NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA217; Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease

Final recommendation post consultation
The guidance should be transferred to the static list as no significant new evidence has been identified that is likely to lead to change in the recommendations. Whether the recommendations in section 1.3 on systems for prescribing and reviewing treatment with donepezil, galantamine, rivastigmine and memantine need updating should be considered as part of the review of clinical guideline 42: Dementia supporting people with dementia and their carers in health and social care.

1. Background

This guidance was issued in March 2011.

At the GE meeting of 8 April 2014 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

The guidance should be transferred to the ‘static guidance list’.

3. Rationale for selecting this proposal

Since the publication of TA217, no significant new evidence has been identified that is likely to lead to a change in the current recommendations. Therefore there is no value in undertaking a review of this guidance at this point, and it is appropriate to move the guidance to the ‘static guidance list’.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Healthcare Improvement Scotland **Response to proposal:** No comment We have no comment to make on the proposal to move this guidance to the static list.	**Comment from Technology Appraisals** Comment noted.

Respondent: College of Mental Health Pharmacy **Response to proposal:** Disagree Comments relating to recommendation 1.3 of the guidance: • "Only specialists in the care of patients with dementia should initiate treatment"- This is now out of date. With the continual rise in patients being diagnosed with dementia in the UK, memory clinics are struggling to cope with the increasing workload. The majority of GPs in our area initiate treatment with AChEIs following advice from the memory clinics under shared care guidelines. Cost pressures have reduced dramatically and the dementia drugs are generally quite safe and well tolerated so GPs are confident to prescribe these drugs. In addition, having all medication prescribed by one sole prescriber (the GP) will ensure more effective medicines reconciliation, with improved safety. We no longer feel that it is practical to restrict initiation of prescribing of anti-dementia drugs to specialists only. • "Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms". "Patients who continue on treatment should be reviewed regularly using cognitive, global, functional and behavioural assessment. Treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care". Recent evidence however suggests that long-term use of AChEIs is beneficial and not dependent on severity of dementia.	**Comment from Technology Appraisals** Comments on initiation of AChE inhibitors noted. The recommendations in technology appraisal 217 have already been incorporated in clinical guideline 42. A review proposal for clinical guideline 42 has recently undergone consultation.. As the recommendations in 1.3 relate to conditions for the implementation of the guidance (including who should prescribe the technologies) it is appropriate that the clinical guideline review process should consider whether recommendation 1.3 in technology appraisal 217 should be updated. Comments and reference to clinical studies on prolonged use of AChE inhibitors and their efficacy in people with different symptom severity are noted. NICE technology appraisal recommendations are only made within a technology's marketing

A large multicenter study (Howard et al 2012) of community-dwelling patients with moderate or severe AD investigated the long-term effects of donepezil over 12 months compared with stopping donepezil after 3 months, switching to memantine or combining donepezil with memantine. Continued treatment with donepezil was associated with continued cognitive benefits and patients with a Mini Mental State (MMSE) score as low as 3 were still benefiting from treatment. This suggests that patients should continue treatment with AChEIs for as long as possible and there should not be a cut-off cognitive assessment score where treatment is stopped automatically. A meta-analysis evaluating the efficacy of the three AChEIs and memantine in relation to the severity of AD found that the efficacy of all drugs except memantine was independent from dementia severity in all domains. The effect of memantine on functional impairment was better in more severe patients. Results demonstrated that patients in differing stages of AD retain the ability to respond to treatment with AChEIs and memantine. Medication effects are therefore substantially independent from disease severity and patients with a wide range of severities can benefit from drug therapy. This suggests that the severity of a patient's illness should not preclude treatment with these drugs (Di Santo et al 2013). In view of these findings, we feel that whilst assessing tolerability of these drugs is important, their clinical effects are difficult to assess and evidence now suggests that patients should continue on treatment for as long as possible. Therefore reviews to determine efficacy may no longer be indicated and this should be reflected in the updated guidelines.	authorisation. The marketing authorisations for donepezil, galantamine, rivastigmine and memantine stipulate the severity of Alzheimer's disease for which each technology is indicated. These indications have not changed since technology appraisal 217. The summaries of product characteristics for donepezil, galantamine, rivastigmine and memantine state that treatment should be maintained if it is having a therapeutic effect.

Respondent: Eisai **Response to proposal:** Agree We agree with NICE that no new evidence from donepezil has emerged to change the guidance.	**Comment from Technology Appraisals** Comment noted.

Respondent: Royal College of Nursing **Response to proposal:** Disagree Our members felt that there is currently a tension between continuing to monitor efficacy of these drugs whilst at the same time receiving more patients through the system as priority is given to early diagnosis. Through a number of policy papers, not least the National Dementia Strategy, the expected time from referral to diagnosis is, quite rightly, reducing. In addition to this the awareness raising campaigns have been successful and referral rates have increased. However, providing a service that offers earlier diagnosis for an increasing number of people whilst also continuing to exponentially grow a follow up caseload of those on treatment may become very difficult to sustain with limited resources. It was felt that the guidance should state that a monitoring mechanism should be in place but that the details of that monitoring system should be left to local services to develop. For example, some members commented that the trust in which they work are currently thinking of trialling a new process whereby any person who has received mental health services and has been discharged can self-refer in again if they think there is a need. Under this new system those people who are stable on treatment and who have a means of alerting services would be discharged and only be readmitted to the service if there was a change. Those with no such means of alerting the service would be regarded as vulnerable and therefore not discharged. This would release staff to respond to those presenting for assessment and diagnosis. However, as the guidance currently stands it would render such a service as non-compliant. With this in mind our members felt that there is a need to review the guidance and that it should not be placed on the static list at this time.	**Comment from Technology Appraisals** Comments on implementation of the technology appraisal guidance 217 noted. The recommendations in technology appraisal 217 have already been incorporated in clinical guideline 42. A review proposal for clinical guideline 42 has recently undergone consultation. As the recommendations in 1.3 relate to conditions for the implementation of the guidance (including the monitoring and review of patients) it is appropriate that the clinical guideline review process should consider whether recommendation 1.3 in technology appraisal 217 should be updated.

Respondent: Royal College of Psychiatrists **Response to proposal:** Disagree	**Comment from Technology Appraisals**
1. We need a section called "when to stop the medications" e.g. side-effects, not effective etc. as I have seen some psychiatrists who think that these medications are for life. Also, we need to include tools other than MMSE because of the copyright issue.	Comments noted. The recommendations in technology appraisal 217 state that "treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms" which is consistent with the guidance in the summary of product characteristics for these technologies. The tools for assessing severity are not stipulated in the recommendations.
2. The three Cholinesterase Inhibitors have been available for in excess of 15 years in some cases, and Memantine for at least 10 years. The safety record of these in both short and long term is well established. Although there is limited evidence from new clinical trials, long term cohort observational studies, while limited by the caveats applied to this type of study, do tend to show benefits from long term usage of these drugs and the Domino Trial was supportive of continuing treatment into the severe stage of Alzheimer's disease. In my view there is now no justification for having these drugs prescribed directly by Specialists. They should be treated the same as other drugs used for people with dementia – namely after a diagnosis is made the drugs should be prescribed by primary care from the outset. Continuing the current "shared care" arrangement simply creates safety issues for the patients concerned. In my local region a variety of arrangements exist, including one in which all the prescribing has to be done by Specialists, one with a more recognisable shared care arrangement and one where GPs can prescribe from the outset. An audit of information on the Patient Information and Emergency Care System showed that although the use of these drugs by the patient was recorded virtually 100% in cases	The recommendations in technology appraisal 217 have already been incorporated in clinical guideline 42. A review proposal for clinical guideline 42 has recently undergone consultation. As the recommendations in 1.3 relate to conditions for the implementation of the guidance (including who should prescribe and review the technologies) it is appropriate that the clinical guideline review process should consider whether recommendation 1.3 in technology appraisal 217 should be updated.

where the GP was responsible for prescribing them from the outset this fell to 50% when the Specialists had to do all the prescribing. These systems are designed to be populated and maintained by Primary Care. In addition these drugs are, or are soon to be, generic so the cost issues associated with prescribed by GPs from the outset are minimal. In my view I can see no justification for continuing the current guidance unless a positive choice is being made to expose people with dementia to increased safety risks. 3. We would like to highlight specific areas of the guidelines that we particularly feel are out of date and require updating. With the continual rise in patients being diagnosed with dementia in the UK, memory clinics are struggling to cope with the increasing workload. Prescribers are few within these clinics and a considerable amount of their time is apportioned to issuing prescriptions for dementia medication and conducting straightforward medication reviews. Many clinics are overwhelmed with having to perform routine reviews on relatively stable patients to the detriment of assessing new cases. As a result, the majority of GPs in the area covered by our Trust now initiate treatment with acetylcholinesterase inhibitors (AChEIs) or memantine following advice from memory clinics under shared care guidelines. Cost pressures have reduced dramatically and the dementia drugs are generally quite safe and well tolerated, so GPs are confident to prescribe these drugs. We no longer feel that it is practical to restrict initiation of prescribing of anti-dementia drugs to specialists only. (See Clinical Guideline CG42, page 26 1.6.2.3 and TA217). In addition, regular reviews by memory clinics are no longer required or practical. The current guidance states that: “Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms”. “Patients who continue on treatment should be reviewed regularly using cognitive, global, functional and behavioural assessment. Treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care”. (See Clinical Guideline CG42, page 27 1.6.2.3 lines 3-8). Recent evidence from two publications however suggests that long-term use of AChEIs	The recommendations in technology appraisal 217 have already been incorporated in clinical guideline 42. A review proposal for clinical guideline 42 has recently undergone consultation. As the recommendations in 1.3 relate to conditions for the implementation of the guidance (including who should prescribe and review the technologies) it is appropriate that the clinical guideline review process should consider whether recommendation 1.3 in technology appraisal 217 should be updated.

is beneficial and not dependent on severity of dementia. A large multicenter study (Howard et al 2012) of community-dwelling patients with moderate or severe AD investigated the long-term effects of donepezil over 12 months compared with stopping donepezil after 3 months, switching to memantine or combining donepezil with memantine. Continued treatment with donepezil was associated with continued cognitive benefits and patients with a Mini Mental State (MMSE) score as low as 3 were still benefiting from treatment. This suggests that patients should continue treatment with AChEIs for as long as possible and there should not be a cut-off cognitive assessment score where treatment is stopped automatically. A meta-analysis evaluating the efficacy of the three AChEIs and memantine in relation to the severity of AD found that the efficacy of all drugs except memantine was independent from dementia severity in all domains. The effect of memantine on functional impairment was better in more severe patients. Results demonstrated that patients in differing stages of AD retain the ability to respond to treatment with AChEIs and memantine. Medication effects are therefore substantially independent from disease severity and patients with a wide range of severities can benefit from drug therapy. This suggests that the severity of a patient's illness should not preclude treatment with these drugs (Di Santo et al 2013). In view of these findings, we feel that whilst assessing tolerability of these drugs is important, their clinical effects are difficult to assess and evidence now suggests that patients should continue on treatment for as long as possible. Therefore reviews to determine efficacy may no longer be indicated and this should be reflected in the updated guidelines.	

Respondent: Association of British Neurologists **Response to proposal:** Agree Having considered the documents provided, the ABN agrees that no new evidence has emerged to alter the current guidance on prescription of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. We have no objection to the proposal that TA217 should be moved to the static list of technology appraisals.	**Comment from Technology Appraisals** Comment noted.

Respondent: Alzheimer's Society **Response to proposal:** Disagree We recognise that the changes made to TAR217 at last update (March 2011) have contributed towards greater access to these drugs (as evidenced in NICE Proposal Paper, Appendix 3). The attendant benefits for people living with dementia who receive them is of course very welcome. However, the Society's view is that the current guidance is now in need of minor updates, for the reasons outlined below, and as such should not be placed on the static list. 1. Any consideration of dementia drug guidance must reflect increasing changes to the way the condition is now actually managed between primary and secondary care. Many GPs are now carrying out routine reviews of these drugs and some are initiating prescription. This clearly has benefits in terms of patient convenience and freeing up resources at memory services (for diagnosis and seeing more complex cases), but it places a burden on GPs to remain au fait with guidance and research of the kind summarised in TAR217. This alone argues for a more thorough consideration of TAR217. There is no mention in the NICE proposal of the existing evidence base, for example, to decide whether prescription of these drugs should routinely be initiated by a non-specialist. A minor review of TAR217 would greatly inform the development of shared care protocols in this area. 2. We disagree with NICE's statement (p. 3 of the Proposal) that "no significant new	**Comment from Technology Appraisals** Comments noted. The recommendations in technology appraisal 217 have already been incorporated in clinical guideline 42. A review proposal for clinical guideline 42 has recently undergone consultation. As the recommendations in 1.3 relate to conditions for the implementation of the guidance (including who should prescribe the technologies) it is appropriate that the clinical guideline review process should consider whether recommendation 1.3 in technology appraisal 217 should be updated. Comments noted. Any recommendations in

evidence has been identified that is likely to lead to a change in the current recommendations". Our reading of the research evidence is that best practice is no longer to substitute memantine for an AChEI when the person's Alzheimer's has become severe, which is a central recommendation of the current guidance. The DOMINO trial1 in particular clearly shows that patients who have benefited from donepezil up to this point will benefit from staying on donepezil beyond it2. We recognise that a change in any guidance to prescribe donepezil for severe Alzheimer's dementia would take the drug outside its current UK licence, but we note that FDA granted donepezil a licence for severe Alzheimer's disease in the USA3 in 2006. When the patient is kept on donepezil, the main decision becomes whether to add on memantine or not. We accept that the available evidence on this last point seems less clear cut (as summarised on Proposal p.5).	NICE technology appraisal guidance must be made within the technologies' marketing authorisation. As such technology appraisal 217 recommends donepezil, galantamine and rivastigmine for people presenting with mild or moderate Alzheimer's disease and memantine as an option for some people presenting with moderate Alzheimer's disease and for people presenting with severe Alzheimer's disease. The recommendations state that treatment should be continued if having a worthwhile effect on cognitive, global functional or behavioural symptoms. TA217 does not recommend switching treatments or treatment sequences, which is outside the technology appraisal guidance. This is for a doctor to decide in consultation with the patient, and in consideration of the marketing authorisations for the available medicines and the General Medical Council good prescribing guidance.
3. Any argument to recommend extending the use of donepezil is reinforced by the fall in tariff price of generic donepezil (as mentioned in the Proposal paper, p.3), which clearly changes cost-effectiveness arguments in favour of treatment. The costs of the other drugs are also falling as the generic market in them matures.	Comments noted.
4. There is growing anecdotal evidence that routine clinical practice has already changed to reflect points 1-3, and that many clinicians already keep the patient with severe Alzheimer's on donepezil. TAR217 in its current form seems out of step with the best informed clinical practice. Some minor revisions would help maintain its relevance and influence to the benefit of people with dementia and at only marginally increased cost.	Comments noted. Consultation on the minor updates should be incorporated into the review of clinical guideline 42.

In sum, Alzheimer's Society do not envisage that a major review of TAR217 is necessary, but in our view some minor updates to reflect these changes are required.	

Paper signed off by: Helen Knight, Associate Director – Technology Appraisals, 7 April 2015

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