 5, S93-, 2014	Exclude: Abstract only
Finucane,T.E., Tariot,P.N., Cummings,J.L., Katz,I.R., Mintzer,J., Perdomo,C.A., Getting donepezil into the nursing home. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting, Journal of the American Geriatrics SocietyJ.Am.Geriatr.Soc., 51, 133-134, 2003	Exclude: Letter
Flint,A.J., van,Reekum R., 19990322, The pharmacologic treatment of Alzheimer's disease: a guide for the general psychiatrist. [Review] [56 refs], Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie, 43, 689-697, 1998	Exclude: Review article
Fortinsky,R.H., Zlateva,I., Delaney,C., Kleppinger,A., 20100709, Primary care physicians' dementia care practices: evidence of geographic variation, Gerontologist, 50, 179-191, 2010	Exclude: Does not report on Alzheimer's subgroup speciality status of physician prescribing
Geldmacher,D.S., Long-Term Cholinesterase Inhibitor Therapy	Exclude:

Excluded studies - 1. Who should start and review the following pharmacological interventions: donepezil, galantamine, rivastigmine, memantine, for people with Alzheimer's disease and how should a review be carried out?	
for Alzheimer's Disease: Practical Considerations for the Primary Care Physician, Prim.Care Companion J Clin Psychiatry, 5, 251-259, 2003	Review article
Greeff,O.B.W., Alzheimer's disease in family practice, South African Family PracticeS.Afr.Fam.Pract., 51, 364-367, 2009	Exclude: Narrative review
Hefner,G., Brueckner,A., Hiemke,C., Fellgiebel,A., Therapeutic drug monitoring for patients with Alzheimer dementia to improve treatment with donepezil, Therapeutic Drug MonitoringTher.Drug Monit., 37, 353-361, 2015	Exclude: Reports only upon outcomes of drug monitoring and does not report which health care professionals are involved
Herrmann,N., 20070613, Treatment of moderate to severe Alzheimer's disease: rationale and trial design. [Review] [48 refs], Canadian Journal of Neurological SciencesCan.J.Neurol.Sci., 34, Suppl-8, 2007	Exclude: Does not report outcomes of interest
Herrmann,Nathan, Gauthier,Serge, Diagnosis and treatment of dementia: 6. Management of severe Alzheimer disease. [References], Canadian Medical Association Journal, 179, 1279-1287, 2008	Exclude: Narrative review
Hincu,A.M., Dumitru,M.M., Efficiency of early treatment in Alzheimer's disease, European NeuropsychopharmacologyEur.Neuropsychopharmacol., 24, S640-, 2014	Exclude: Abstract only
Jani,J., Prettyman,R., Use of a prescribing protocol in routine clinical practice: Experience following the introduction of donepezil, Psychiatric BulletinPsychiatr.Bull., 25, 174-177, 2001	Exclude: Does not report on prescribing practices
Janssen Pharmaceutica,N.V., Treatment of Severe Alzheimer's Disease in a Residential Home, Nursing Home, or Geriatric Residential Setting: Evaluation of Efficacy and Safety of Galantamine Hydrobromide in a Randomised, Doubleblind, Placebo-Controlled Study, ClinicalTrials.gov [http://clinicaltrials.gov], -, 2006	Exclude: Protocol only
Jeschke,E., Ostermann,T., Vollmar,H.C., Tabali,M., Bockelbrink,A., Witt,C., Willich,S.N., Matthes,H., Prescribing practices in a German network of anthroposophic physicians for the treatment of patients with dementia: A prospective observational study, European Journal of Integrative MedicineEur.J.Integr.Med., 2, 229-230, 2010	Exclude: Conference abstract Only covers people with dementia (does not specify Alzheimer's Disease)
Kennedy,S., Sud,D., 20140731, A guide to prescribing anti-dementia medication, Nursing Times, 110, 16-18, 2014	Exclude: Narrative summary
Kim,R., Teschemaker,A., Lee,E., Prescribing patterns of medications with cholinergic and anticholinergic properties in the U.S. ambulatory care setting, Journal of the American Pharmacists AssociationJ.Am.Pharm.Assoc., 50, 305-, 2010	Exclude: Abstract only
Kozubski,W., Hasselbalch,S., Jakab,G., Kalisvaart,C.J., Kurz,A., McCarthy,J., Triau,E., Tsolaki,M., Bergendorff,L., Xu,Y., Kumar,N., Richardson,S., Johannsen,P., Donepezil-Treated Alzheimer's Disease Patients With Apparent Initial Cognitive Decline Demonstrate Significant Benefits When Therapy Is Continued: Results From a Randomized, Placebo-Controlled Trial, European NeuropsychopharmacologyEur.Neuropsychopharmacol., 13, S405-, 2003	Exclude: Abstract only
Krall,W.J., Sramek,J.J., Cutler,N.R., 19990720, Cholinesterase inhibitors: a therapeutic strategy for Alzheimer disease. [Review]	Exclude:

Excluded studies - 1. Who should start and review the following pharmacological interventions: donepezil, galantamine, rivastigmine, memantine, for people with Alzheimer's disease and how should a review be carried out?	
[129 refs], Annals of PharmacotherapyAnn.Pharmacother., 33, 441-450, 1999	Review article
Lachaine,J., Lambert-Obry,V., Dionne,P.A., Health care resources utilization in Alzheimer's disease: An analysis with the Quebec provincial drug reimbursement program database, Value in HealthValue Health, 16, A622-, 2013	Exclude: Abstract only
Larsson,H., Bengtsson,M.W., Johansson,M.K., Hernborg,A., Lindahl,U., Seling,K., Schioler,H., Hoffmann,M., Treatment of alzheimer disease in sweden 2006- 2010. Incidence, Prevalence, and duration of drug treatment-trends and regional variation, Pharmacoepidemiology and Drug SafetyPharmacoepidemiol.Drug Saf., 20, S299-, 2011	Exclude: Abstract only
Lin,P., Management of Alzheimer's disease in primary care practice: Relative efficacy of pharmacologic options, Clinical GeriatricsClin.Geriatr., 13, 13-23, 2005	Exclude: Narrative review
Linkins,K.W., Lloyd,J.R., Treatment of Alzheimer's disease patients in a managed care organization: A descriptive study of costs and utilization, Drug Benefit Trends, 12, 6BH-12BH, 2000	Exclude: Health economics reporting only
Maneno,M.K., Lee,E., Wutoh,A.K., Zuckerman,I.H., Jackson,P., Lombardo,F.A., Scott,K.R., Xue,Z., 20060518, National patterns of dementia treatment among elderly ambulatory patients, Journal of the National Medical AssociationJ.Natl.Med.Assoc., 98, 430-435, 2006	Exclude: Does not include outcomes of interest
Marin,D.B., Sewell,M.C., Schlechter,A., Alzheimer's disease: Accurate and early diagnosis in the primary care setting, Geriatrics, 57, 36-40, 2002	Exclude: Non prescribing Narrative review only
Massoud,Fadi, Dorais,Marc, Charbonneau,Claudie, Lescrauwaet,Benedicte, Boucher,Jean Marc, Le Lorier,Jacques, Drug utilization review of cholinesterase inhibitors in Quebec. [References], The Canadian Journal of Neurological Sciences / Le Journal Canadien Des Sciences Neurologiques, 35, 508-509, 2008	Exclude: Does not sub-analyse outcomes by physician speciality
Mayeux,R., 20100622, Clinical practice. Early Alzheimer's disease. [Review] [54 refs][Erratum appears in N Engl J Med. 2010 Sep 16;363(12):1190], New England Journal of MedicineNew Engl.J.Med., 362, 2194-2201, 2010	Exclude: Narrative review
Meranus,D., Monsell,S., Thomas,G., Kukull,W., Cholinesterase inhibitors and memantine use in the national Alzheimer's coordinating center's uniform data set: A longitudinal assessment of real-world medication use in dementia, Alzheimer's and DementiaAlzheimer's Dementia, 8, 711-, 2012	Exclude: Abstract only
Oremus,M., Wolfson,C., Bergman,H., Vandal,A.C., Physicians' efficacy requirements for prescribing medications to persons with Alzheimer's disease, Canadian Journal on AgingCan.J.Aging, 26, 139-148, 2007	Exclude: Only provides information on hypothetical prescribing practices
Pedone,C., Lapane,K.L., Mor,V., Bernabei,R., 20040618, Donepezil use in US nursing homes, Aging-Clinical & Experimental Research, 16, 60-67, 2004	Exclude: Does not report outcomes of interest in prescribing roles
Peisah,C., Brodaty,H., Managing Alzheimer's disease the role of the GP, Medicine TodayMed.Today, 5, 16-24, 2004	Exclude: Guideline only
Rakusa,M., Kogoj,A., Stokin,G.B., Why acetylcholine esterase inhibitors or memantine (AEI/M) are not prescribed to patients with alzheimer's disease (AD), European Journal of	Exclude: Abstract only

Excluded studies - 1. Who should start and review the following pharmacological interventions: donepezil, galantamine, rivastigmine, memantine, for people with Alzheimer's disease and how should a review be carried out?	
NeurologyEur.J.Neurol., 18, 68-, 2011	
Rattinger,G.B., DeLisle,S., Onukwugha,E., Mullins,C.D., Prescribing patterns among dementia patients at the Veterans Affairs Maryland Health Care System (VAMHCS), Value in HealthValue Health, 12, A14-, 2009	Exclude: Abstract only
Sonde,L., Johnell,K., 20130806, Is drug treatment for dementia followed up in primary care? A Swedish study of dementia clinics and referring primary care centres, PLoS ONE [Electronic Resource], 8, e57161-, 2013	Exclude: Data includes population with AD and VaD (does not sub-analyse outcomes by type of dementia)
Truter,I., Prescribing for alzheimer's disease: A database analysis of a south african pharmacy group, Basic and Clinical Pharmacology and ToxicologyBasic Clin.Pharmacol.Toxicol., 105, 132-, 2009	Exclude: Abstract only
Truter,I., Prescribing patterns and cost of drugs for Alzheimer's disease, Value in HealthValue Health, 14, A288-, 2011	Exclude: Abstract only
Truter,I., 20100412, Prescribing of drugs for Alzheimer's disease: a South African database analysis, International PsychogeriatricsInt.Psychogeriatr., 22, 264-269, 2010	Exclude: Abstract only
van den Bussche,H., Kaduszkiewicz,H., Koller,D., Eisele,M., Steinmann,S., Glaeske,G., Wiese,B., 20120202, Antidementia drug prescription sources and patterns after the diagnosis of dementia in Germany: results of a claims data-based 1-year follow-up, International Clinical PsychopharmacologyInt.Clin.Psychopharmacol., 26, 225-231, 2011	Exclude: Emailed author for relevant data on prescribing but did not receive response.
Villar-Fernandez,I., Bjerrum,L., Feja,C., Rabanaque,M.J., 20100126, Variability in the prescription of cholinesterase inhibitors and memantine, Dementia & Geriatric Cognitive Disorders, 28, 373-379, 2009	Exclude: Does not report who was the prescriber
Wagle,K.C., Natali,B., Taffet,G.E., Cholinesterase inhibitor initiation in hospital setting, Journal of the American Geriatrics SocietyJ.Am.Geriatr.Soc., 59, 1988-1989, 2011	Exclude: Letter
Wagle,K.C., Poon,I., Nijgha,C., Rowan,P., Braun,U., Taffet,G., Cholinesterase inhibitor use in an inpatient setting, Journal of the American Geriatrics SocietyJ.Am.Geriatr.Soc., 60, S215-, 2012	Exclude: Abstract only
Watts-Tobin,M.A., Horn,N., 20000512, Prescribing donepezil in clinical practice, British Journal of PsychiatryBr.J.Psychiatry, 175, 393-, 1999	Exclude: Letter only
Wucherer,D., Eichler,T., Kilimann,I., Hertel,J., Michalowsky,B., Thyrian,J.R., Teipel,S., Hoffmann,W., Antidementia drug treatment in people screened positive for dementia in primary care, Journal of Alzheimer's DiseaseJ.Alzheimer's Dis., 44, 1015-1021, 2015	Exclude: Outcomes of interest including speciality of the prescriber was were not reported

Appendix G: Evidence tables

Table 1: Aupperle et al., 2000	
Bibliographic reference	Aupperle,P.M., Coyne,A.C., 20000717, Primary vs subspecialty care: a structured follow-up of dementia patients and their caregivers, American Journal of Geriatric PsychiatryAm.J.Geriatr.Psychiatry, 8, 167-170, 2000
Full citation	Aupperle,P.M., Coyne,A.C., 20000717, Primary vs subspecialty care: a structured follow-up of dementia patients and their caregivers, American Journal of Geriatric PsychiatryAm.J.Geriatr.Psychiatry, 8, 167-170, 2000
Ref Id	534613
Country/ies where the study was carried out	USA
Study type	Observational: Retrospective cohort analysis
Aim of the study	To examine a cohort of people with Alzheimer's disease and their caregivers 1 year after receiving a diagnostic evaluation To compare usage of health services of those treated only by primary care physician (MED) with those receiving care by a geriatric psychiatrist (GERO)
Study dates	1997-1998
Source of funding	Not reported (pilot study)
Sample size	Original population receiving diagnosis N= 80 At 1 year follow up N= 58 (mean age 78.8 years) MED (n=31); mean age = 82.9 years GERO (n=27); mean age = 80.4 years
Inclusion criteria	All dementia patients and caregivers who received a neuropsychiatric evaluation and a diagnosis of Alzheimer's disease (AD) at a university based diagnostic clinic were surveyed 1 year after the initial assessment.
Exclusion criteria	Exclusion criteria was not reported

Table 1: Aupperle et al., 2000	
Details	All participants with a diagnosis of AD received an initial evaluation and were surveyed at 1 year follow up Data collected at baseline taken from initial evaluation Demographic data collected at initial assessment Assessment of physical impairment by Cumulative Illness Rating Scale (CIRS) taken from standardised chart reviews Data collected at baseline and follow up Assessments of cognition (Clinical Dementia Rating Scale; CDR) Caregiver distress (Zarit Burden Interview; Zarit) Physician practices (prescription of donepezil) Utilisation of health services by patient Follow up data was collected by telephone contact with caregiver Data Analysis Nonparametric and correlational assessment of data was performed Loss of data at 1 year follow up Deceased (n=7) Not contacted (n=6) Caregivers not willing to participate (n=9)
Interventions	Two sub groups identified: Those being seen only by a primary care physician (MED) Those being seen in addition by a member of a geriatric psychiatry facility in collaboration with a case manager such as a geriatric social worker or geriatric nurse (GERO). Case management included education about AD, a detailed review of caregiver coping skills, behavioural management, community resources, long term care planning, legal and financial planning.
Results	Clinical outcome (including cognitive, functional, behavioural ability) Clinical Dementia Rating Scale CDR – Primary care physician baseline mean = 1.8 (SD= 0.7); 1 year follow up mean = 2.5 (SD= 0.6) Geriatric Psychiatrist baseline mean = 1.9 (SD= 0.7); 1 year follow up mean = 1.8 (SD= 0.7)

Table 1: Aupperle et al., 2000	
	Over prescribing/under prescribing and potentially avoidable adverse events Not reported Medication errors Not reported Access to health care and social care support Service Usage (past 6 months) Number of hospitalisations at 1 year follow up Primary Care physician n=12 (38.7%) Geriatric Psychiatrist n=4 (14.8%) Use of Home health aide at 1 year follow up: Primary Care physician n=14 (45.2% Geriatric Psychiatrist n=5 (18.5%) Use of Dementia day program at 1 year follow up Primary Care physician n=5 (16.1%) Geriatric Psychiatrist n = 7 (25.9%) Concordance and compliance Provider practices Prescription of donepezil- Primary care physician baseline n=17 (53.1%); 1 year follow up n=11 (35.5%) Geriatric Psychiatrist baseline n=15 (46.9%); 1 year follow up n= 20 (64.5%] Patient and carer experience and satisfaction Caregiver distress ratings Zarit Burden Interview: Primary Care Physician baseline mean = 30.8 (SD= 16.9); 1 year follow up mean = 21.6 (SD= 12.2)

Table 1: Aupperle et al., 2000	
	Geriatric Psychiatrist baseline mean = 38.3 (SD=13.4); 1 year follow up mean = 19.2 (SD=12.9) Resource use and cost Not reported
Overall Risk of Bias	Pilot study only provides limited outcomes
Other information	Was the allocation sequence adequately generated? N/a Was the allocation adequately concealed? N/a Were baseline outcome measurements similar? Yes Were baseline characteristics similar? Yes Were incomplete outcome data adequately addressed? Yes Was knowledge of the allocated interventions adequately prevented during the study? N/a Was the study adequately protected against contamination? N/a Was the study free from selective outcome reporting? Yes

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Table 2: Aupperle et al., 2003	
Bibliographic reference	Aupperle,P.M., MacPhee,E.R., Coyne,A.C., Blume,J., Sanchez,B., 20030716, Health service utilization by Alzheimer's disease patients: a 2-year follow-up of primary versus subspecialty care, Journal of Geriatric Psychiatry & Neurology, 16, 15-17, 2003
Full citation	Aupperle,P.M., MacPhee,E.R., Coyne,A.C., Blume,J., Sanchez,B., 20030716, Health service utilization by Alzheimer's disease patients: a 2-year follow-up of primary versus subspecialty care, Journal of Geriatric Psychiatry & Neurology, 16, 15-17, 2003
Ref Id	534614
Country/ies where the study was carried out	USA
Study type	Observational: Retrospective cohort analysis (Follow up of Aupperle, 2000)
Aim of the study	To examine a cohort of people with Alzheimer's disease and their caregivers at 2 year follow up after receiving a diagnostic evaluation To compare usage of health services of those treated only by primary care physician (MED) with those receiving care by a geriatric psychiatrist (GERO)
Study dates	1997-1998
Source of funding	Not reported
Sample size	Original population receiving diagnosis N= 80 At 2 year follow up N= 39 (mean age 78.4 years) MED (n=22); mean age = not reported GERO (n=17); mean age = not reported
Inclusion criteria	This was a 2 year follow up of a cohort of dementia patients and caregivers who received a neuropsychiatric evaluation and a diagnosis of Alzheimer's disease (AD) at a university based diagnostic clinic and were originally surveyed 1 year after their initial assessment.

Table 2: Aupperle et al., 2003	
Exclusion criteria	Exclusion criteria not reported
Details	All participants with a diagnosis of AD received an initial evaluation and had previously been surveyed at 1 year follow up Data collected at baseline taken from initial evaluation Demographic data collected at initial assessment Assessment of physical impairment by Cumulative Illness Rating Scale (CIRS) taken from standardised chart reviews Data collected at baseline and at 2 year follow up: Assessments of cognition (Clinical Dementia Rating Scale; CDR) Physician practices (prescription of donepezil) Utilisation of health services by patient Follow up data was collected by telephone contact with caregiver Data Analysis Nonparametric and correlational assessment of data was performed Loss of data at 2 year follow up Information relating to attrition was not specifically reported at 2 year follow up.
Interventions	The cohort at 2 year follow up was a subset of the original cohort diagnosed with AD: Two sub groups identified: Those being seen only by a primary care physician (MED) Those being seen in addition by a member of a geriatric psychiatry facility in collaboration with a case manager such as a geriatric social worker or geriatric nurse (GERO). Case management included education about AD, a detailed review of caregiver coping skills, behavioural management, community resources, long term care planning, legal and financial planning.
Results	Clinical outcome (including cognitive, functional, behavioural ability) Clinical Dementia Rating Scale CDR Primary care physician baseline mean= 1.8 (SD= 0.7); 2 year follow up mean = 2.3 (SD not reported) Geriatric Psychiatrist baseline mean = 1.9 (SD= 0.7); 2 year follow up mean = 1.5 *SD not reported)

Table 2: Aupperle et al., 2003	
	Over prescribing/under prescribing and potentially avoidable adverse events Not reported Medication errors Not reported Access to health care and social care support Service Usage (past 6 months) Number of hospitalisations at 2 year follow up Primary Care physician n=5 (22.7%) Geriatric Psychiatrist n=2 (11.8%) Resident in nursing home at 2 year follow up Primary Care physician n=5 (22.7%) Geriatric Psychiatrist n=0 (0.0%) Use of assisted living at 2 year follow up Primary Care Physician n=4 (18.2%) Geriatric Psychiatrist n = 1 (5.9%) Assisted living/nursing home at 2 year follow up Primary Care physician n= 9 (40.9%) Geriatric Psychiatrist n=1 (5.9%) Concordance and compliance Provider practices Prescription of donepezil- Primary care physician [baseline n=17 (53.1%); 2 year follow up n=10 (45.5%)] Geriatric Psychiatrist [baseline n=15 (46.9%); 2 year follow up n= 13 (76.5%)]

Table 2: Aupperle et al., 2003	
	Patient and carer experience and satisfaction Caregiver distress ratings Not reported Resource use and cost Not reported
Overall Risk of Bias	Follow up of Aupperle (2000) but outcomes not comparative Incomplete reporting of CDR. Only provides mean change and not SD
Other information	Was the allocation sequence adequately generated? N/a Was the allocation adequately concealed? N/a Were baseline outcome measurements similar? Yes Were baseline characteristics similar? Yes Were incomplete outcome data adequately addressed? Yes Was knowledge of the allocated interventions adequately prevented during the study? N/a Was the study adequately protected against contamination? N/a Was the study free from selective outcome reporting? No

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Table 3: Watanabe et al., 2012	
Bibliographic reference	Watanabe,N., Yamamura,K., Suzuki,Y., Umegaki,H., Shigeno,K., Matsushita,R., Sai,Y., Miyamoto,K., Yamada,K., 20121002, Pharmacist-based Donepezil Outpatient Consultation Service to improve medication persistence, Patient preference & adherence, 6, 605-611, 2012
Full citation	Watanabe,N., Yamamura,K., Suzuki,Y., Umegaki,H., Shigeno,K., Matsushita,R., Sai,Y., Miyamoto,K., Yamada,K., 20121002, Pharmacist-based Donepezil Outpatient Consultation Service to improve medication persistence, Patient preference & adherence, 6, 605-611, 2012
Ref Id	539883
Country/ies where the study was carried out	Japan
Study type	A two part observational study, before and after establishing an outpatient advisory service, conducted in a geriatric outpatient clinic of a university hospital.
Aim of the study	To examine the effectiveness of a donepezil outpatient consultation service (DOCS) for people with Alzheimer's disease (AD) compared to those who do not attend the DOCS. To assess patients and caregivers changes in understanding about donepezil treatment and AD To monitor medication persistence rate
Study dates	April 2008 to September 2010 enrolment of non DOCS group October 2010 to March 2012 enrolment of DOCS group
Source of funding	Not reported
Sample size	non DOCS group N= 59 (15 male; 44 female; mean age 79.0 years; mean baseline CDR=1.32) DOCS group N= 52 (21 male; 31 female; mean age 77.2 years; mean baseline CDR= 1.27)
Inclusion criteria	Patients and caregivers of patients diagnosed with AD and receiving donepezil who were attending a University outpatient consultation service were enrolled. All participants had AD according to Diagnostic Statistical Manual of Mental Disorders criteria
Exclusion criteria	Not reported

Table 3: Watanabe et al., 2012	
Details	All patients and caregivers of patients who had been diagnosed with AD and were prescribed donepezil at a university geriatric outpatient clinic were included: Patients or family members who wished to use the DOCS after an outpatient appointment were offered an appointment.. A pharmacist provided advice to each patient/ family. All patients attending were surveyed to assess changes in their understanding of donepezil and AD treatment. Medical persistence rate was estimate using Kaplan-Meier analysis and Cox proportional hazards model was used to analyse factors influencing medical persistence Information related to use of donepezil was collected (adherence, timing of drug intake, patients swallowing function), instructions about dosing. A 6-item survey of understanding about the clinical features of Alzheimer's disease and donepezil therapy for caregivers was prepared in consultation with geriatricians. The 6 questions included: Do you know the difference between forgetfulness and dementia? Do you think dementia is an illness? Do you know about the effects of donepezil? Do you know the side effects of donepezil? Do you know that you must not stop the drugs even if taking the drug does not cause any change in symptoms? Do you know that you must not take two doses together, even if you have forgotten to take a dose? Graded by giving a score of 1 for every correct answer and a 0 for each incorrect answer. The survey was repeated four weeks after first DOCS consultation and if information was not clear further instructions were provided via textbook.
Interventions	Two groups were identified: The group who were enrolled into an advisory service before it was established (non DOCS) The group who were enrolled into an advisory service after it was established (DOCS)

Table 3: Watanabe et al., 2012	
Results	Clinical outcome (including cognitive, functional, behavioural ability) Not reported Over prescribing/under prescribing and potentially avoidable adverse events Not reported Medication errors Not reported Access to health care and social care support Duration of first outpatient consultation: DOCS group - mean (SD) = 46.4 (7.2) minutes Duration of consultation at 4 week follow up: DOCS group - mean (SD) = 27.8 (6.1) minutes Concordance and compliance Medication persistence rate: Duration of donepezil treatment: Non DOCS group- mean (SD) = 248.6 (184.1) days DOCS group mean (SD) = 379.1 (202.6) days Use of donepezil at one year DOCS group = 38 patients (73.1%) Non DOCS group = 29 patients (49.2%) Patient and carer experience and satisfaction Level of understanding in AD and donepezil: DOCS group (n=52) Score of understanding at initial consultation mean = 2.5 (SD=1.7)

Table 3: Watanabe et al., 2012	
	Score of understanding at 4 week follow up mean = 5.7 (SD=0.7) Resource use and cost Not reported
Overall Risk of Bias	Limited outcomes considered at follow up. Validation for scale used in survey of understanding not clearly reported Short follow up period (only 4 weeks) to assess effectiveness of outcomes from DOCS
Other information	Was the allocation sequence adequately generated? n/a. Was the allocation adequately concealed? n/a Were baseline outcome measurements similar? Unclear (unclear bias) Were baseline characteristics similar? Unclear (unclear bias) Were incomplete outcome data adequately addressed? Unclear (unclear risk) Was knowledge of the allocated interventions adequately prevented during the study? N/a Was the study adequately protected against contamination? Yes (low risk) Was the study free from selective outcome reporting? Yes (low risk)

Appendix H: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in table 1. The Medline search strategy is shown in table 2. The same strategy was translated for the other databases listed.

Table 1: Economic search summary

Database	Date searched	Number retrieved
Medline (Ovid)	30/09/2015	337
Medline in-process	30/09/2015	51
Embase (Ovid)	30/09/2015	975
NHS Economic Evaluation Database (NHS EED); legacy database	30/09/2015	34

Table 2: Economic search strategy (Medline)

Line number/Search term/Number retrieved
1 Alzheimer Disease/73878
2 (alzheimer* or alzeimer*).tw.93580
3 (dementia adj2 (senile or presenile)).tw.3240
4 (cortical adj4 sclerosis).tw.421
5 or/1-4 106130
6 (donepezil or aricept* or asenta or eranz or memac or memorit).tw.2239
7 Galantamine/1332
8 (galantamin* or reminyl* or lycoremin* or galanthamine or nivalin* or razadyne or jilkon).tw.1575
9 (rivastigmin* or exelon* or nimvastid or prometax).tw.1130
10 Memantine/1779
11 (memantin* or axura or namenda or ebix* or maruxa* or nemdatine* or akatinol).tw.2172
12 or/6-11 6326
13 5 and 12 3229
14 limit 13 to english language 2901
15 animals/ not humans/ 4017726
16 14 not 15 2444
17 Economics/26916
18 exp "Costs and Cost Analysis"/193551
19 Economics, Dental/1885
20 exp Economics, Hospital/20760
21 exp Economics, Medical/13952
22 Economics, Nursing/3939
23 Economics, Pharmaceutical/2630
24 Budgets/10182
25 exp Models, Economic/11098
26 Markov Chains/10893
27 Monte Carlo Method/21842
28 Decision Trees/9367
29 econom$.tw.168501
30 cba.tw.8963
31 cea.tw.17078
32 cua.tw.822

Line number/Search term/Number retrieved
33 markov$.tw.12775
34 (monte adj carlo).tw.22549
35 (decision adj3 (tree$ or analys$)).tw.9090
36 (cost or costs or costing$ or costly or costed).tw.331008 A
37 (price$ or pricing$).tw.24748
38 budget$.tw.18293
39 expenditure$.tw.37453
40 (value adj3 (money or monetary)).tw.1436
41 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.2959
42 or/17-41700143
43 "Quality of Life"/131403
44 quality of life.tw.152464
45 "Value of Life"/5509
46 Quality-Adjusted Life Years/7993
47 quality adjusted life.tw.6743
48 (qaly$ or qald$ or qale$ or qtime$).tw.5506
49 disability adjusted life.tw.1400
50 daly$.tw.1357
51 Health Status Indicators/21060
52 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.16630
53 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.1048
54 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.2981
55 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.21
56 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.341
57 (euroqol or euro qol or eq5d or eq 5d).tw.4478
58 (qol or hql or hqol or hrqol).tw.27447
59 (hye or hyes).tw.54
60 health$ year$ equivalent$.tw.38
61 utilit$.tw.122025
62 (hui or hui1 or hui2 or hui3).tw.927
63 disutili$.tw.237
64 rosser.tw.71
65 quality of wellbeing.tw.5
66 quality of well-being.tw.348
67 qwb.tw.178 A
68 willingness to pay.tw.2497
69 standard gamble$.tw.693
70 time trade off.tw.798
71 time tradeoff.tw.219
72 tto.tw.640
73 or/43-72 347837
74 42 or 73 1000590
75 16 and 74 337

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Appendix I: GRADE profiles

GRADE tables for who should prescribe and review AChEIs or memantine for people with Alzheimer's disease

Speciality versus non speciality prescribing:

Prescribing donepezil

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Geriatric Psychiatrist (GERO)	Primary care physician (MED)	Relative (95% CI)	Absolute	Quality
Clinical outcome (including cognitive, functional & behavioural ability)											
Outcome 1: Mean Clinical Dementia Rating (CDR) scores at 1 year follow up											
Aupperle (2000)	Retrospective cohort study	very serious1	no serious	no serious	serious2	none	26	31	Mean (SD) rating: MED= 2.5 (0.6) GERO= 1.8 (0.7) MD= 0.70 higher (0.36 to 1.04 higher)		Very low
Concordance & compliance											
Outcome 1: Provider practices- prescription of donepezil at 1 year follow up											
Aupperle (2000)	Retrospective cohort	very serious1	no serious	no serious	serious2	none	20/26	11/31	RR=0.46 (0.27 to 0.78)	41 fewer per 100 (from 59 fewer to 24 fewer)	Very low

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Geriatric Psychiatrist (GERO)	Primary care physician (MED)	Relative (95% CI)	Absolute	
Access to health and social care support											
Outcome 1: Service usage (past 6 months): Number of people receiving hospitalisation											
Aupperle (2000)	Retrospective cohort study	very serious1	no serious	no serious	serious2	none	4/26	12/31	RR= 2.52 (0.92 to 6.87)	23 more per 100 (from 1 more to 41 more)	Very low
Outcome 2: Service usage (past 6 months): Number of people receiving home health aide											
Aupperle (2000)	Retrospective cohort study	very serious1	no serious	no serious	serious2	none	5/26	14/31	RR= 2.35 (0.98 to 5.65)	26 more per 100 (1 more to 44 more)	Very low
Outcome 3: Service usage (past 6 months): Number of people attending dementia day program											
Aupperle (2000)	Retrospective cohort study	very serious1	no serious	no serious	serious2	none	7/26	5/31	RR = 0.60 (0.22 to 1.67)	10 fewer per 100 (from 25 fewer to 3 more)	Very low
Patient and carer experience and satisfaction											
Outcome 1: Carer distress rating (Zarit Burden Interview) at 1 year follow up											
Aupperle (2000)	Retrospective cohort study	very serious1	no serious	no serious	serious2	none	26	31	Mean (SD rating): MED = 19.2 (12.9) GERO= 21.6 (12.2) MD= 2.40 higher (-4.16 lower to 8.96 higher)		Very low

1. *Downgraded due to observational study and retrospective design, pilot study only*
2. *Small sample size*

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Geriatric Psychiatrist (GERO)	Primary care physician (MED)	Relative (95% CI)	Absolute	Quality
Concordance & compliance											
Outcome 1: Provider practices- prescription of donepezil at 2 year follow up											
Aupperle (2003)	Retrospective cohort study	very serious 1,2	no serious	no serious	serious3	none	13/17	10/22	RR=0.59 (0.35 to 1.01)	31 fewer per 100 (from 53 fewer to 1 more)	Very low
Access to health and social care support											
Outcome 1: Service usage (past 6 months): Number of people receiving hospitalisation											
Aupperle (2003)	Retrospective cohort study	very serious 1, 2	no serious	no serious	serious3	none	2/17	5/22	RR= 1.93 (0.43 to 8.77)	11 more per 100 (from 1 fewer to 29 more)	Very low
Outcome 2: Service usage (past 6 months): Number of people in nursing home											
Aupperle (2003)	Retrospective cohort study	very serious 1, 2	no serious	no serious	serious3	none	0/17	5/22	RR= 8.61 (0.51 to 145.35)	23 more per 100 (1 more to 40 more)	Very low
Outcome 3: Service usage (past 6 months): Number of people receiving assisted living											
Aupperle (2003)	Retrospective cohort study	very serious 1, 2	no serious	no serious	serious3	none	1/17	4/22	RR = 3.09 (0.38 to 25.19)	12 more per 100 (from 1 fewer to 28 more)	Very low

1. *Downgraded due to observational study and retrospective design,*
2. *Follow up study of Aupperle (2000) but provides indirect outcomes and selective reporting of outcomes*
3. *Small sample size and wide confidence intervals in effect estimates*

Advisory service versus non advisory service

Reviewing donepezil

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Not receiving advisory service (Non DOCS)	Receiving advisory service (DOCS)	Relative (95% CI)	Absolute	Quality
Concordance & compliance											
Outcome 1: Medication persistence rate: Mean duration of donepezil treatment											
Watanabe (2012)	Before and after observational cohort	very serious1	no serious	very serious2	no serious	none	59	52	Mean (SD rating): Non- DOCS= 248.6 (184.1) days DOCS = 379.0 (202.6) days MD= 130.4 higher (58.02 more to 202.8 more)		Very low
Concordance and compliance											
Outcome 2: Medication persistence rate: Use of donepezil at 1 year follow up											
Watanabe (2012)	Before and after study	very serious1	no serious	very serious2	no serious	none	29/59	38/52	RR= 1.49 (1.09 more to 2.02 more)	24 more per 100 (11 more to 36 more)	Very low
Patient and carer experience and satisfaction											
Outcome 1: Average level of carer understanding at 4 week follow up											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Not receiving advisory service (Non DOCS)	Receiving advisory service (DOCS)	Relative (95% CI)	Absolute	
Watanabe (2012)	Before and after study	very serious1	no serious	veryserious2	no serious	none	26	31	Mean (SD rating): DOCS before consultation = 2.5 (1.7) DOCS after consultation 5.7 (0.7) MD= 3.20 higher (2.70 higher to 3.70 higher)		Very low

1. *Downgraded due to observational study. Short follow up period (4 weeks) for outcomes, validation of scale used for survey of understanding not clearly reported*
2. *Non UK setting and indirect setting for advisory consultation service*