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

This guidance was issued in March 2011.

The review date for this guidance is April 2014.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remits

To appraise the clinical and cost effectiveness of medicines which are licensed, at the time NICE prepares its appraisal consultation document, for treatment of severe Alzheimer's disease, including memantine and cholinesterase inhibitors. The comparison should be in each case between drug therapy (in combination with supportive care) and current treatment alternatives (including best supportive care alone).

As part of the planned review of guidance on treatment of Alzheimer's disease *[NICE TA111: donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease, November 2006, last amended August 2009]*, to appraise the clinical and cost effectiveness of memantine (Ebixa) for treatment of moderate Alzheimer's disease.

3. Current guidance

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.

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.

1.3 Treatment should be under the conditions:

- Only specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of older people) should initiate treatment. Carers' views on the patient's condition at baseline should be sought.

- 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. Carers' views on the patient's condition at follow-up should be sought.

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.

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.

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.

4. Rationale[1]

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'.

5. Implications for other guidance producing programmes

CCP has no objections to the proposal to move TA217 to the static list. All the recommendations have already been incorporated into CG42 (Dementia Supporting people with dementia and their carers in health and social care), so this move has no effect on the guideline. CG42 is due for its 8-year surveillance review in November 2014.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from March 2010 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

There have been no changes in the marketing authorisations for donepezil, galantamine, rivastigmine or memantine since technology appraisal 217 (TA217). Since the publication of technology appraisal 217, generic versions of donepezil, galantamine, rivastigmine and memantine are available. This has resulted in a reduced cost for most formulations of these technologies; up to more than 90% of the list price of the branded original versions.

<u>AChE inhibitors</u>

Differentiation between AChE inhibitors in terms of clinical effectiveness

In TA217 the Committee concluded that there was insufficient evidence to differentiate between AChE inhibitors in terms of clinical effectiveness. Since TA217 data has been published from 1 RCT comparing galantamine with donepezil in 218 people with mild to moderate Alzheimer's disease (MMSE 10-24) over 16 weeks in 9 hospitals in China. The primary outcome measure was the 11 point Alzheimer's Disease Assessment Scale- cognitive subscale (ADAS-cog11).The study found that the frequency and types of adverse events and cognitive outcomes overall were similar in the 2 groups, both showing improved scores, but scores on the language-specific measures of ADAS-cog11 and the proportion of people who had low overall cognitive impairment were significantly higher with galantamine than donepezil[3].

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

Although there are no further head-to-head trials of AChE inhibitors for Alzheimer's disease, several studies have assessed longer term outcomes with AChE inhibitors since TA217.

There has been data published from a double blind placebo controlled trial of galantamine for mild to moderate Alzheimer's disease over a longer (2 year) follow up than was available for the galantamine trials that were appraised in TA 217. The trial included 1023 people in the placebo group and 1028 people in the galantamine group. The primary efficacy outcome was change from baseline to month 24 in the MMSE score. Secondary outcomes included measurement of activities of daily living using the Disability Assessment in Dementia tool. Galantamine was associated with a statistically significantly slower decline in cognition and activities of daily living compared with placebo The study additionally found that there was a statistically significant decreased mortality rate in the group of people who received galantamine relative to the people who received placebo (odds ratio 0.56, 95% confidence interval [CI], 0.35 to 0.88)[4]. Data from a smaller trial in which people with mild to moderate Alzheimer's disease who had responded to galantamine treatment over 12 months (had a less than 4 point cognitive decline measured by the Alzheimer's Disease Assessment Scale- cognitive subscale [ADAS- cog]) were randomly assigned to either continue receiving galantamine or receive placebo in a double blind 24 month phase has also been published. The study included 126 people in the intention to treat population in the double blind phase. People who continued taking galantamine were less likely to stop the study drug because of lack of efficacy than people receiving placebo (Hazard Ratio [HR] 1.80, 95% CI 1.02 to 3.18) but there was no difference for the change on ADAS-cog of more than 4 points outcome between both groups[5]. A prospective open label study carried out in Sweden found that over 3 years follow up people who received galantamine were cognitively and globally stabilised and found a better short term response in a subgroup of people who were older, had lower cognitive and functional abilities at baseline, a faster pre-treatment progression rate, and a lower incidence of the APOE 4 (apolipoprotein E4) allele[6]. A Canadian naturalistic, prospective, open label observational study of 3800 of people taking rivastigmine found that the proportions of people improving verses deteriorating at 6 months for their baseline assessment were greater for attention, apathy, anxiety, irritability and sleep disturbance measures[7].

Memantine

New evidence for clinical effectiveness of memantine in people with moderate to severe Alzheimer's disease

In TA217 the Committee concluded that memantine could not be considered cost effective compared with the AChE inhibitors in people with moderate disease because it generated fewer quality adjusted life years (QALYs) at a higher cost. Since the publication of TA217 there is limited new data available for the clinical effectiveness of memantine in a population with moderate Alzheimer's disease. One small Randomised Controlled Trial (RCT) had a primary aim of comparing brain biomarkers using MRI in people who took memantine or donepezil for 6 months, but also measured some clinical outcomes (including Mini Mental State Examination (MMSE), Clinical Dementia Rating Scale, Alzheimer's Disease Assessment Scale cognitive part (ADAS- cog), Clinical Dementia Rating Scale (CDR), Blessed Dementia Rating Scale, neuropsychiatric inventory (NI and disability assessment for

dementia (DAD)). This study included people with mild and moderate Alzheimer's disease and as such also assessed people with milder Alzheimer's disease symptoms than the European marketing authorisation for memantine covers. No statistically significant differences were observed in clinical scales between the 32 people taking donepezil and the 31 people taking memantine[1].

In its deliberations for TA217, the Committee considered that memantine was likely to have a positive effect on quality of life of people with severe disease because they are more likely to experience behavioural symptoms and heard from the manufacturer and clinical specialists at the Committee meetings for TA217 that memantine appears to have cognitive, functional, global and behavioural effects, particularly in people with aggression, agitation and/or psychotic symptoms. The Committee accepted that memantine may therefore have the potential to reduce the need for antipsychotics but noted that there were no randomised controlled trials to support the assumption. There has subsequently been a RCT which compared memantine with placebo in 153 people with Alzheimer's disease with clinically significant agitation. The primary outcome was Cohen- Mansfield Agitation Inventory (CMAI) score at 6 weeks. Secondary outcomes included CMAI score at 12 weeks, Neuropsychiatric inventory (NPI) score at 6 and 12 weeks, Clinical Global Impression Change (CGI-C) and standardised MMSE (severe Impairment battery). There were no statistically significant differences between memantine and placebo in CMAI, NPI or CGI-C at 6 or 12 weeks. Memantine was statistically significantly better for cognitive outcomes (MMSE) than placebo at 12 weeks. The researchers highlighted that it still needs to be determined whether memantine has a role for people with milder agitation in Alzheimer's disease than was assessed in this study[2].

Memantine in combination with an AChE inhibitor for people with moderate Alzheimer's disease

The risks and benefits of adding memantine to AChE inhibitor treatment were considered in TA217. The Assessment Group for that appraisal pooled data from 2 trials in which memantine was used adjunctively to an AChE inhibitor and a manufacturer submitted a meta-analysis of 6 trials of memantine used adjunctively to an AChE inhibitor compared to placebo. The Assessment Group's analysis found no benefit of memantine combination therapy, whereas the manufacturer showed memantine to be significantly superior to placebo in most outcomes both as an adjunct and monotherapy. The Committee concluded in TA217 that memantine as an adjunct to an AChE inhibitor could not be recommended as there was insufficient evidence for efficacy verses memantine monotherapy.

Since TA217 there have been further studies comparing a combination of memantine with an AChE inhibitor with memantine alone or an AChE inhibitor alone. These studies found either no benefit, or limited benefit of combination treatment compared to monotherapy[8,9,10,11]. One systematic review of combination therapy with an AChE inhibitor and memantine published since technology appraisal 217[12] showed statistically significant differences in favour of combination therapy in people with moderate to severe Alzheimer's disease but concluded that it was unclear whether these differences were clinically significant. A second systematic review concluded that the current evidence from RCTs shows no benefit of combination therapy over monotherapy at 1 year.

On 18th October 2012 the Committee for Medicinal Products for Human Use adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Acrescent, a tablet containing a combination of memantine hydrochloride and donepezil hydrochloride, manufactured by Lundbeck as there was insufficient evidence to suggest the benefits of Acrescent outweighed the risks for people with moderate to moderately severe Alzheimer's disease[14].

New treatments

Results from 2 randomised trials which compared SB-742457 (a 5-hydroxytryptamine 6 receptor antagonist) with placebo or donepezil over 24 weeks in people with mild to moderate Alzheimer's disease have been published since TA 217[19, 20]. Both trials found SB-742457 to be well tolerated. The larger of the two trials[20] which included 574 people failed to detect efficacy for SB-742457.

There are published pooled results from 2 randomised controlled trials with identical protocols that assessed the efficacy and safety of solanezumab (an anti-amyloid beta peptide antibody) vs. placebo in people with mild to moderate Alzheimer's disease (MMSE 16-26) receiving various concomitant treatments[21]. In the solantuzumab arm 578 people were receiving an AChE inhibitor, 286 people were receiving an AChE inhibitor with memantine, 46 people were receiving memantine monotherapy and 110 people were receiving 'no standard of care'. In the placebo arm of the trials 566, 286, 68 and 102 people were receiving an AChE inhibitor, an AChE inhibitor with memantine, memantine monotherapy and 'no standard of care' respectively. The baseline disease severity of the groups of people receiving different concomitant treatments differed and different efficacy outcomes of solanezumab relative to placebo were observed across the 4 groups.

A further phase II study assessed the tolerability, safety and efficacy of 2 doses of orM-12741 (a selective alpha-2C adrenoceptor antagonist) compared with placebo in 100 people with moderate Alzheimer's disease (MMSE scores of 12-21) who also had behavioural symptoms (a score of more than 15 on the Neuropsychiatric inventory) over 12 weeks[22]. All participants had ongoing stable AChE inhibitor treatment and were allowed to take memantine and selective serotonin reuptake inhibitor (SSRI) treatment. People receiving orM-12741 had statistically significantly better scores on measures of quality of episodic memory, quality of memory and caregiver distress on the Neuropsychiatric inventory than placebo.

An ongoing trial is assessing the effect of adding on choline alphophoscerate to donepezil in people who have moderate Alzheimers disease (MMSE score 15-24) who also have ischaemic brain damage as a result of a cerebrovascular event[23].

8. Implementation

A submission from Implementation is included in Appendix 3.

Since the publication of technology appraisal 217 the number of units of donepezil, rivastigmine and memantine prescribed and dispensed per month (in community and hospitals settings) has increased. The number of units of galantamine that have been dispensed in the community per month has remained stable since the publication of technology appraisal 217 whereas galantamine prescribing in hospitals

has decreased. The number of units of galantamine and rivastigmine dispensed in August 2013 were broadly similar; many more units of donepezil were dispensed than the other 2 AChE inhibitors.

9. Equality issues

In technology appraisal guidance 217 the Committee confirmed that, as in NICE technology appraisal guidance 111 (which technology appraisal 217 updated), 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. Clinicians 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.

GE paper sign off: Helen Knight, Associate Director. 25 March 2014

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to a specific date.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	**The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.**	**Yes**

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Dementia: Supporting people with dementia and their carers in health and social care. NICE Clinical Guideline CG42. Issued: November 2006. Review date: April 2014.

Dementia Quality Standard. QS1. Issued: June 2010.

Quality standard for supporting people to live well with dementia. QS30. Issued: April 2013.

Mental wellbeing of older people in care homes. NICE Quality Standard QS50. Issued: December 2013.

Monitoring

Transcranial Direct Current Stimulation (TDCS) for Alzheimer's disease. Currently being monitored by the NICE Interventional Procedures Programme.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Donepezil: symptomatic treatment of mild to moderately severe Alzheimer's dementia.	No change.
Galantamine: symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type.	No change.
Rivastigmine: symptomatic treatment of mild to moderately severe Alzheimer's dementia.	No change.
Memantine: treatment of patients with moderate to severe Alzheimer's disease.	No change.

Registered and unpublished trials

Trial name and registration number	Details
A Confirmatory Trial of SK-PC-B70M in Mild to Moderate Alzheimer's Disease NCT01249196; SMART_AD_III_2009.	Donepezil vs. SK-PC-B70M vs. placebo N=256 Completed ~August 2013
Hippocampus Study: Comparative Effect of Donepezil 10mg/d and Placebo on Clinical and Radiological Markers NCT00403520; E2020-E033-415.	N=240 Current status unknown. Estimated completion date: August 2010
Donepezil Treatment of Psychotic Symptoms in Dementia Patients NCT00190021; BMHC-3495CTIL.	N=80 Current status, estimated completion date unknown.
The DAT-study: Cerebrolysin Compared to Donepezil in Patients With Dementia of Alzheimer's Type NCT01822951; EVE-AT-0412; 2012-004944-31.	Not yet open for recruiting. N=510 Estimated completion date: December 2016.
A 24-weeks, Multi-center [sic], Randomized, Double-blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Donepezil Hydrochloride in Chinese Subjects With Severe Alzheimer's Disease NCT01404169; E2020-C086-339.	N=260 Estimated primary completion date: August 2014 Estimated study completion date: September 2014
Delaying the Progression of Driving Impairment in Individuals With Mild Alzheimer's Disease NCT00476008; NAM-MD-49.	Memantine vs. placebo N=60 Completed ~January 2013
Efficacy and Safety of Rivastigmine Transdermal Patch in Patients With Mild to Moderate Alzheimer's Disease NCT00423085; CENA713D1301; CENA713D1301E1	vs. placebo. N=859 Completed ~April 2010

Trial name and registration number	Details
Discontinuation of Cholinesterase Inhibitors for the Treatment of Severe Alzheimer's Disease NCT02035982; 107-2010; Grant #12-74.	Galantamine, donepezil or rivastigmine vs. placebo N = 50 Estimated primary completion date: February 2014.
Comparative Efficacy, Safety, and Tolerability of Rivastigmine 10 and 15 cm^2 Patch in Patients With Alzheimer's Disease (AD) Showing Cognitive Decline NCT00506415; CENA713D2340	N=1584 Completed ~May 2011
The Efficacy of a Combination Regimen in Patients With Mild to Moderate Probable Alzheimer's Disease NCT01921972; Modul E.2 II	Galantamine + placebo vs. galantamine + memantine N = 232 Completed
Effect of Memantine Oral Pump on Language in Patients With Probable Alzheimer's Disease NCT01849042; ROMEO-AD; 14394A	Trial of memantine as an add-on to donepezil N = 188 Estimated primary completion date: August 2014 Estimated study completion date: March 2015
Efficacy of Donepezil in the posterior variant of Alzheimer's disease (Posterior Cortical Atrophy) Study	N = 20 Completed ~2011

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Appendix 3 – Implementation submission

Routine healthcare activity data

3.1 ePACT data

This section presents net ingredient cost and the number of prescription items (volume) of Donepezil (figure 1), Galantamine (figure 2), Memantine (figure 3) and Rivastigmine (figure 4) prescribed and dispensed in primary care and hospitals that have been dispensed in the community in England between October 2008 and September 2013.

Figure 1 Net ingredient cost and volume of Donepezil hydrochloride prescribed and dispensed in primary care and in hospitals that have been dispensed in the community in England

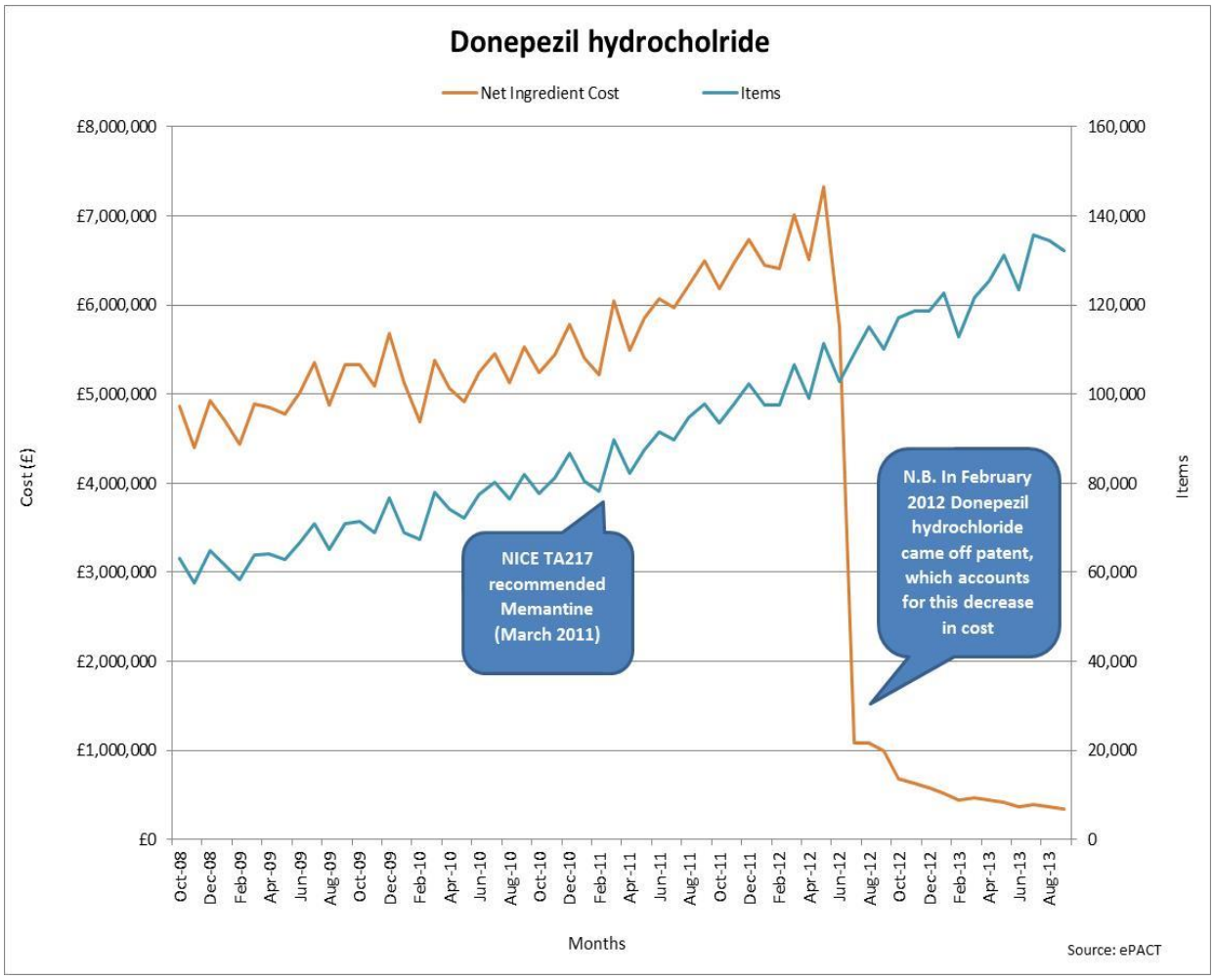


Figure 2 Net ingredient cost and volume of Galantamine prescribed and dispensed in primary care and in hospitals that have been dispensed in the community in England

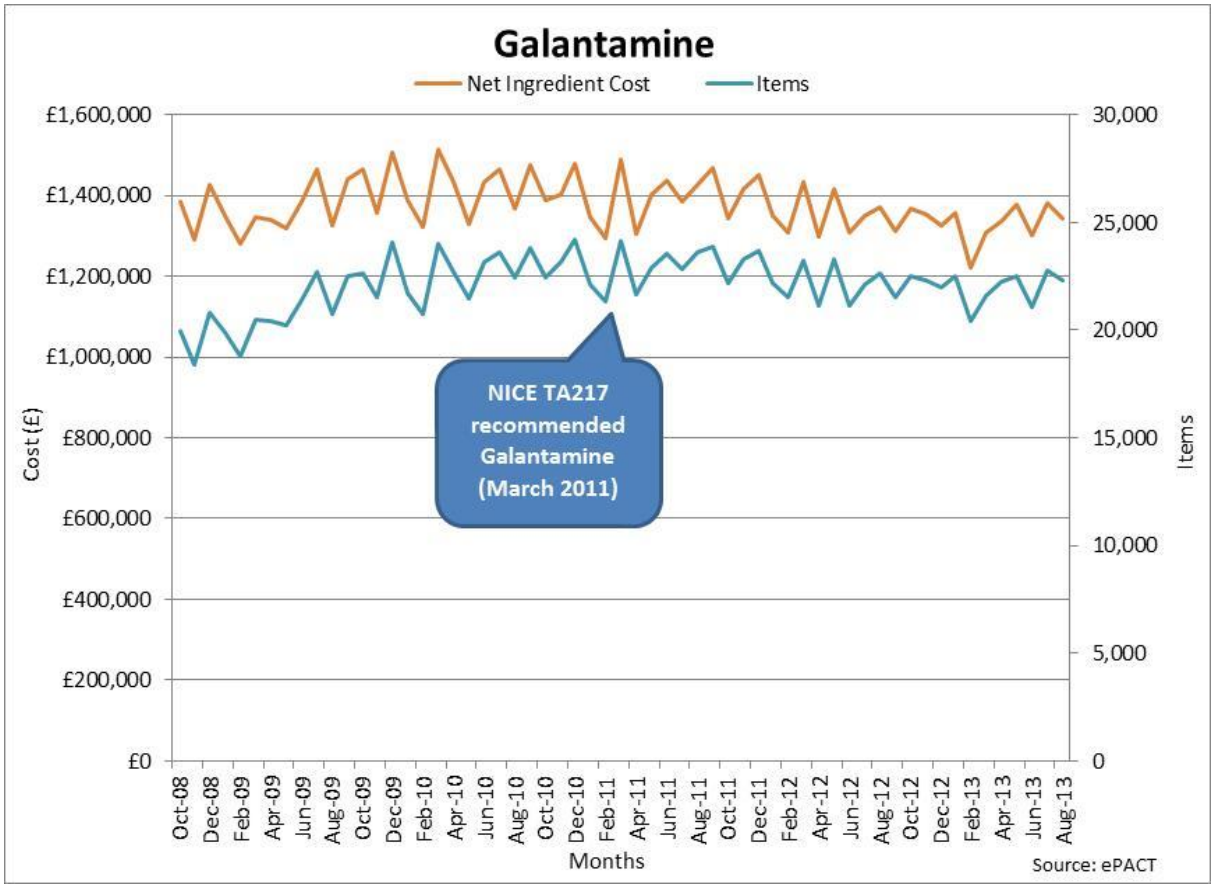


Figure 3 Net ingredient cost and volume of Memantine hydrochloride prescribed and dispensed in primary care and in hospitals that have been dispensed in the community in England

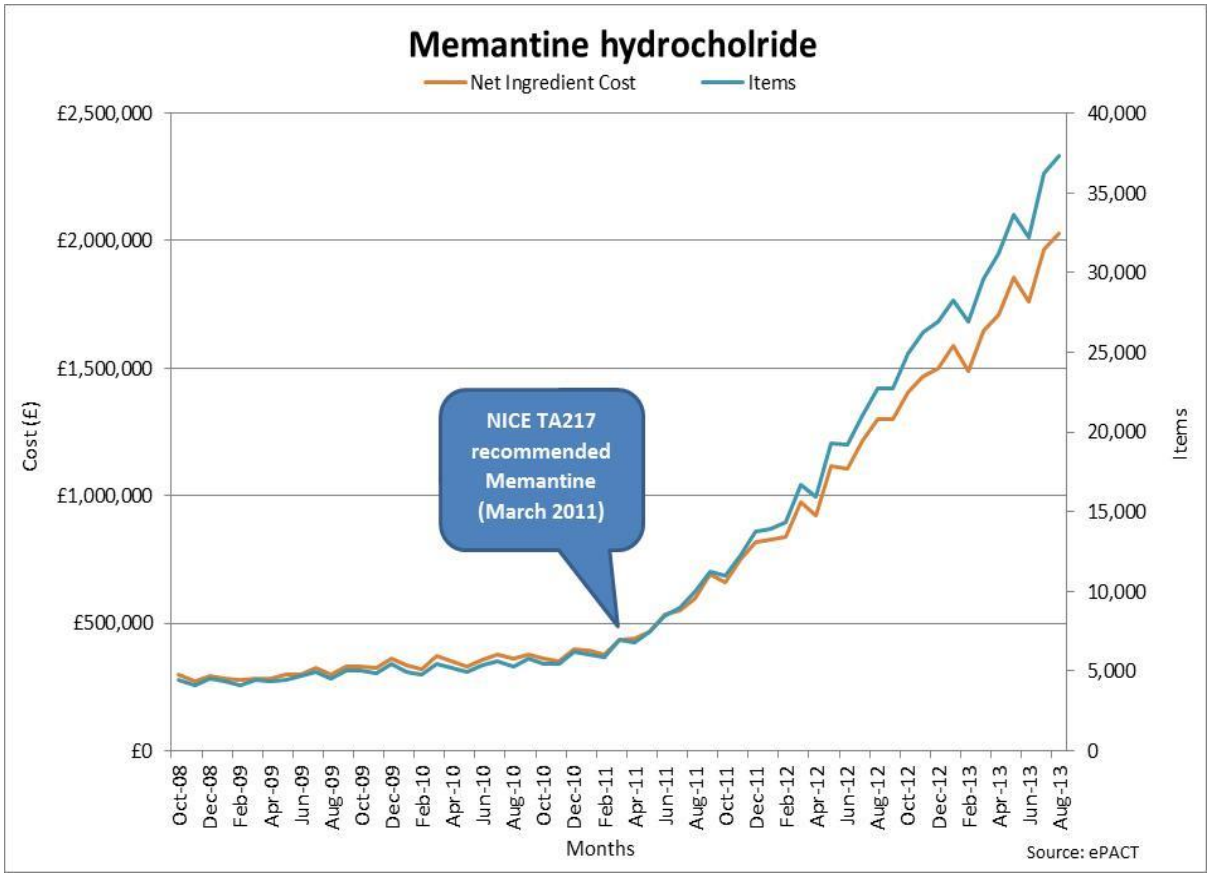
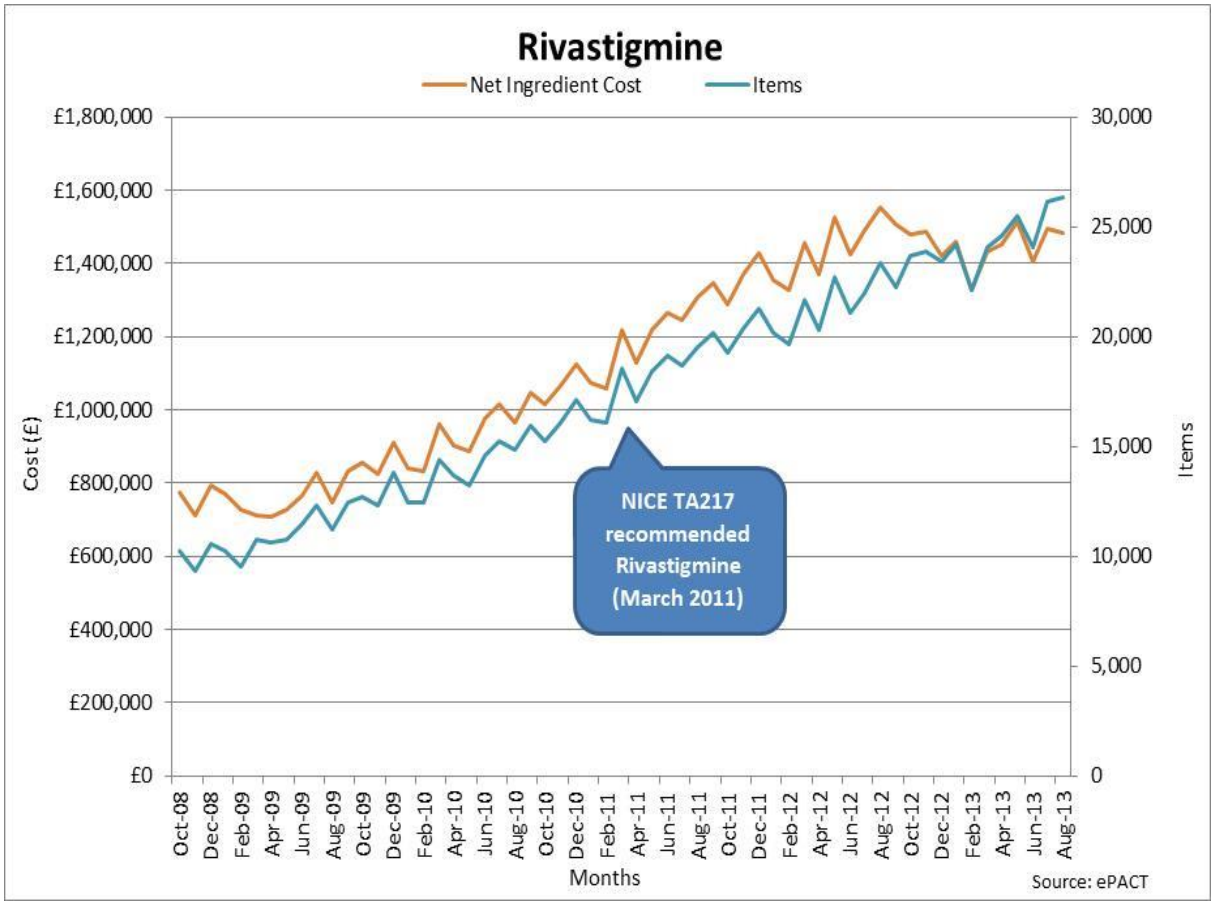


Figure 4 Net ingredient cost and volume of Rivastigmine prescribed and dispensed in primary care and in hospitals that have been dispensed in the community in England



3.2 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit index data on the net ingredient cost (NIC) and volume of Donepezil (figure 5), Galantamine (figure 6), Memantine (figure 7) and Rivastigmine (figure 8) prescribed and dispensed for use in hospitals in England between July 2000 and October 2012.

Figure 5 Net ingredient cost and volume of Donepezil prescribed and dispensed in hospitals in England

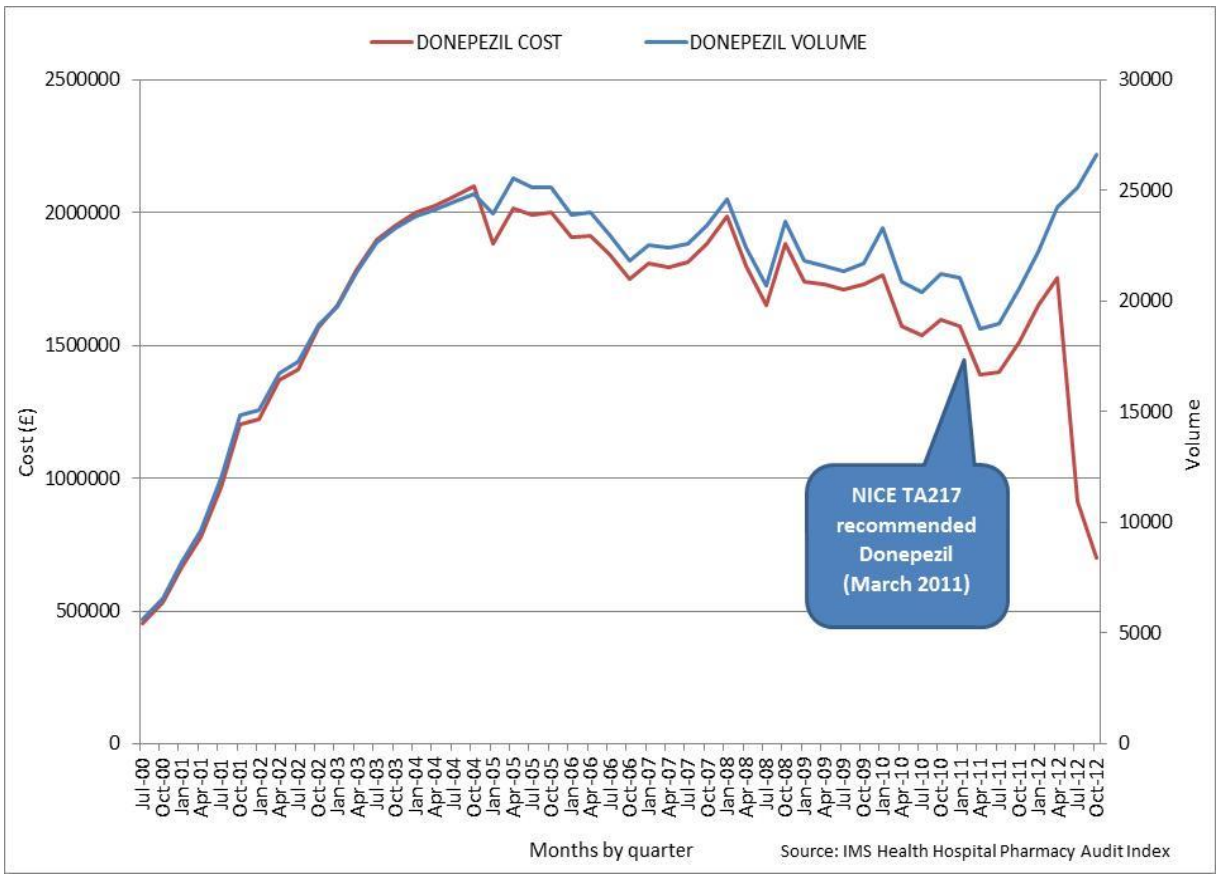


Figure 6 Net ingredient cost and volume of Galantamine prescribed and dispensed in hospitals in England

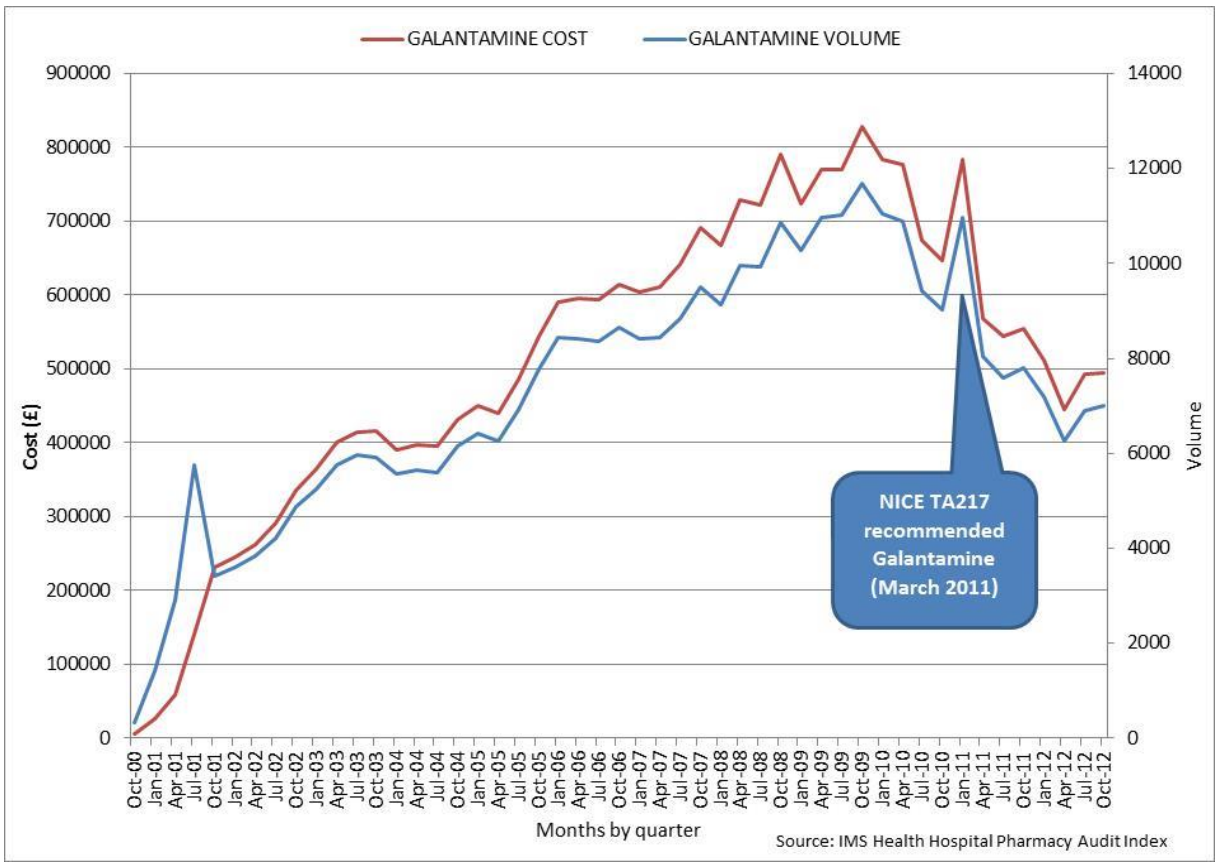


Figure 7 Net ingredient cost and volume of Memantine prescribed and dispensed in hospitals in England

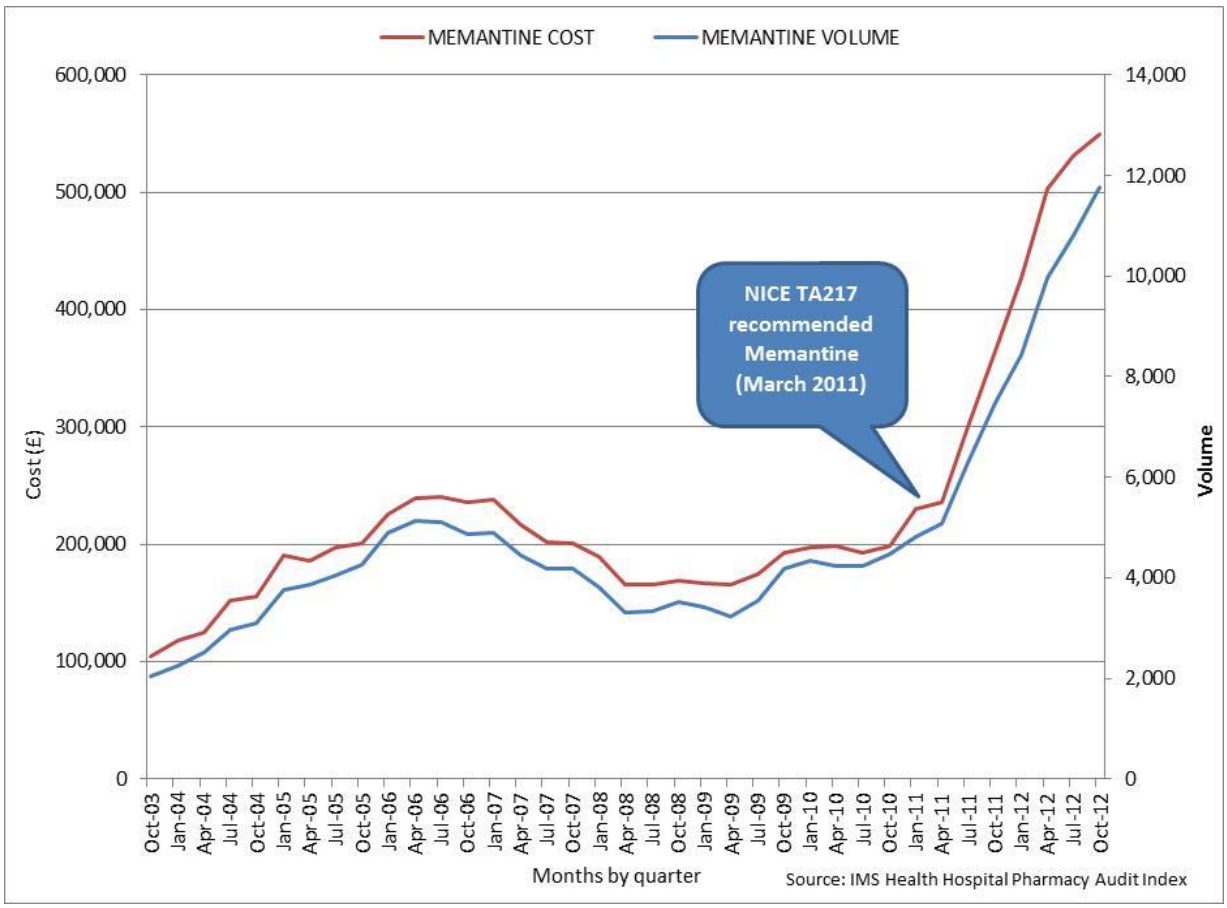
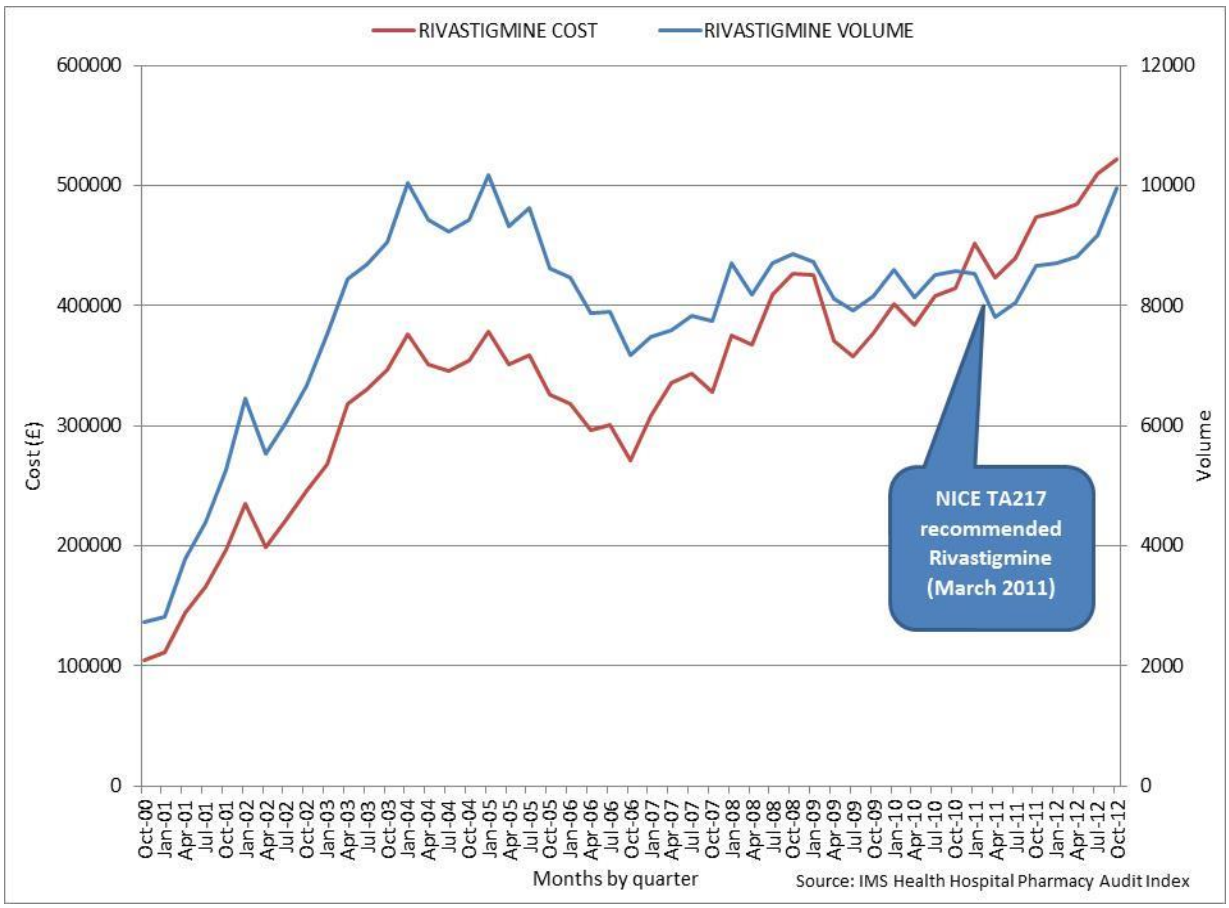


Figure 8 Net ingredient cost and volume of Rivastigmine prescribed and dispensed in hospitals in England



3.3 Implementation studies from published literature

Information is taken from the uptake database website.

Health and Social Care Information Centre (2012) Use of NICE-appraised medicines in the NHS in England - 2010 and 2011, Experimental Statistics

This is the 3rd report published by the HSCIC on behalf of the DH to look at the variation in use of positively appraised medicines in relation to the expected use as predicted by NICE. In all, 52 medicines in 25 groups, relating to 35 technology appraisals were considered. Out of the 12 groups where a comparison could be made, observed use by the NHS in England was higher than the predicted use for 6 and lower for 6. For one drug group use was lower on one measure, and higher on another.

3.4 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing specific to add.

Addendum: Healthcare activity data definitions

ePACT

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The

estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.