Use of Anti-epileptic Drugs in Post-stroke Seizures:
A Cross-sectional Survey Among British Stroke Physicians

Introduction
The incidence of seizures after stroke has been estimated at 4-20%. It is also estimated that epilepsy affects 1% of patients aged over 65 and that the majority of these cases (20-40%) are secondary to cerebrovascular disease. The risk factors for developing seizures have been identified as cerebral haemorrhage, cortical location of lesion and the severity of stroke, for example those involving multiple lobes. The incidence of seizures has a bimodal distribution with a peak two weeks post-stroke and a second peak 6-12 months post-stroke. Early or “acute symptomatic” seizures, are seizures occurring in the first two weeks following an acute stroke. Late or “remote symptomatic” seizures, are those occurring after the first two weeks following an acute stroke.

Most of the seizures are either simple partial seizures or complex partial seizures and, less commonly, generalised tonic clonic seizures. One study showed 35% of the patients with early seizures went on to develop epilepsy; a pre-disposition to unprovoked seizures, compared to 90% of those with late seizures. A large prospective hospital-based study by Bladin et al. found that 9.0% of patients with stroke experienced seizures, although epilepsy only occurred in 2.5%.

There are currently no clear guidelines on use of anti-epileptic drugs (AED) in the management of seizures after a stroke. There is no clear consensus on when to start an AED which is the best AED to use and for how long to treat patients with an AED. Current practice is often based on the existing guidelines for adult onset epilepsy, both idiopathic and localisation related, and individual physicians experience and preferences. This study aims to look at consultant stroke physicians’ preferences in the use of AEDs with particular emphasis on the choice of AED, initiation of drug therapy, the duration of treatment, and the withdrawal of treatment in the adult and elderly population.

Methods
A questionnaire comprising four clinical vignettes and a series of clinical questions was designed to capture the required information. Figure 1 contains the four vignettes.

Each of the four vignettes was followed by a similar series of clinical questions. The questions

Figure 1: Clinical vignettes of the questionnaire

1. Younger adult – Acute post-stroke seizure
A 50-yr-old man has suffered a lobar intracerebral haemorrhage. Twenty-four hours after the event, he suffers an otherwise unprovoked complex partial seizure. He has no history of any previous seizures. If the patient is willing and there are no contraindications to start any anti epileptic medication, which medication would you prefer to start?

2. Younger adult – Late onset / remote post-stroke seizure
A 55-yr-old female with previous MCA territory ischaemic stroke suffers an unprovoked complex partial seizure six months after her stroke. She has no history of any previous seizures. If the patient is willing and there are no contraindications to start any anti epileptic medication, which medication would you commence?

3. Elderly – Acute post-stroke seizure
An 82-yr-old female suffers an unprovoked complex partial seizure 24 hours after a MCA territory ischaemic stroke. She has no history of any previous seizures. If the patient is willing and there are no contraindications to start any anti epileptic medication, which medication would you prefer to start?

4. Elderly – Late onset / Remote post-stroke seizure
An 82-yr-old female suffers an otherwise unprovoked complex partial seizure eight months after a MCA territory ischaemic stroke. She has no history of any previous seizures. If the patient is willing and there are no contraindications to start any anti epileptic medication, which medication would you commence?
for the first vignette are shown in Figure 2.

The questionnaire was sent by e-mail to all members of the British Association of Stroke Physicians (BASP), as it was not practical to selectively email the consultants alone. The association has 408 consultant physician members, 203 trainee members and 11 nurse specialists. Two reminder emails were sent over a period of two months to maximise the response rate. The questionnaire was also set up as an online survey and the website link was sent to all members via the BASP membership email service.

The questionnaire also collected basic demographic data, including the year of qualification, parent specialty and epilepsy training details. The responses did not gather any identifiable data allowing responses to be anonymous.

Results
Eighty-two fully completed questionnaires were received. Ten trainee responses were excluded from final analysis. The parent speciality of the 72 consultant physicians who responded was: Geriatrics 77%, Neurology 14%, General Medicine 6% and Rehabilitation Medicine 3%. Figure 3 and Tables 1-4 summarise the results.

We found that 83% of consultant physicians would initiate the same AED in both partial and generalised seizures, and therefore only 17% of physicians would select an AED based upon the presenting seizure type. All respondents would choose to titrate up the first line AED to an optimal dose if it did not initially control seizure activity. If the first line AED failed to control seizures at an optimal dose, 87% physicians said they would add in a second AED, 9% would switch to another AED as a monotherapy and 5% would seek advice from an expert colleague in this situation.

Discussion
The survey has a few limitations. Firstly, the small number of fully completed questionnaires returned limits any generalisation of results. Secondly, the clinical scenarios could be understood differently by individual physicians, particularly when responding to postal or online questionnaires where the information provided is limited. The accuracy of responses is also affected by the artificial situation created by using a theoretical model to capture a real-life scenario. The group of physicians chosen for the survey and the responses is not representative of the wider international community of physicians involved in this area.

In the United Kingdom guidelines produced by the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) on the diagnosis and management of epilepsy are widely used. However, neither of these guidelines provides specific advice on the use of AEDs in patients with post-stroke epilepsy. SIGN guidelines do make a distinction between idiopathic generalised epilepsies and focal (localisation-related) epilepsies of which post-stroke epilepsy is an example. There are also guidelines from the International League Against Epilepsy (ILAE), specifically analysing the evidence for AED use in elderly patients, defined as age over 60 years, but again it does not provide specific recommendations in post-stroke seizures.

NICE guidelines suggest considering AED for a patient after a first unprovoked seizure if the patient has a neurological deficit or abnormality on brain imaging, which could be said to apply to stroke patients. The decision to start AED therapy also depends on the perceived risk of recurrent seizures, whose associated risks outweigh the potential side effects of the medications. The risk of recurrence of post-stroke seizures is 50-90% in those with late-onset seizures. Both NICE and SIGN guidelines recommend carbamazepine, sodium valproate, lamotrigine or oxcarbazepine as first line treatments for partial seizures and secondary generalised seizures. The International League Against Epilepsy (ILAE) suggest that
Table 1. Early onset seizures – indication to start AED

<table>
<thead>
<tr>
<th></th>
<th>After 1st seizure</th>
<th>After 1st seizure (&gt;7 days post-event)</th>
<th>After second seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients</td>
<td>47%</td>
<td>34%</td>
<td>18%</td>
</tr>
<tr>
<td>Elderly patients</td>
<td>63%</td>
<td>14%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Table 2. Early onset seizures – duration of treatment if seizure free

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>1-2 years</th>
<th>Long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients</td>
<td>19%</td>
<td>53%</td>
<td>14%</td>
</tr>
<tr>
<td>Elderly patients</td>
<td>13%</td>
<td>38%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Table 3. Late onset seizures – indication to commence AED

<table>
<thead>
<tr>
<th></th>
<th>After 1st seizure</th>
<th>After 2nd seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Elderly patients</td>
<td>71%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Table 4. Late onset seizures – duration of treatment if seizure free

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>1-2 years</th>
<th>Long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients</td>
<td>1%</td>
<td>37%</td>
<td>62%</td>
</tr>
<tr>
<td>Elderly patients</td>
<td>1%</td>
<td>23%</td>
<td>76%</td>
</tr>
</tbody>
</table>

lamotrigine and gabapentin are as effective as carbamazepine in partial-onset seizures and that lamotrigine is better tolerated than carbamazepine in older people. In our survey, valproate and lamotrigine were the preferred agents. Six percent of respondents preferred levetiracetam which is not one of the first line agents as recommended by the guidelines. Both guidelines suggest discontinuing AED after two years seizure free, although this is a generalised statement and not specific to post-stroke seizures. In our survey, the majority of respondents preferred to withdraw medications after one to two years for early onset seizures (53% in younger patient vignette and 38% in the elderly patient vignette) and continue medications life-long for late onset seizures (62% in the younger patient vignette and 76% in the elderly patient vignette).

Both SIGN and NICE guidelines recommend initial AED monotherapy with trial of a second first-line agent as monotherapy if the first-line drug fails after it has been titrated to a maximum dose. This is in contrast with the results of our survey where the majority of stroke physicians stated they would first titrate up the dose of a first-line AED, then add in a second agent if this treatment fails, using a combination approach rather than switching to another AED as monotherapy. Choosing to treat with an AED may also be influenced by other factors such as the patients wish to continue driving in the future, occupation, and impact of further seizures on acute or long term care needs. The Driver and Vehicle Licensing Agency (DVLA) in the UK has explicit guidelines regarding driving after seizures. Following a first seizure, a standard group 1 driving license is revoked for six months and a group 2 licence (heavy goods vehicle or public service vehicle) is revoked for 5 years from the date of seizure. In case of recurrent seizures or epilepsy the revoking period is one year (group 1 license) and 10 years (group 2 license) since the last seizure. In cases where the AED is being withdrawn, the agency advises no driving for six months after commencement of withdrawal of medication.

Conclusion

Current management is based on national guidelines which do not specifically cover seizures in stroke patients and expert opinion which, as shown by the results of our study, does not reach consensus either. This is an area demanding further research to allow development of evidence based guidelines to improve management of this common problem.

Based on best available evidence, we would recommend treating the initial seizure post-stroke if it occurs more than seven days after the event. We would suggest, after careful discussion with the patient or relatives about the risks and intended benefits of AED therapy, treating with an appropriate first-line AED, such as lamotrigine or sodium valproate for at least 1 year before considering tapering the dose. For late-onset seizures, we would recommend long term treatment as the recurrent rate is higher. We would consider newer AEDs, such as lamotrigine, in older patients given the preferable side effects profile in this patient cohort. If the first-line AED fails to control seizures after being titrated up to an optimal dose as a monotherapy then switching to another first line agent is recommended with titration up to a maximal dose. Combination therapy with two or more AEDs is only indicated once two first line agents have been used as monotherapy at optimal doses and should be managed under expert supervision.

The poor response rate in the survey may relate to a lack of interest in this area amongst physicians, despite post-stroke epilepsy being an important syndrome which is likely to increase with increasing survival after stroke due to improved stroke management. Our small sample of BASP physicians demonstrated variation in AED prescribing depending on patient age and whether the seizures were early or late in onset. Our survey demonstrated the need for further exploration of the best treatments in localisation related epilepsy and research is needed in a clinical trial setting to allow more focussed guidance to be developed.

REFERENCES

12. For Medical Practitioners. At a glance Guide to the current Medical Standards of Fitness to Drive. Issued by the Drivers Medical Group, DVLA, Swansea. August 2010. www.dft.gov.uk/dvla/~dmdapd medial/at_a_glance.ashx