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Sodium channel blockers for neuroprotection in multiple sclerosis (Review)

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[Intervention Review]

Sodium channel blockers for neuroprotection in multiple sclerosis

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ABSTRACT

Background

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease of the central nervous system (CNS), which can occur in many parts of the CNS and result in a wide range of symptoms including sensory impairment, fatigue, walking or balance problems, visual impairment, vertigo and cognitive disabilities. At present, the most commonly used MS treatments are immunomodulating agents, but they have little effect on the disability. Experimental studies show that sodium (Na^+) accumulation leads to intracellular calcium (Ca^{2+}) release, and the increased calcium levels can activate nitric oxide synthase and harmful proteases and lipases. These factors contribute to axonal injury in people with MS. If partial blockade of voltage-gated sodium channels could result in neuroprotection, this would be of benefit for preventing disability progression in these people. Neuroprotection is emerging as a potentially important strategy for preventing disability progression in people with MS.

Objectives

To assess the efficacy and safety of sodium channel blockers for neuroprotection in people with MS to prevent the occurrence of disability and alleviate the burden of the disease.

Search methods

We searched the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Specialised Register (27 August 2015) which, among other sources, contains references from the Cochrane Central Register of Controlled Trials (CENTRAL) (*Cochrane Library* 2015, Issue (8), MEDLINE (1966 to August 2015), EMBASE (1974 to August 2015), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981 to August 2015), Latin American and Caribbean Health Science Information Database (LILACS) (1982 to August 2015), ClinicalTrials.gov (http://clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Portal (ICTRP) search portal (http://apps.who.int/trialsearch). In addition, we searched four Chinese databases, ongoing trials registers and relevant reference lists.

Selection criteria

Randomised controlled trials (RCTs) that examined sodium channel blockers used alone or as an add-on to any approved treatments for MS.

Data collection and analysis

Two review authors independently selected trials, assessed trial quality and extracted the data.

Main results

Only one study evaluating lamotrigine in secondary progressive MS was eligible. One hundred and twenty people were included, 61 randomly assigned to lamotrigine treatment and 59 to placebo treatment. The average age of participants in the two groups was 51.9 years and 50.1 years, respectively. The proportion of male participants was 27.5%. The period of follow-up was 2 years. No data were found on disability progression and people who experienced relapses. No significant differences were found for serious adverse events between the two groups. Treatment with lamotrigine was associated with more rashes (20% vs 5%, P value 0.03) and transient, dose-related deterioration of mobility (66% vs 34%, P value 0.001) than placebo. Furthermore, no significant difference between the two groups was found in the magnetic resonance imaging (MRI) measurements of cerebral atrophy, Expanded Disability Status Score changes, Multiple Sclerosis Functional Composite score changes. This study was judged to be at high risk of bias. This review will be updated when the three ongoing studies we identified are completed.

Authors' conclusions

The quality of evidence was judged to be very low due to the low number of available studies and included participants. There is a lack of evidence to address the review question on the efficacy of sodium channel blockers for people with MS. Assessment of the three ongoing trials might change this conclusion. Further high-quality large scale studies are needed.

PLAIN LANGUAGE SUMMARY

The use of the sodium channel blockers in people with multiple sclerosis (MS)

Background

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease of the central nervous system. It can result in a wide range of symptoms including sensory impairment, fatigue, walking or balance problems, visual impairment, vertigo and cognitive disabilities. At present, the most commonly used MS treatments are immunomodulating agents, such as beta interferon, glatiramer acetate, natalizumab, fingolimod, teriflunomide and dimethyl fumarate. Although these agents have all been shown to reduce relapse frequency, they have little effect on the disability that characterises the progressive forms of the disease. Animal studies show the sodium (Na^+) accumulation leads to intracellular calcium (Ca^{2+}) release, and the increased calcium levels can activate the release of harmful elements. These elements contribute to axonal injury exacerbating the neurological disability. If partial blockade of voltage-gated sodium channels could result in neuroprotection in patients with MS, this would be of benefit in preventing the progression of disability in these patients. Neuroprotection is emerging as a potentially important strategy for preventing disability progression in MS.

Study characteristics

We searched for randomised controlled trials (RCTs), in which participants were randomly assigned to a treatment group or a control group. In most settings these studies provide the highest quality evidence. We were interested in studies that compared a sodium channel blocker with placebo, or used it as an add-on to any approved treatments for MS.

Key results

We found only one study including a total of 120 participants. No data were found on disability progression and people who experienced relapses. No significant difference between two groups was found in measurements of cerebral atrophy, expanded disability score changes, or MS functional composite score changes. Treatment with lamotrigine was associated with more rashes (20% versus 5%) and transient, dose-related deterioration of mobility. There is a lack of evidence to address the review question on the efficacy of sodium channel blockers for people with MS. This review will be updated when the three ongoing studies we identified are completed.

Quality of evidence

The quality of evidence was judged as very low due to the low number of available studies and included population. There is a lack of evidence to address the review question on the efficacy of sodium channel blockers for people with MS. Assessment of the three ongoing trials might change this conclusion. Further high-quality large-scale studies are needed.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease of the central nervous system (CNS), which mainly affects individuals between 20 and 50 years of age (Miller 2012). The lesions of MS can occur in many parts of the CNS and result in a wide range of symptoms including sensory impairment, fatigue, walking or balance problems, visual impairment, vertigo and cognitive disabilities (National MS Society 2012). In 1996, the clinical course of MS was described as having four different patterns (Lublin 1996):

- relapsing-remitting MS (RRMS), characterised by unpredictable exacerbations of existing symptoms or appearance of new symptoms;
- secondary progressive MS (SPMS), a progressive form after an initial relapsing-remitting course;
- primary progressive MS (PPMS), which is progressive from the onset without relapses; and
- progressive-relapsing MS (PRMS), which is progressive from the onset but is then punctuated by relapses.

Based on previous studies, a relapsing-remitting course occurs in approximately 85% of people, while 10% to 15% present with a primary progressive or progressive-relapsing form (Miller 2012).

Recently, the 2013 revision of the clinical course of MS was published, reflecting increased understanding of MS and its pathology (Lublin 2014; Lublin 2014a). In this revision, the core MS phenotypes described in 1996 were retained with some modifications. Primary progressive MS is considered as a part of the spectrum of progressive disease. Progressive-relapsing MS has been eliminated. The revised clinical course of MS comprises: relapsing-remitting MS and progressive disease, including primary progressive MS and secondary progressive MS. These classifications should be further classed as either active (defined as the occurrence of clinical relapse or the presence of new T2 or gadolinium-enhancing lesions) or non-active (Lublin 2014; Lublin 2014a). The new revisions would be useful to clinical trial design and to guide clinical decision-making.

At present, the worldwide incidence rate of MS is 3.6 cases per 100,000 person-years in women and 2.0 cases in men (Alonso 2008), while the prevalence is between 20 to 144 people per 100,000 (Simpson 2011). It is estimated that the disease affects about 400,000 people in the United States, with 200 more people diagnosed every week and more than 2.1 million people worldwide affected (National MS Society 2012). Recent studies show an almost universal increase in the prevalence of MS (Al-Hashel 2008; Etemadifar 2011; Marrie 2010). Due to longer survival and its increasing incidence over time, the prevalence of MS is expected to increase in the future.

MS takes a significant physical, psychological and economic toll on patients' families and caregivers, and this burden rises as the disease progresses. A cross-sectional study found that 20% of caregivers spent more than 3.5 hours per day aiding the person with MS. Caregiving time was influenced by the cognitive and activities of daily living (ADL) status of the person with MS and the number of caregiving activities performed (Finlayson 2008). Another survey carried out in the United States indicated that the total annual per-patient cost of MS was USD 47,215 with 53% attributed to direct medical and non-medical costs, 37% to production losses and 10% to informal care (Kobelt 2006).

At present, the most commonly used MS treatments are immunomodulating agents, such as beta interferon, glatiramer acetate, natalizumab, fingolimod, teriflunomide and dimethyl fumarate. Although these agents have all been shown to reduce relapse frequency, they have little effect on the disability that characterises the progressive forms of the disease (Goodin 2002; Miller 2012). Stopping or reversing disease progression remains an important unmet need in people with MS. Accumulating studies indicate that the degree of disability is predominantly related to the extent of axonal injury (Bjartmar 2001; Hyland 2011; Kapoor 2006). Immunomodulating agents only have a limited neuroprotective effect, probably because immune attack is only one of several potential mechanisms of axonal injury. So far there are no clearly effective agents which prevent the accumulation of deficits that lead to the progression from an inflammatory phase to a neurodegenerative phase (Tselis 2010). Hence, in addition to immunomodulating agents, novel therapeutic strategies are required to reduce axonal degeneration to prevent disability progression in MS.

Description of the intervention

Research on the potential neuroprotective effect of sodium channel blockers has increased since the important role of increased sodium (Na^+) permeability in axonal degeneration was recognised (Stys 1992). This Na^+ accumulation leads to intracellular calcium (Ca^{2+}) release, and the increased calcium levels can activate nitric oxide synthase and harmful proteases and lipases (Herzog 2003; Kapoor 2008; Nikolaeva 2005; Waxman 2008). These factors contribute to axonal injury. The deleterious effects of nitric oxide on mitochondrial function result in a reduction in adenosine triphosphate (ATP) levels and a rundown of sodium-potassium adenosine triphosphatase (Na^+K^+ -ATPase), thereby compromising the axon's ability to maintain normal transmembrane sodium. This process provides a positive feedback loop that imports still more intracellular calcium, thereby further amplifying the damage. Thus, decreasing this Na^+ current into the axon would be expected to be protective. More recently, administration of sodium channel blockers (phenytoin, flecainide or lamotrigine) has been shown to decrease axon degeneration and improve neurological status in the experimental autoimmune encephalomyelitis rodent model of MS (Kapoor 2008; Waxman 2008). An important implication of these findings is that partial blockade of voltage-sensitive axonal sodium channels could result in neuroprotection in people with MS (Kapoor 2008).

How the intervention might work

In clinical practice, sodium channel blockers, such as carbamazepine, topiramate, lamotrigine and riluzole, are widely used for treating epileptic seizures, and it is becoming increasingly evident that they might also be effective in several neurological disorders, including migraine, neurodegeneration and neuropathic pain (Ettinger 2007; Mantegazza 2010; Rogawski 2004). In MS, carbamazepine, a type of sodium channel blocker, is used to treat tonic flexion spasms, Lhermitte's sign and neuropathic pain (Thompson 2010). Phenytoin, lidocaine and its orally-absorbed derivative mexiletine have also been used for these applications in people with MS with some degree of success (Waxman 2008).

In a clinical trial which aimed to assess whether the sodium channel blocker lamotrigine is also neuroprotective in people with SPMS, 120 people with SPMS were treated with lamotrigine (target dose 400 mg/day) or placebo for two years. The primary outcome was rate of reduction in partial (central) cerebral volume over two years. Unfortunately, treatment with lamotrigine neither altered cerebral volume loss nor had a beneficial effect on other secondary outcomes, except that the rate of deterioration of the timed 25-foot walk was markedly lower in the lamotrigine group (Kapoor 2010).

From the perspective of clinical practice, if partial blockade of voltage-gated sodium channels could result in neuroprotection in people with MS, this would be of benefit for preventing the progression of disability in these people.

Why it is important to do this review

Neuroprotection is emerging as a potentially important strategy for preventing disability progression in MS and consequently the burden of the disease. The field is relatively new, and gathering experience from current clinical trials could provide more information for clinical practice and further studies. No systematic review currently exists in the peer-reviewed literature that focuses on the effects of sodium channel blockers on MS disease progression.

OBJECTIVES

To assess the efficacy and safety of sodium channel blockers for neuroprotection in people with multiple sclerosis to prevent the occurrence of disability and alleviate the burden of the disease.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials (RCTs), irrespective of blinding, publication status or language. We planned to use only data from the first period of any included cross-over trials.

Types of participants

We included participants of any age and gender, with a diagnosis of definite MS according to the Poser (Poser 1983), McDonald (McDonald 2001) or revisions to the McDonald diagnostic criteria (Polman 2005; Polman 2011). Participants with any pattern of disease course (relapsing-remitting, secondary progressive, primary progressive and progressive-relapsing) were included.

Types of interventions

We included all RCTs that examined sodium channel blockers used alone or as an add-on to any approved treatments for MS.

Comparisons included:

- sodium channel blockers versus placebo only;
- sodium channel blockers plus approved treatments (such as beta interferon) versus placebo plus approved treatments.

Types of outcome measures

We assessed the following outcomes at the end of the treatment period and scheduled follow-up period (at six months, one, two and three years, and at the end of the follow-up time).

Primary outcomes

- The number of participants who experienced disability progression. Disability progression was defined as a one-point increase in the Expanded Disability Status Score (EDSS) score (or a half-point increase for participants with a baseline score ≥ 5.5) that was confirmed three or six months later, in the absence of relapse (Freedman 2011; Gold 2012; Jacobs 1996; Johnson 1995; PRISMS 1998; Polman 2006). In addition, other definitions of disability progression reported in the trials (such as the Multiple Sclerosis Functional Composite) were accepted (Cohen 2012).
- The number of participants experiencing at least one relapse. Definitions of relapse given in the original studies were accepted.
- Adverse events (AEs) as reported in the trial:
  - the number of participants experiencing at least one AE, irrespective of whether it was mild or severe (no period restriction);
  - the number of participants experiencing treatment discontinuation caused by an AE.

Secondary outcomes

- Magnetic resonance imaging (MRI) measurements of cerebral atrophy. Atrophy can be measured in several ways, such as whole brain volume, grey matter volume, white matter volume, mean cross-sectional cervical spinal cord area, and T1 and T2 lesion volumes. Any measures of cerebral atrophy using MRI were considered. We planned to calculate the change from baseline in these measures (such as whole brain volume, grey matter volume, white matter volume, T1 and T2 lesion volumes).
- Mean change in Expanded Disability Status Score (EDSS).
- Mean change in Multiple Sclerosis Functional Composite (MSFC).
- MRI parameters of disease activity: changes in the number of new gadolinium (Gd)-enhancing lesions or number of high signal intensity lesions on T2 weighted MRI or number of low signal intensity lesions on T1 weighted MRI.
- Annualised relapse rate (total number of relapses observed within a treatment group out of the total person-time of follow-up for that treatment group).
- Global measures of activities of daily living (ADL): the mean change in the Rankin scale or Barthel Index score (Cohen 2012).
- Quality of life assessed using any validated disease-specific or generic instruments, such as Short Form 36 (SF-36) scores (Ware 1992) or MSQoL-54 questionnaire scores (Vickrey 1995).

Search methods for identification of studies

We applied no language restrictions to the search.

Electronic searches

The Trials Search Co-ordinator searched the Specialised Register of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group (last searched 27 August 2015), which contains the following:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8, 2015).
- MEDLINE (PubMed) (1966 to 27 August 2015).
- EMBASE (Embase.com) (1974 to 27 August 2015).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO host) (1981 to 27 August 2015).
- Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to 27 August 2015).
- ClinicalTrials.gov (http://clinicaltrials.gov).
- World Health Organization (WHO) International Clinical Trials Registry Portal (ICTRP) search portal (http://apps.who.int/trialsearch).

Information on the Trial Register of the Review Group and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group module.

The keywords used to search for studies for this review are listed in Appendix 1.

In addition, we searched the following Chinese databases using the keyword 'sodium channel blockers'.

- The China Biological Medicine Database (CBM) (1978 to October 2014) (http://sinomed.imicams.ac.cn/zh/)
- The Chinese National Knowledge Infrastructure (CNKI) (1979 to October 2014) (http://epub.cnki.net/grid2008/index/ZKCALD.htm)
- Chinese Science and Technique Journals Database (VIP) (1989 to October 2014) (http://vip.fjinfo.gov.cn/index.asp)
- Wanfang Data (1984 to October 2014) (http://www.wanfangdata.com/)

Searching other resources

We performed an expanded search by:

1. Screening reference lists of published reviews and retrieved articles;
2. Contacting authors of published studies if data reported were incomplete;
3. Screening abstract books of: Conference Proceedings Citation Index - Science (CPCI-S) (wokinfo.com/products_tools/multidisciplinary/webofscience/cpci/) and China Medical Academic Conferences (CMAC) 1995 to present) in Chinese Medical Current Contents (CMCC) (www.lib.polyu.edu.hk/databases/chinese-medical-current-contents-cmcc-).

Data collection and analysis

Selection of studies

Two review authors (Yang, Zhang) independently assessed the abstracts of studies resulting from the electronic searches and excluded those that were obviously irrelevant. We obtained the full text of all potentially relevant studies for further assessment to determine if the trial met the review's inclusion/exclusion criteria. We listed publications that did not meet the inclusion criteria in the 'Characteristics of excluded studies' table with the reason for exclusion. Discrepancies were resolved by discussion among the review authors.

Data extraction and management

Two review authors (Yang, Zeng) independently extracted the data from the included studies using a data extraction form. We summarised all studies that met the inclusion criteria in the 'Characteristics of included studies' table provided in the RevMan software (Review Manager 2014) and included details on study design, participants, interventions and outcomes measures. If necessary, we planned to contact principal investigators of included studies to seek data and clarification. Discrepancies were resolved by discussion among the review authors.

Assessment of risk of bias in included studies

Two review authors (Yang, Zeng) independently assessed the methodological quality of the included studies using the Cochrane 'Risk of bias' tool (Higgins 2011). We rated the following domains separately for each of the included studies as 'low risk of bias', 'high risk of bias' and 'unclear' if the risk of bias was uncertain or unknown.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other sources of bias

We planned to report these assessments in the 'Risk of bias' table for each individual study. On the basis of these criteria, we divided studies into the following three categories:

A - all 'Risk of bias' criteria rated as 'low risk': low risk of bias.
B - one or more of the 'Risk of bias' criteria rated as 'unclear': unclear risk of bias.
C - one or more of the 'Risk of bias' criteria rated as 'high risk': high risk of bias.

We planned to resolve any disagreements among authors arising at any stage through discussion or with a third author (Wen).

Measures of treatment effect

We planned to express results for dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI), and express results for continuous outcomes as mean difference (MD) (if the same scale for each trial was available) or standardised mean difference (SMD) (if different scales were used). For counts of rare events we planned to use rate ratios, which compare the rate of events in the two groups by dividing one by the other, while for counts of common events we planned to use the mean difference to compare the difference in the mean number of events (possibly standardised to a unit time period) experienced by participants in the intervention group compared with participants in the control group.

Unit of analysis issues

In cases of studies with non-standard designs (e.g. cross-over trials, cluster-randomised trials), we planned to manage the data according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For example, if we found relevant cross-over trials, we planned to only analyse the data from the first period and conduct a sensitivity analysis excluding these studies.

Dealing with missing data

If data were missing, we planned to contact the investigators for additional information. If some data remained unavailable, we planned to undertake sensitivity analyses in which we would impute missing data and compare results for both best-case and worst-case scenarios.

Assessment of heterogeneity

We planned to determine statistical heterogeneity according to the I^2 statistic. We planned to consider that a value greater than 50% would indicate substantial heterogeneity. We planned to consider the potential sources of the heterogeneity (clinical heterogeneity and methodological heterogeneity). We planned to perform meta-analysis using the random-effects model regardless of the level of heterogeneity.

Assessment of reporting biases

We planned to assess publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997) as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

Data synthesis

We planned to perform statistical analysis using the Cochrane Review Manager software (Review Manager 2014) to synthesise the available data and perform sensitivity analysis to evaluate the effect of missing data. We planned to give a descriptive analysis of the results if the outcome data from different studies could not be pooled.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses if a sufficient number of studies was included:

- Type of sodium channel blocker (e.g. lamotrigine, topiramate)
- Pattern of disease course (e.g. relapsing-remitting, secondary progressive)
- Co-interventions (e.g. beta interferon, glatiramer acetate)
- Different definition of outcome measurements (e.g. disability progression measured by EDSS or MSFC)

Sensitivity analysis

We planned to conduct a sensitivity analysis to assess the robustness of our results by repeating the analysis with the following adjustments, if it was necessary in relation to trial quality.

- Excluding studies with inadequate concealment of allocation
- Excluding studies in which outcome evaluation was not blinded
- Excluding studies in which loss to follow-up was greater than 10%
- Excluding studies with missing data
- Excluding cross-over studies

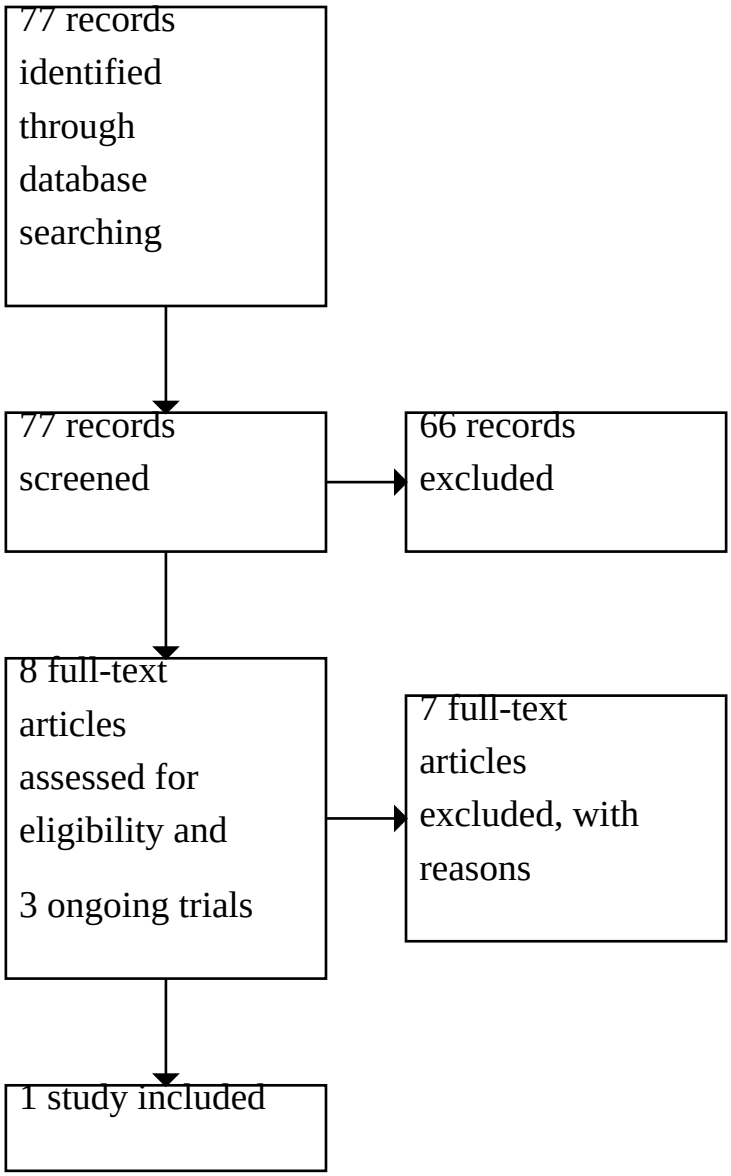
RESULTS

Description of studies

Results of the search

Initial searches returned a total of 77 references. After reading titles and abstracts, we obtained 11 full-text studies for further assessment. Seven studies were excluded because they did not meet our inclusion criteria. (Characteristics of excluded studies). Only one study was eligible for inclusion (Kapoor 2010) (Characteristics of included studies). Three ongoing RCTs were identified, but they were not yet recruiting (NCT02104661; NCT01910259; NCT00917839) (Characteristics of ongoing studies) (Figure 1).

Figure 1. Study flow diagram.



Included studies

Characteristics of participants

One study (Kapoor 2010) met the review's inclusion criteria. The study included 120 participants randomly assigned to treatment and control (61 to lamotrigine and 59 to placebo).The average age of participants in the two groups was 51.9 years and 50.1 years, respectively. The proportion of male participants was 27.5%. The period of follow-up was 2 years. There were no significant differences between the two groups in terms of baseline characteristics, such as age, sex, EDSS and disease duration.

Interventions

Participants received lamotrigine or placebo up to 400 mg daily, depending on the maximum tolerated dose achieved during an initial 8-week dose-escalation period.

Outcome measures

The primary outcome was the rate of change of partial (central) cerebral volume over 24 months. Secondary outcomes were:

1. imaging outcome: whole brain volume, grey matter volume, white matter volume, mean cross sectional cervical spinal cord area, and T1 and T2 lesion volumes;
2. clinical outcome measurements: EDSS; the multiple sclerosis functional composite and its three components (25-foot timed walk, 9-hole peg test, and paced auditory serial addition test); and the multiple sclerosis impact scale; and
3. adverse events.

Excluded studies

Seven studies were excluded. Four were reviews (Kapoor 2008; Mahdavi 2011; Mantegazza 2010; Waxman 2008). Two studies were case series without a control group (Sakurai 1999; Zhang 1999) and one was a journal article (Smith 2006).

In addition, three ongoing RCTs were identified (NCT02104661; NCT01910259; NCT00917839) (Characteristics of ongoing studies). There are no data available to date.

Risk of bias in included studies

Allocation

Participants were randomly assigned (1:1) to lamotrigine or placebo via a website by minimisation. Participants were given a randomisation number, which was matched to a confidential treatment number by the study pharmacist. The risk of selection bias was low.

Blinding

In this study, treating physicians, evaluating physicians, and participants were masked to treatment allocation and outcome measurements. The risks of performance bias and detection bias were low.

Incomplete outcome data

Twelve participants (9 in the lamotrigine group and 3 in the placebo group) were lost to imaging follow-up, leaving 108 who had imaging for the primary outcome at 24 months (52 on lamotrigine and 56 on placebo). Sixteen participants (11 on lamotrigine and 5 on placebo) withdrew from treatment but continued to be followed up. The combined rate of loss to follow-up and withdrawal from treatment was 23%. The risk of attrition bias was high.

Selective reporting

No obvious selective reporting was found. The risk of reporting bias was low.

Other potential sources of bias

We were unable to investigate potential publication bias by using a funnel plot as only one trial was included.The risk of other potential bias was low.

Effects of interventions

1.1 The number of participants who experienced disability progression

No data were available.

1.2 The number of participants experiencing at least one relapse

No data were available.

1.3 Adverse events (AEs)

Treatment with lamotrigine was associated with more rashes (20% vs 5%, P value 0.03), and transient, dose-related deterioration of mobility (66% vs 34%, P value 0.001) than placebo. There were no significant differences in terms of serious adverse events between two groups. Serious adverse events included: fall with fractured limb (n = 2), subdural haematoma (n = 1), stroke (n = 1), severe constipation (n = 1), and anaemia (n = 1) in the lamotrigine group; and cholecystitis (n = 1) and urinary tract infection (n = 1) in the placebo group.

2.1 Magnetic resonance imaging (MRI) measurements of cerebral atrophy

The mean change in partial (central) cerebral volume per year was -3.18 mL (SD -1.25) in the lamotrigine group and -2.48 mL (SD -0.97) in the placebo group (mean difference -0.71 mL, 95% CI -2.56 to 1.15; P value 0.40). The mean change in white matter volume per year was -0.87 mL (SD -0.22) in the lamotrigine group and 0.41 mL (SD 0.10) in the placebo group (mean difference -1.28 mL, 95% CI -2.60 to 0.05; P value 0.059).The mean change in grey matter volume per year was -9.70 mL (SD -1.56) in the lamotrigine group and -9.24 mL (SD -1.47) in the placebo group (mean difference -0.46 mL, 95% CI -9.11 to 8.18; P value 0.92). The mean change in cross-sectional cervical cord area per year was -1.60 mm^2 (SD -2.51) in the lamotrigine group and -1.26 mm^2 (SD -1.99) in the placebo group (mean difference -0.34 mm^2, 95% CI -0.85 to 0.17; P value 0.18).

2.2 The mean change in Expanded Disability Status Score (EDSS)

The mean change in EDSS from 0 to 24 months was 0.21 in the lamotrigine group and 0.23 in the placebo group (P value 0.73).

2.3 The mean change in Multiple Sclerosis Functional Composite (MSFC)

The mean change of MSFC (Z score per year) was -0.17 in the lamotrigine group and -0.18 in the placebo group (mean difference -0.01, 95% CI -0.12 to 0.14; P value 0.88).

2.4 MRI parameters of disease activity

No data were available.

2.5 Annualised relapse rate

No data were available.

2.6 Global measures of activities of daily living (ADL)

No data were available.

2.7 Quality of life.

The mean change in multiple sclerosis impact scale per year was -2.7 (SD -0.31) in the lamotrigine group and 0.91 (SD 1.07) in the placebo group (mean difference -1.18, 95% CI -4.59 to 2.23; P value 0.50).

DISCUSSION

Summary of main results

In this review of sodium channel blockers for neuroprotection for people with multiple sclerosis (MS), no data were found on disability progression and people who experienced relapses. One trial with involving a total of 120 participants with secondary progressive MS showed no significant difference for serious adverse events between the two groups. Treatment with lamotrigine was associated with more rashes, and transient, dose-related deterioration of mobility than placebo. Furthermore, no significant difference between the two groups was found in the MRI measurements of cerebral atrophy, expanded disability score changes, or multiple sclerosis functional composite score changes. This review will be updated when the three ongoing studies have been completed.

Overall completeness and applicability of evidence

In short, the evidence evaluating sodium channel blockers for people with MS was scarce. There was only one small trial providing limited evidence on this topic. This study only included people with secondary progressive MS. There is a need for further well-conducted RCTs to assess the efficacy of sodium channel blockers in people with MS. We could find evidence of neither beneficial nor harmful effects of lamotrigine based on the limited data available. If further trials become available for inclusion, we will update the review to include them. As there was only one trial, we could not assess heterogeneity and perform the preplanned sensitivity and subgroup analyses.

Quality of the evidence

The quality of reporting in general was good. This study was rated as 'low risk of bias' in participant allocation, blinding of outcome measurements, and selective reporting. However, it was judged to be at high risk of bias overall due to the rating of 'high risk' for incomplete outcome data. Three ongoing studies were found and will be assessed when completed. The quality of evidence was judged to be very low due to the low number of available studies and participants.

Potential biases in the review process

There was only one trial, so we could not assess publication bias. However, we cannot deny the possibility that there were additional trials which were unpublished or published in sources not covered by our search.

Agreements and disagreements with other studies or reviews

We were not aware of any published systematic reviews or other studies.

AUTHORS' CONCLUSIONS

Implications for practice

There is a lack of evidence to address the review question on the efficacy of sodium channel blockers for people with multiple sclerosis (MS). The quality of evidence was judged to be very low due to the low number of available studies and included participants. Assessment of the three ongoing trials, when completed, might change this conclusion.

Implications for research

Further high-quality large-scale studies are needed to assess the efficacy of sodium channel blockers for people with MS and should focus on the choice of the trial drugs, the selection of the participants, and especially the choice of the primary outcome measure of this type of drug, such as widely-used outcome measures of disability, including Expanded Disability Status Scale (EDSS), progression, the number of people experiencing at least one relapse, and adverse events. Whether a number of different imaging outcome measures could be used to evaluate the efficacy of sodium channel blockers should be further investigated.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Kapoor 2010

Study characteristics	
Methods	Randomized placebo controlled trial Treating physicians, evaluating physicians, and participants were blinded Ex during trial: 11 on lamotrigine and 5 on placebo Losses to FU: 9 in the lamotrigine group and 3 in the placebo group
Participants	Country: UK 120 participants Age: mean 51.9±7.1 years in Rx, mean 50.1±6.7 years in control Sex: 27.5% men People with secondary progressive multiple sclerosis aged 18-55 years were eligible if they had an Expanded Disability Status Scale (EDSS) score of 4 to 6.5 and if their disability had increased in the preceding 2 years because of steady disease progression rather than relapse. Comparability: similar
Interventions	Rx: lamotrigine (target dose 400 mg/day). Control: placebo Duration: 2 years

Kapoor 2010 *(Continued)*

Outcomes	Primary outcome: the rate of change of partial (central) cerebral volume over 24 months. Secondary imaging outcome measurements were whole brain volume, grey matter volume, white matter volume, mean cross sectional cervical spinal cord area, and T1 and T2 lesion volumes. Secondary clinical outcome measurements were the EDSS; the Multiple Sclerosis Functional Composite and its three components (25-foot timed walk, 9-hole peg test, and paced auditory serial addition test); and the Multiple Sclerosis Impact Scale. Adverse events.
Notes	Participants were excluded if they were eligible for disease-modifying treatments under the 2001 recommendations of the Association of British Neurologists, if drugs that block sodium or calcium channels had been used in the past 2 weeks, if corticosteroids had been used in the past 2 months, or if immunomodulatory drugs had been used in the previous 6 months (1 year for mitoxantrone). Exclusion criteria were pregnancy, major systemic disease, or disabling temperature-dependent multiple sclerosis symptoms.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1) to lamotrigine or placebo via a website by minimisation.
Allocation concealment (selection bias)	Low risk	Participants were given a randomisation number, which was matched to a confidential treatment number by the study pharmacist. The study pharmacist assigned participants either to lamotrigine or to placebo (of identical appearance).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treating physicians and participants were masked to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluating physicians were masked.
Incomplete outcome data (attrition bias) All outcomes	High risk	Twelve participants were lost to imaging follow-up. 14.75% (9/61) in the lamotrigine group and 5.08% (3/59) in the placebo group.
Selective reporting (reporting bias)	Low risk	No obvious selective reporting was found.
Other bias	Low risk	None known.

C: concealment of allocation
Ex: exclusion
FU: follow up
Rx: treatment

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kapoor 2008	This is a review.

Study	Reason for exclusion
Mahdavi 2011	This is a review.
Mantegazza 2010	This is a review.
Sakurai 1999	This is a case series study without a control group.
Smith 2006	This is a comment.
Waxman 2008	This is a review.
Zhang 1999	This is a case series study without a control group.

Characteristics of ongoing studies *[ordered by study ID]*

NCT00917839

Study name	The Neuroprotective Effect of lamotrigine and Interferon Beta 1a in Patients With Relapsing-Remitting Multiple Sclerosis
Methods	RCT
Participants	Inclusion Criteria: definitive multiple sclerosis according to Mc Donald criteria clinical isolated syndrome according to Mc Donald criteria EDSS Score 0 to 5 Pre-treatment with interferon beta 1a (Avonex) since at least 2 months before inclusion Exclusion Criteria: relapse within 30 days prior to randomisation steroid pulse therapy within 30 days prior to randomisation pregnancy or poor contraception contraindication for lamotrigine depressive symptoms drugs with possible interaction with lamotrigine according to instruction leaflet other medical relevant conditions but multiple sclerosis clinically relevant laboratory results contraindication for MRI missing informed consent
Interventions	Experimental: lamotrigine 7 weeks initial phase with increasing dose beginning with 25 mg oral 12 months treatment phase with fixed dose of 100 mg oral Placebo Comparator: Placebo (300mg Mannitol with 2% Aerosil)

NCT00917839 *(Continued)*

Outcomes	Primary Outcome Measures: N-Acetyl-Aspartate / creatine - quotient in normal appearing white matter by MR-spectroscopy Safety of lamotrigine in combination with interferon beta 1a (30 mcg) once weekly intramuscular Secondary Outcome Measures: relapse rate EDSS scores Fatigue Severity Score N-Acetyl-Aspartate / creatine - quotient in normal appearing white matter by MR-spectroscopy
Starting date	Unknown
Contact information	Norman Putzki, MD, +4171494 ext 1663, norman.putzki@kssg.ch
Notes	ClinicalTrials.gov identifier: NCT00917839

NCT01910259

Study name	MS-SMART: Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial
Methods	RCT
Participants	Inclusion Criteria: Confirmed diagnosis of SPMS at randomisation Steady progression rather than relapse must be the major cause of increasing disability in the preceding 2 years. Progression can be evident from either an increase of at least one point in EDSS or clinical documentation of increasing disability in patients notes EDSS 4.0 to 6.5 Aged 25 to 65 Men or women of childbearing age must be using an appropriate method of contraception to avoid any unlikely teratogenic effects of the 3 drugs from time of consent, to 6 weeks after treatment inclusive Females have a negative pregnancy test within 7 days prior to being enrolled (baseline visit) unless not of child-bearing potential e.g. have undergone a hysterectomy, bilateral tubal ligation or bilateral oophorectomy or they are postmenopausal Willing and able to comply with the trial protocol and have the ability to understand and complete questionnaires Willing and able to give full written informed consent Able to undertake MRI Exclusion Criteria: Pregnancy or breast-feeding females People unable to tolerate baseline MRI scan or scan not of adequate quality for analysis (e.g. too much movement artefact)

NCT01910259 *(Continued)*

	People fitted with pacemakers or permanent hearing aids
	Significant organ co-morbidity (e.g. malignancy or renal or hepatic failure)
	Routine screening blood values (LFT) >/ 3 x upper limit of normal (ULN) of site reference ranges (AST/ALT, bilirubin, ¥GT)
	Potassium >5.5mmol/l
	Sodium <125mmol/l
	Creatinine >130µmol/l
	Neutrophil count <1.0 x109 /l
	Platelet count <100 x109 /l
	Relapse within 3 months of baseline visit
	People who have been treated with IV or oral steroids within 3 months of baseline visit (these participants can undergo future screening visits once the 3 month window has expired)
	Commencement of fampridine within 6 months of baseline visit
	Use of immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine) or first generation disease modifying treatments (β-interferons, glatiramer) within 6 months of baseline visit
	Use of immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine) or first generation disease modifying treatments (β-interferons, glatiramer) within 6 months of baseline visit
	Use of fingolimod/fumarate/teriflunomide/laquinomod/or other experimental disease modifying treatment (including research in an investigational medicinal product) within 12 months of baseline visit
	Use of mitoxantrone/natalizumab/alemtuzumab/daclizumab if treated within 12 months of baseline visit
	Primary progressive MS
	Relapsing-remitting MS
	Known hypersensitivity to the active substances and their excipients to any of the active drugs for this trial
	Use of: lithium, chlorpropamide, triamterene, spironolactone,
	Use of potassium supplements
Interventions	Experimental: Amiloride; Amiloride 5 mg twice per day (5 mg once per day for first 4 weeks) for 96 weeks
	Experimental: Riluzole; Riluzole 50 mg twice per day (50 mg once per day for first 4 weeks) for 96 weeks
	Experimental: Ibudilast 50 mg twice per day (50 mg once per day for first 4 weeks) for 96 weeks
	Placebo Comparator: Matched placebo 1 capsule twice per day (1 capsule a day for first 4 weeks) for 96 weeks
Outcomes	Primary Outcome Measures:
	MRI-derived Percentage Brain Volume Change
	Secondary Outcome Measures:
	Multi-arm trial strategy assessment

NCT01910259 *(Continued)*

	Count of new and enlarging T2 lesions Pseudo-atrophy Clinical measure of neuroprotection Health economics Others
Starting date	Recruiting
Contact information	Moira Ross +44 (0)131 537 2553 moira.ross@ed.ac.uk
Notes	ClinicalTrials.gov identifier: NCT01910259

NCT02104661

Study name	Protective Role of Oxcarbazepine in Multiple Sclerosis (PROXIMUS)
Methods	RCT
Participants	Inclusion Criteria: A diagnosis of definite multiple sclerosis Treatment with DMDs for at least 6 months EDSS score between 3.5 and 6.0 No history of relapses in the preceding 6 months A history of slow progression of disability, objective or subjective, over a period of at least 6 months Age 18 to 60 years Exclusion Criteria: Pregnant or breastfeeding or unwilling to use adequate contraception. Participants who do not take a DMDs for MS. A clinical relapse or pulsed intravenous or oral steroids in the 6 months preceding the baseline assessment. Participants presenting with medical disorder deemed severe or unstable by the CI such as poorly controlled diabetes or arterial hypertension, severe cardiac insufficiency, unstable ischemic heart disease, abnormal liver function tests (>2.5 times ULN) and abnormal complete blood count (in particular leukopenia, as defined by a lymphocyte count <500, neutrophil count <1.5 or platelet count <100, or thrombocytopenia <1.5 LLN), or any medical condition which, in the opinion of the chief investigator, would pose additional risk to the participant. Infection with hepatitis B or hepatitis C or human immunodeficiency virus. Participants receiving other sodium or calcium channel blockers in the previous 12 weeks Exposure to any other investigational drug within 30 days of enrolment in the study. Judged clinically to have a suicidal risk in the opinion of the investigator based upon a clinical interview and the Columbia Suicide-Severity Rating Scale (CSSRS). Prior history of malignancy unless an exception is granted by the Chief Investigator.

NCT02104661 *(Continued)*	
	History of uncontrolled drug or alcohol abuse within 6 months prior to enrolment into the study. Past untoward reactions to OxCbz or CBZ
Interventions	Experimental: Oxcarbazepine Treatment Treated for 48 weeks with OxCarbazepine 150mg twice a day alongside current DMDs. Placebo Comparator: Oxcarbazepine Placebo Treated for 48 weeks with matched placebo 1 tablet twice a day alongside current DMDs.
Outcomes	Primary Outcome Measures: Relative reduction of CSF neurofilament light chain levels Secondary Outcome Measures: Safety of Oxcarbazepine Relative reduction of CSF neurofilament levels Change in clinical outcome measured by neurological examination Change in clinical outcome measured by cognitive assessment Change in patient reported outcomes measured by questionnaires Others
Starting date	Not yet recruiting
Contact information	Monica Calado Marta m.calado-marta@qmul.ac.uk
Notes	ClinicalTrials.gov identifier: NCT02104661

RCT: randomised controlled trial
DMD: Disease-modifying drugs
MS: Multiple Sclerosis
SPMS: secondary progressive MS
EDSS: Expanded Disability Status Score
MRI: Magnetic Resonance Imaging

APPENDICES

Appendix 1. Keywords in search

sodium channel blockers[MeSH Terms] OR "sodium channel blockers"[All Fields] OR sodium channel blockers[Text Word]

WHAT'S NEW

Date	Event	Description
5 June 2023	Amended	Editorial note added: no update planned, no new version forthcoming

HISTORY

Protocol first published: Issue 3, 2013

Review first published: Issue 10, 2015

CONTRIBUTIONS OF AUTHORS

Drafted the protocol: Chunsong Yang, Lingli Zhang, Zilong Hao, Linan Zeng and Jin Wen.
Developed a search strategy: Chunsong Yang and Linan Zeng.
Searched for trials: Chunsong Yang and Linan Zeng.
Obtained copies of relevant references: Chunsong Yang and Jin Wen.
Selected trials for inclusion and appraised the quality of papers: Chunsong Yang, Lingli Zhang, Zilong Hao and Jin Wen.
Extracted data from papers and data management: Chunsong Yang, Lingli Zhang and Linan Zeng.
Wrote the review and interpreted the results: Chunsong Yang, Lingli Zhang, Zilong Hao, Linan Zeng and Jin Wen.

Chunsong Yang and Zilong Hao contributed equally to this work.
The review will be updated by Chunsong Yang and Lingli Zhang.

DECLARATIONS OF INTEREST

Yang C: none known

Hao Z: none known

Zhang L: none known

Zeng L: none known

Wen J: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the publication of the protocol (Yang 2013), we made the following changes:

- The classification of the clinical course of MS was updated in the Background.
- We now give a description of how to rate the quality of studies in the section 'Assessment of risk of bias in included studies'.
- Because only one study was included, we did not implement the planned methods as described in the protocol related to data synthesis, subgroup analysis and investigation of heterogeneity.

NOTES

Editorial note

No update planned, no new version forthcoming.

INDEX TERMS

Medical Subject Headings (MeSH)

Disease Progression; Immunosuppressive Agents [therapeutic use]; Lamotrigine; Multiple Sclerosis [drug therapy]; Multiple Sclerosis, Chronic Progressive [*drug therapy]; Neuroprotection; Randomized Controlled Trials as Topic; Sodium Channel Blockers [adverse effects] [*therapeutic use]; Triazines [adverse effects] [*therapeutic use]

MeSH check words

Female; Humans; Male; Middle Aged