

Management of aggression, agitation and behavioural disturbances in dementia: carbamazepine

Evidence summary

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[nice.org.uk/guidance/esuom40](https://www.nice.org.uk/guidance/esuom40)

Key points from the evidence

The content of this evidence summary was up-to-date in March 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Four very small short-term randomised placebo-controlled trials (RCTs: total n=97) with many limitations give conflicting results about the efficacy of carbamazepine for managing aggression, agitation and behavioural disturbances in people with dementia. Larger, longer-term RCTs are required to confirm its efficacy and safety for this indication.

Regulatory status: off-label. The topic was prioritised because there is uncertainty about the balance of risks and benefits of carbamazepine in people with dementia.

Effectiveness	Safety
<ul style="list-style-type: none">• A 12-week crossover RCT (4 weeks' treatment, n=19) and a 6-week RCT (n=21) found no statistically significant differences between carbamazepine and placebo in global behavioural symptom scores.• In a 17-week crossover RCT (8 weeks' treatment, n=6), carbamazepine statistically significantly reduced aggression scores compared with placebo (p<0.05).• Global behavioural symptom scores improved statistically significantly with carbamazepine compared with placebo in a 6-week RCT (n=51: p=0.0003), as did other measures of behaviour and aggression.• The studies have many limitations and do not give any information on the long-term safety and efficacy of carbamazepine in older people with dementia.	<ul style="list-style-type: none">• In the largest RCT (n=51), adverse effects were statistically significantly more common with carbamazepine compared with placebo (p=0.03). Statistical analyses were not performed in the other RCTs.• According to the summary of product characteristics (SPC) for Tegretol, hyponatraemia, leukopenia, thrombocytopenia, eosinophilia, central nervous system (CNS) adverse reactions gastrointestinal disturbances, fluid retention and allergic skin reactions occur commonly or very commonly with carbamazepine (in 1 in 100 people or more).• CNS adverse effects such as drowsiness, dizziness and ataxia may potentially lead to falls and fractures, particularly in frail, older people.

Patient factors	Resource implications
<ul style="list-style-type: none">• No information is available comparing carbamazepine with other active treatments for managing aggression, agitation and behavioural disturbances in people with dementia.• Adverse effects are particularly common in older people and carbamazepine has a high potential for drug interactions, which can increase toxicity. If CNS adverse effects are seen, the SPC suggests monitoring plasma levels and dividing the daily dosage into smaller fractional doses, both of which may be unacceptable to some patients.	<ul style="list-style-type: none">• The dosage of carbamazepine in the studies was usually 300–400 mg daily. The cost (excluding VAT) of 1 months' treatment with carbamazepine 400 mg daily ranges from £5.20 to £27.16 depending on the formulation (Drug Tariff, January 2015).

Introduction and current guidance

The [NICE/SCIE guideline on dementia](#) recommends non-pharmacological interventions tailored to the individual person's preferences, skills and abilities as first-line treatment. People who develop non-cognitive symptoms or behaviour that challenges should be offered a pharmacological intervention in the first instance only if they are severely distressed or there is an immediate risk of harm to the person or others. Antipsychotic drugs have been associated with an increased risk of cerebrovascular adverse events and greater mortality when used in this population and NICE advises that treatment with an antipsychotic drug should be offered only after various conditions have been met. An acetylcholinesterase inhibitor or memantine may be offered in some circumstances.

Other drugs have been used off-label for non-cognitive symptoms of dementia; however, evidence to support their use is limited. The [NICE full guideline on dementia](#) concluded that there was insufficient evidence to support the use of anticonvulsant mood stabilisers, such as sodium valproate, valproate semisodium or carbamazepine, for the treatment of depression or anxiety in people with dementia. This evidence summary reviews the best available evidence for the use of carbamazepine for managing aggression, agitation and behavioural disturbances in dementia. It includes the 2 studies on carbamazepine that were considered by NICE ([Olin et al. 2001](#) and [Tariot et al. 1998](#)) and 2 additional studies. Another [evidence summary](#) considers valproate preparations for these indications.

[Full text of introduction and current guidance.](#)

Product overview

Carbamazepine is licensed for treating epilepsy and trigeminal neuralgia, and preventing manic-depressive psychosis in people who do not respond to lithium (see summaries of product characteristics for carbamazepine, for example, [Tegretol tablets](#)). It is not licensed for the management of aggression, agitation and behavioural disturbances in dementia; therefore, use for this indication is off-label.

[Full text of product overview.](#)

Evidence review

- This evidence summary is based on 4 very small randomised double-blind placebo-controlled trials (RCTs) that assessed the effects of carbamazepine in people with dementia and aggression, agitation or behavioural disturbances.
- A crossover RCT by Chambers et al. (1982: not available online) included 19 inpatients with dementia and associated wandering, overactivity, restlessness or physical aggression. Participants received 4 weeks' treatment with carbamazepine or placebo, followed by a 3-week washout period and 4 weeks' treatment with the alternative treatment. The study found no statistically significant differences between carbamazepine and placebo in global behaviour rating scores at any week over the 12-week period.
- A 17-week crossover RCT by [Cooney et al. \(1996\)](#) included 6 people who had severe Alzheimer's disease and were verbally or physically aggressive. Participants received 8 weeks' treatment with carbamazepine or placebo, followed by a 1-week washout period and 8 weeks' treatment with the alternative treatment. Treatment with carbamazepine reduced [RAGE scale](#) scores (a measure of aggression) statistically significantly more than placebo ($p < 0.05$) but it is unclear whether the results were [clinically important](#).
- An RCT by [Olin et al. \(2001\)](#) included 21 people with severe Alzheimer's disease and significant agitation for over a month who had been treated unsuccessfully with antipsychotics. Only 16 people completed the 6-week study. There was no statistically significant difference between the carbamazepine and placebo groups in Clinical Global Impression of Change or global Brief Psychiatric Rating Scale scores (BPRS: a measure of behaviour). The hostility item on the BPRS scale was statistically significantly improved with carbamazepine compared with placebo (difference 1.55 points on a 7-point scale, $p = 0.009$).

- A 6-week RCT by [Tariot et al. \(1998\)](#) included 51 people with severe Alzheimer's disease, vascular dementia or mixed dementia who had been significantly agitated for at least 2 weeks. Carbamazepine was statistically significantly more effective than placebo in improving global BPRS scores from baseline at week 6 (difference 6.8 points on a 126-point scale; $p=0.0003$), mainly due to improvements in agitation and hostility ($p=0.0001$ and $p=0.0007$ respectively). Statistically significantly more people taking carbamazepine improved in terms of Clinical Global Impression compared with placebo (77% were at least minimally improved compared with 21% with placebo; $p=0.001$).
- In [Chambers et al. \(1982\)](#), no participants discontinued treatment because of adverse effects but the authors reported that carbamazepine was 'poorly tolerated'. By contrast, carbamazepine was reported to be 'well-tolerated' in the study by [Cooney et al. \(1996\)](#). In the study by [Olin et al. \(2001\)](#), 1 person in the carbamazepine group and 4 in the placebo group discontinued treatment (3 with agitation). Adverse events occurred in 4/9 people in the carbamazepine group and 8/12 people in the placebo group (p value not reported) and were reportedly 'mild'. Four people withdrew from the study by [Tariot et al. \(1998\)](#) (3 with severe agitation and 1 with tics and sedation), all of whom were taking carbamazepine. In this study, adverse effects were statistically significantly more common in the carbamazepine group than in the placebo group (16/27 people compared with 7/24 people; $p=0.03$), although these were considered clinically significant in only 2 people (1 with tics and 1 with ataxia).
- According to the [summary of product characteristics for Tegretol](#), central nervous system adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia), gastrointestinal disturbances (nausea, vomiting), fluid retention and allergic skin reactions occur commonly or very commonly with carbamazepine (in 1 in 100 people or more). This is particularly true when treatment is initiated, if the initial dosage is too high, and when treating older people. Other common or very common side effects include hyponatraemia, leukopenia, thrombocytopenia and eosinophilia.
- The 4 RCTs have many limitations. For example, methods of randomisation and blinding were not reported in 3 studies and [allocation concealment](#) was not reported in any. All the studies were small and may have had insufficient [power](#) to detect differences between the treatment groups. Follow-up was short so no information is available on the long-term efficacy or safety of carbamazepine for managing aggression, agitation and behavioural disturbances in people with dementia. Also, all the studies were [placebo](#)-controlled and it is not known how carbamazepine compares to other drugs that have been used for this indication. Although some outcomes measured using rating scales were found to be statistically significant in some studies, the [effect sizes](#) appear small and it is unclear whether they are clinically important.

- The average age of people included in the 4 RCTs was 79 years and the majority (80%) were female, limiting applicability to men and younger people. The studies generally included people with severe dementia and it is unclear whether the results apply to people with less severe disease. Due to the potential for drug interactions and adverse effects, the dosage of carbamazepine should be selected with caution in older people.

[Full text of evidence review.](#)

Context and estimated impact for the NHS

The dosage of carbamazepine in the studies was usually 300–400 mg daily. According to the [Drug Tariff](#) (January 2015), the cost (excluding VAT) of 1 months' treatment with carbamazepine 400 mg daily ranges from £5.20 to £27.16 depending on the formulation (tablets, chewable tablets, modified release tablets or syrup).

[Full text of context and estimated impact for the NHS.](#)

Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with dementia who are thinking about trying carbamazepine.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

Dementia can be caused by many brain disorders, most of which progress gradually over several years. The symptoms of dementia occur in 3 groups:

- cognitive dysfunction, resulting in problems with memory, language, attention, thinking, orientation, calculation, and problem-solving
- non-cognitive symptoms and behaviour that challenges
- difficulties with activities of daily living, such as driving, shopping, eating, and dressing ([NICE clinical knowledge summary on dementia](#)).

Non-cognitive symptoms of dementia (which are the focus of this evidence summary) include hallucinations, delusions, anxiety, agitation and aggressive behaviour. Behaviour that challenges may include aggression, agitation, wandering, hoarding, sexual disinhibition, apathy and disruptive vocal activity such as shouting ([NICE and Social Care Institute for Excellence \[SCIE\] guideline on dementia](#)).

The [NICE/SCIE guideline on dementia](#) gives recommendations on the care of people with all types of dementia, including managing behavioural and psychological symptoms of dementia. It recommends that people with dementia who develop non-cognitive symptoms that cause them significant distress, or who develop behaviour that challenges, should be offered an assessment at an early opportunity to establish likely factors that may generate, aggravate or improve such behaviour. According to NICE and a [best practice guide](#) produced by the Alzheimer's Society and endorsed by the Department of Health, non-pharmacological interventions tailored to the individual person's preferences, skills and abilities are recommended as first-line treatment.

NICE advises that people with dementia who develop non-cognitive symptoms or behaviour that challenges should be offered a pharmacological intervention in the first instance only if they are severely distressed or there is an immediate risk of harm to the person or others. Antipsychotic drugs have been associated with an increased risk of cerebrovascular adverse events and greater mortality in people with dementia (see the [NICE key therapeutic topic on low-dose antipsychotics in people with dementia](#) and the [May 2012 edition of Drug Safety Update](#) for more information) and NICE advises that treatment with an antipsychotic drug may be offered only after various conditions have been met. An acetylcholinesterase inhibitor or memantine may be offered in some circumstances but the evidence to support their use for this indication is generally limited. Other

drugs that have been used (many off-label) for non-cognitive symptoms of dementia include antidepressants, anticonvulsants, benzodiazepines, adrenergic beta-blockers and hypnotics. However, evidence to support their use is lacking.

The [NICE full guideline on dementia](#) concluded that there was insufficient evidence to support the use of anticonvulsant mood stabilisers, such as sodium valproate, valproate semisodium or carbamazepine, for the treatment of depression or anxiety in people with dementia. This evidence summary reviews the best available evidence for the use of carbamazepine for managing aggression, agitation and behavioural disturbances in dementia. It includes the 2 studies on carbamazepine that were considered by NICE ([Olin et al. 2001](#) and [Tariot et al. 1998](#)) and 2 additional studies. Another [evidence summary](#) considers valproate preparations for these indications.

See the [NICE clinical knowledge summary on dementia](#) for a general overview of the condition. A [NICE pathway](#) brings together all related NICE guidance and associated products on dementia in a set of interactive topic-based diagrams. Non-cognitive symptoms and behaviour that challenges are included in a [NICE quality standard on dementia](#). In 2010, the Department of Health published an [implementation plan](#) for [Living well with dementia: a national dementia strategy](#).

Product overview

Drug action

According to the [summary of product characteristics for Tegretol](#), the mechanism of action of carbamazepine has only been partially explained. It stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges and reduces synaptic propagation of excitatory impulses. Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects of carbamazepine, the depressant effect on dopamine and noradrenaline turnover may be responsible for its antimanic properties.

Carbamazepine should be initiated at a low dose and increased gradually to avoid adverse effects. Due to the potential for drug interactions, the dosage should be selected with caution in older people.

Regulatory status

Carbamazepine is licensed for treating epilepsy (generalised tonic-clonic and partial seizures), managing the pain of trigeminal neuralgia, and preventing manic-depressive psychosis in people

who do not respond to lithium (see summaries of product characteristics for carbamazepine, for example, [Tegretol tablets](#)). It is available as standard and modified release formulations.

Carbamazepine is not licensed for the management of aggression, agitation and behavioural disturbances in dementia; therefore, use for this indication is off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using carbamazepine preparations outside their authorised indications.

Cost

According to the [Drug Tariff](#) (January 2014), excluding VAT, carbamazepine costs:

- £6.79 for 28 x 100 mg tablets, £5.59 for 28 x 200 mg tablets and £5.02 for 56 x 400 mg tablets
- £3.16 for 56 x 100 mg chewable tablets and £5.88 for 56 x 200 mg chewable tablets
- £5.20 for 56 x 200mg modified release tablets and £10.24 for 56 x 400 mg modified release tablets
- £6.12 for 300 ml x 100 mg/5 ml suspension.

Evidence review

This evidence summary is based on 4 very small randomised double-blind placebo-controlled trials (RCTs) that assessed the effects of carbamazepine in people with dementia and aggression, agitation or behavioural disturbances. Several other studies were identified but not included because they were open or uncontrolled, or not randomised.

Clinical effectiveness

Chambers et al. (1982: not available online)

- **Design:** This randomised placebo-controlled double-blind crossover trial was undertaken in a hospital in Scotland.
- **Patients:** It included 19 female inpatients (mean age 79.8 years) with dementia and associated wandering (87%), overactivity (84%), restlessness (87%) or physical aggression (37%).

- **Intervention and comparison:** One group received carbamazepine for 4 weeks, followed by matching placebo for 4 weeks, with a 3-week withdrawal period after each treatment phase. The other group received placebo followed by carbamazepine over the same timescales. The dose of carbamazepine was increased from 100 mg to 300 mg daily over the first week of treatment. All psychotropic medication was withdrawn but thioridazine 10 mg was permitted as required.
- **Outcomes:** Ward nurses completed a behaviour rating scale every week for 12 weeks covering 10 domains (physical aggression, noisiness, interference, wandering, bizarre behaviour, restlessness, co-operation, activity, attention seeking and smearing of food/faeces) that were each scored on a 6-point scale and combined to give a global behaviour rating score. A clinical psychologist completed the Clifton Assessment Schedule (CAS), an assessment of cognitive function and behaviour, at the start and end of both 4-week treatment periods. Carbamazepine levels were monitored weekly and a psychiatrist adjusted the dosage as required.
- **Results:** The study found no significant differences between carbamazepine and placebo in global behaviour rating scores at any week over the 12-week period. A significant deterioration from baseline in CAS global scores was seen in the carbamazepine group (mean change -1.7 points on a 12-item scale, $p=0.01$) but there was no significant change from baseline in the placebo group (mean change -0.1 points, p value not reported). Overall, there was no significant difference in CAS scores between the carbamazepine and placebo treatment periods.

Cooney et al. (1996)

- **Design:** This randomised placebo-controlled double-blind crossover trial was undertaken in a residential home in Ireland.
- **Patients:** It included 6 people (4 female, mean age 77.2 years) with severe Alzheimer's disease (according to DSM-III-R criteria) who were verbally or physically aggressive. Of the 6 people, 5 scored 0 on the Mini Mental State Examination (MMSE) a 30-point questionnaire.
- **Intervention and comparison:** Participants received 8 weeks' treatment with carbamazepine or placebo, followed by a 1-week washout period and 8 weeks' treatment with the alternative treatment. Carbamazepine was initiated at a dose of 100 mg twice daily, increased in 50 mg increments every 3 days to a maximum of 300 mg twice daily. No participants took regular psychotropic medication before the study but 4 were prescribed thioridazine as required, which was continued during the study.

- **Outcomes:** Assessments, blind to treatment status, were made at the beginning and end of each treatment period. Aggression was assessed using the RAGE scale, a 21-item scale measuring a range of aggressive behaviour from verbal aggression to marked physical aggression.
- **Results:** Treatment with carbamazepine, but not placebo, statistically significantly reduced RAGE scale scores from baseline ($p < 0.05$) and, when the 2 groups were compared, carbamazepine was statistically significantly better than placebo ($p < 0.05$). However, the clinical importance of the results is unclear.

Olin et al. (2001)

- **Design:** This randomised placebo-controlled double-blind trial was undertaken in people in the US who were living with a caregiver.
- **Patients:** It included 21 people (14 female, mean age 74.7 years) with severe Alzheimer's disease (mean MMSE score 6.0) who had not responded to previous neuroleptic treatment, and were significantly agitated for a month or more and had Brief Psychiatric Rating Scale (BPRS) scores of 4 or more (each of 18 symptoms rated 1–7, with 7 indicating more severe symptoms) on at least 2 of tension, hostility, uncooperativeness and excitement. Most participants had moderately severe agitation, but mild psychotic and mood symptoms. People with poor physical health were excluded.
- **Intervention and comparison:** Participants were randomised to receive 6 weeks' treatment with carbamazepine ($n=9$) or placebo ($n=12$). Carbamazepine was initiated at a dose of 100 mg daily and increased gradually over 2 weeks to 100 mg 4 times daily. If a dose was not tolerated, it was temporarily reduced and increased again as indicated and tolerated. People who took neuroleptic medication, long-acting benzodiazepines and antidepressants in the 2 weeks before the study were excluded. Chloral hydrate 500 mg was permitted during the study, although none was used.
- **Outcomes:** The primary outcomes were the Clinical Global Impression of Change (CGIC) and BPRS total score. Secondary outcomes were the Hamilton Depression Rating Scale for Depression (Ham-D), the Physical Self Maintenance Scale (PSMS), Instrumental activities of Daily Living (IADL), the MMSE, and individual BPRS item scores.
- **Results:** The mean daily dose of carbamazepine was 388 mg in weeks 5 and 6: only 1 person did not take 400 mg by the end of the study. The average length of treatment was 5.4 weeks. Only 16 people completed the 6-week study.

- There was no statistically significant difference between the groups in CGIC, BPRS total scores, Ham-D, PSMS, IADL or MMSE. The hostility item on the BPRS scale was statistically significantly improved with carbamazepine compared with placebo (difference 1.55 points on a 7-point scale, $p=0.009$).

Tariot et al. (1998)

- **Design:** This randomised placebo-controlled double-blind trial was undertaken in 4 US long-term care facilities.
- **Patients:** It included 51 people (41 female, mean age 86.0 years) with severe Alzheimer's disease, vascular dementia or mixed dementia (according to DSM-III-R criteria; $n=33$, 13 and 5 respectively; mean MMSE score 6.0) who had been significantly agitated for at least 2 weeks with BPRS scores of 3 or more on the tension, hostility, uncooperativeness and excitement items. In the 43 people who were taking psychotropic drugs, these were withdrawn for at least 2 weeks before randomisation.
- **Intervention and comparison:** Participants were randomised to receive 6 weeks' treatment with carbamazepine ($n=27$) or placebo ($n=24$). Carbamazepine was initiated at a dose of 100 mg daily and increased by 50 mg every 2–4 days until serum levels were 5–8 micrograms/ml. If adverse effects occurred, the dose was maintained or reduced to the maximum tolerated. All participants were blinded to treatment allocation except a physician who monitored and adjusted participants' doses of treatment based on tolerability information from written reports and laboratory data and a pharmacist, both of whom had no contact with the participants or their families, or the care team and laboratory personnel. Chloral hydrate 250–500 mg was permitted as required during the study.
- **Outcomes:** The primary outcomes were the modified 18-item BPRS total score and the 7-point Clinical Global Impression (CGI) scale, ranging from 'very much improved' to 'very much worse'. The CGI scale was used at week 6 to help ascertain the clinical importance of changes in BPRS scores. Secondary outcomes included the Overt Aggression Scale (OAS), the Behaviour Rating Scale for Dementia (BRSD), the Physical Self Maintenance Scale (PSMS) and the MMSE. Data were analysed by intention to treat.
- **Results:** The mean daily dose of carbamazepine was 304 mg daily at week 6. Carbamazepine was statistically significantly more effective than placebo in improving BPRS scores from baseline at week 6 (-7.7 points compared with -0.9 points; difference 6.8 points on a 126-point scale, 95% confidence interval 3.3 to 10.2 points; $p=0.0003$). Weekly mean total BPRS scores improved steadily with carbamazepine from baseline to week 5 but did increase again at week 6. Analysis of BPRS items found that a statistically significant improvement was

seen in agitation and hostility ($p=0.0001$ and $p=0.0007$ respectively) but not other items. The clinical importance of the results is unclear.

- Statistically significantly more people taking carbamazepine improved in terms of CGI compared with placebo ($p=0.001$). In the carbamazepine group, 20 people (77%) were reported as being at least minimally improved compared with 5 people (21%) in the placebo group. Carbamazepine also statistically significantly improved OAS and BRSD scores (measures of aggression and behaviour) compared with placebo ($p=0.008$ and $p=0.003$ respectively). It is unclear whether these improvements were clinically important.
- Average changes in MMSE and PSMS scores (measures of cognition and function) were not significantly different in people taking carbamazepine and placebo. Staff perception was that 74% of people taking carbamazepine required less time for managing behaviours, compared with 21% of people taking placebo (p value not reported).
- Over 6 weeks, 10 people taking placebo and 12 people taking carbamazepine needed as required chloral hydrate, with use decreasing in the carbamazepine group over that period. At week 6 an average of 1.6 doses were used by people taking carbamazepine in the preceding week compared with 3.5 doses at baseline (reduction 1.9 doses), and 0.5 doses were used by people taking placebo compared with 0.6 doses at baseline (reduction 0.1 dose: $p=0.05$ for carbamazepine compared with placebo at 6 weeks).

Participants who completed the study by [Tariot et al. \(1998\)](#) underwent a 3-week washout from study medication before receiving treatment with carbamazepine in an uncontrolled extension study, [Tariot et al. \(1999\)](#). The extension study investigated whether clinical benefits seen with carbamazepine in the first 6-week study would diminish significantly during washout, and whether washout from carbamazepine would be associated with changes in function or adverse effects compared with placebo ($n=45$). The study also provides limited information on the efficacy and safety of carbamazepine for an additional 6 weeks ($n=32$) and 12 weeks ($n=25$). Investigators were blinded to the original treatment group.

From week 6 to week 9, following washout, a statistically significant worsening of mean BPRS total score (a measure of agitation and aggression) was seen in people in the carbamazepine group compared with the placebo group (mean reduction in BPRS total score 9.8 compared with 1.9, $p=0.0001$), suggesting that ongoing carbamazepine treatment is needed to prevent relapse.

From week 9 to week 21 both groups received open-label carbamazepine treatment (modal dose 300 mg daily) and ongoing statistically significant improvements were seen. The mean BPRS total score was 54.5 at week 9, 44.3 at week 15 and 33.8 at week 21 (week 15 compared with week 9, and week 21 compared with week 9, both $p=0.0001$).

Safety and tolerability

Chambers et al. (1982)

In this study, no participants discontinued treatment because of adverse effects. However, the authors report that carbamazepine was 'poorly tolerated' even though low doses were used and serum levels were below the usual therapeutic range. Overall, 5 participants in the study (treatment groups not reported) experienced dizziness or drowsiness initially, of whom 2 experienced longer term drowsiness which resolved when the dose was reduced. Thioridazine was needed by 1 patient taking carbamazepine and 1 patient taking placebo in the second 4-week period.

Cooney et al. (1996)

This study found that carbamazepine was 'well-tolerated' with no adverse haematological reactions. One person developed sedation on carbamazepine 300 mg daily but this resolved when the dose was reduced to 200 mg daily.

Olin et al. (2001)

In this study, 1 person was withdrawn from carbamazepine treatment because of a worsening of cognitive function. In the placebo group, 3 people discontinued treatment at weeks 1, 3 and 4 because of increased agitation and 1 discontinued at week 1 because of a cerebrovascular event.

Adverse events occurred in 4/9 people in the carbamazepine group and 8/12 people in the placebo group (p value not reported) and were reportedly mild. In the carbamazepine group, diarrhoea was the most common adverse event, occurring intermittently in 3 people for less than 2 weeks. In the placebo group, vomiting occurred most commonly, in 2 people. No haematological adverse events were seen.

Tariot et al. (1998)

In this study, 4 people withdrew from the study, all of whom were taking carbamazepine. One person taking 200 mg daily withdrew because of tics and sedation, which resolved in 48 hours. The other people had no or mild adverse effects but were severely agitated and continued treatment with open-label carbamazepine after withdrawing from the study.

Two people withdrew during the washout period in the extension study by [Tariot et al. \(1999\)](#). One had not responded to carbamazepine during the blind phase and another had a urinary tract infection with associated agitation and was treated with multiple psychotropic drugs. At the end of the washout period, another 2 people withdrew at the request of their doctor, both of whom had severe agitation and were treated with other psychotropic drugs. During carbamazepine treatment there were 2 deaths and 4 adverse events resulting in dropouts. However, neither of the deaths and only 1 serious adverse event (ataxia) was considered related to carbamazepine.

[Tariot et al. \(1998\)](#) found that adverse effects were statistically significantly more common in the carbamazepine group (16/27, 59%) than in the placebo group (7/24, 29%; $p=0.03$), although these were considered clinically significant in only 2 people (1 with tics and 1 with ataxia). Also, no individual adverse effects appeared to occur significantly more often in the carbamazepine group than in the placebo group (p values not reported). Apart from the dropouts, 5 people needed to reduce their dose because of adverse effects. No clinically significant changes were seen in any laboratory measures.

A variety of adverse events reported to be mild or moderate were seen between week 6 and week 21 in the extension study by [Tariot et al. \(1999\)](#). Fatigue or drowsiness, postural instability and falls occurred most commonly ($n=7$, $n=10$ and $n=17$) although causality is difficult to determine because the extension study was uncontrolled. No obvious toxicity was seen in routine measures of cognition or function, or in laboratory tests.

Summary of product characteristics

According to the [summary of product characteristics for Tegretol](#), central nervous system adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia), gastrointestinal disturbances (nausea, vomiting), fluid retention and allergic skin reactions occur commonly (in between 1 in 10 and 1 in 100 people) or very commonly (in 1 in 10 or more people) with carbamazepine. This is particularly true when treatment is initiated, if the initial dosage is too high, and when treating older people. Other common or very common side effects include hyponatraemia, leukopenia, thrombocytopenia and eosinophilia.

The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a result of relative overdosage or significant fluctuation in plasma levels. The [summary of product characteristics](#) states that it may be advisable to monitor plasma levels and divide the daily dosage into smaller fractional doses.

Evidence strengths and limitations

The 4 randomised controlled trials (RCTs) included in this evidence summary have many limitations and may be subject to bias. For example, methods of randomisation and blinding are not reported by Chambers et al. (1982), Cooney et al. (1996) or Olin et al. (2001), and allocation concealment is not reported in any of the studies. Only Tariot et al. (1998) report that analysis was by intention to treat. Different rating scales were used across the studies and may vary in their validity. Also, they generally considered groups of symptoms rather than individual symptoms. It is unclear whether many of the outcomes found to be statistically significant using the scales were clinically important because no minimum clinically important differences were specified. Tariot et al. (1998) note that, although assessors were blinded and experienced, use of a single research team is a limitation of the study. The other 3 studies were smaller single centre studies and are likely to be subject to similar limitations.

In Tariot et al. (1998), there were some baseline differences between the groups. For example, overall, people in the carbamazepine group were older, had a lower MMSE score (indicating more severe illness), had resided in a nursing home longer, and used as-needed chloral hydrate more often. Olin et al. (2001) state that there were no differences between the treatment groups at baseline. The study by Chambers et al. (1982) is poorly reported and gives few details of the study population. Cooney et al. (1996) included only 6 people and it is unclear how the groups compared.

The average age of people included in the 4 studies was 79 years and the majority (80%) were female, limiting applicability to men and younger people. Cooney et al. (1996) and Olin et al. (2001) included people with severe Alzheimer's disease, and Tariot et al. (1998) included people with severe Alzheimer's disease, vascular dementia or mixed dementia. It is unclear whether the results apply to people with less severe disease, or whether carbamazepine may work better for a specific type of dementia.

Although people in poor health or with acute illness were excluded in Olin et al. (2001) and Tariot et al. (1998), it is likely that people in all of the studies had multiple medical problems and would have been on other treatments. Therefore, they appear to be representative of a population with dementia. Many participants had previously used psychotropic drugs and the study populations may have been treatment-resistant.

All the studies were placebo-controlled and it is not known how carbamazepine compares to other drugs that have been used to manage aggression, agitation and behavioural disturbances in people with dementia; for example, sodium valproate and valproate semisodium. Also, the studies were

small (n=6, n=19, n=21 and n=51) and may have had insufficient power to detect differences between the treatment groups.

Due to the potential for drug interactions and adverse effects, the dosage of carbamazepine should be selected with caution in older people. The dosage used in the 3 larger studies was 300–400 mg daily and mean serum carbamazepine levels were at the lower end of the therapeutic range for epilepsy in all 4 studies (see summary of product characteristics for Tegretol). Carbamazepine was generally well-tolerated at this dose: only Chambers et al. (1982) found that it was poorly tolerated. It is possible that efficacy may be improved at a higher dose, but likely that this would be at the expense of more adverse effects.

In the RCTs, length of treatment ranged from 4 weeks to 8 weeks and no information is available on the long-term efficacy or safety of carbamazepine for managing aggression, agitation and behavioural disturbances in this frail, older population with dementia. The extension study provides some information for up to 21 weeks but, because of the 3-week washout period, the maximum continuous treatment period was 12 weeks, and the study was not controlled. Therefore, no firm conclusions can be drawn.

Context and estimated impact for the NHS

Cost effectiveness

No cost-effectiveness studies were identified that compared the use of off-label doses of carbamazepine with other treatments or placebo for the management of aggression, agitation and behavioural disturbances in dementia.

Costs of 1 months' treatment with carbamazepine in adults based on a dose of 400 mg daily are shown in table 1.

Table 1 Costs of carbamazepine treatment

	Cost (excluding VAT: <u>Drug Tariff</u> , January 2015)	Cost (excluding VAT) of 1 months' treatment at 400 mg daily ^a
100 mg tablets	£6.79 for 28	£27.16
200 mg tablets	£5.59 for 28	£11.18
400 mg tablets	£5.02 for 56	Not applicable

100 mg chewable tablets	£3.16 for 56	£6.32
200 mg chewable tablets	£5.88 for 56	£5.88
200 mg modified release tablets	£5.20 for 56	£5.20
400 mg modified release tablets	£10.24 for 56	Not applicable
100 mg/5 ml suspension	£6.12 for 300 ml	£11.42
<p>^a Carbamazepine should be given in 2 or 3 divided doses, particularly in older people (see the relevant summaries of product characteristics)</p>		

Current drug usage

No information on the use of carbamazepine for the management of aggression, agitation and behavioural disturbances in dementia in UK clinical practice was identified.

The [NHS prescription cost analysis for England 2013](#) reports that 2.4 million community prescriptions for carbamazepine were dispensed in 2012, costing £23.6 million (net ingredient cost). The indications for these prescriptions are not provided but it is likely that most will have been for licensed indications. In addition, these data do not include hospital prescriptions.

Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with behavioural disturbances associated with dementia or their carers' who are thinking about trying carbamazepine.

Relevance to NICE guidance programmes

The use of carbamazepine for the management of aggression, agitation and behavioural disturbances is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

In 2006, NICE published a guideline on [dementia: supporting people with dementia and their carers in health and social care](#) (NICE guideline CG42), which has been incorporated into a [NICE pathway](#).

NICE guidance is also available on [donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease](#) (NICE technology appraisal 217).

NICE guidance referring to the licensed use of carbamazepine includes:

- [The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care](#) (NICE guideline CG137)
- [Neuropathic pain – pharmacological management](#) (NICE guideline CG173).

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Clive Ballard has no specific conflicts of interest related to carbamazepine. He has received research grants and honoraria from Lundbeck Limited related to the use of memantine for the treatment of agitation in people with dementia and from Acadia Pharmaceuticals for the treatment of psychosis in people with Parkinson's disease and people with Alzheimer's disease. He has also received honoraria from Bristol-Myers Squibb, Otsuka, Eli Lilly and Orion pharmaceutical companies for an advisory role related to the management of neuropsychiatric symptoms in people with dementia.

Sube Banerjee has received consultancy fees, speakers' fees, research funding or educational support to attend conferences from pharmaceutical companies involved in the manufacture of antidepressants, antipsychotics and antidementia drugs.

Nigel Barnes declared no relevant interests.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

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