Women of child-bearing age and pre-menopausal women – what are the main considerations for initiating antiepileptic therapy?

Dr James Morrow: The primary considerations for antiepileptic therapy in men and women are similar vis-à-vis efficacy. Everybody wants an effective drug that will abolish seizures. The choice of drug in this respect often depends on seizure type. Balanced against this is tolerability, so the drug also needs to have few or no side effects.

Women present a special complexity in terms of tolerability because there are several issues to consider and the weighting of these issues may change over time. For example, for a young person – a teenager – going onto antiepileptic drugs (AEDs), compliance is important: a drug that is taken once or twice a day has an advantage over one that is taken many times a day.

Cognitive issues will also be important. However, as women get older it is important to consider interactions with the oral contraceptive pill, as well as fertility issues: for instance, there are some potential linkages with conditions such as polycystic ovary syndrome (PCOS). Some drugs have been shown to have a higher teratogenic potential than other drugs, and there is also evidence of a long-term risk to bone health with some AEDs. No drug as yet ticks all the boxes all the way through the various ages, so the emphasis changes over time as well as for particular individuals.

What are the risks of taking antiepilepsy medication while pregnant?

I help to run the UK Epilepsy and Pregnancy Register, which is one of four major epilepsy pregnancy registers worldwide. It has been running for 11 years now and useful information is just starting to emerge. One always has to accept the codicil that these registers are not randomised controlled trials and therefore there may be inherent biases. Nevertheless, they do seem to demonstrate that there are potential differences among the AEDs in terms of risk of major congenital malformations.

So far the spotlight has shone on sodium valproate. The UK register highlights the fact that sodium valproate is associated with a significantly higher risk of having a child with major malformation than, for instance, carbamazepine or lamotrigine.

However, one should always emphasise that, although there is a higher risk, that risk is only between 6 and 7%: in other words, a woman taking sodium valproate still has at least a 93% chance of having a perfectly normal child (better odds, incidentally, than those reported for valproate–lamotrigine polytherapy). Therefore, the results are generally reassuring, but there are differences, which raises the potential of being able to reduce risk.

The larger issues with major congenital malformations concern delay in cognitive and behaviour development. There are studies emerging from Gus Baker’s group in Liverpool, and we have a paper in the pipeline, that show that children exposed to sodium valproate in utero seem to have higher levels of neurodevelopmental, cognitive or behavioural delay than do other children. This is an issue that is going to emerge over the next few years and may be another reason for choosing one drug over another.

Can you elaborate on the differences between the older and newer drugs?

Carbamazepine and sodium valproate are considered the older drugs while lamotrigine is considered a new drug, but the latter has been around for 15 years. They are not true equivalents, however: women who take sodium valproate cannot easily switch to carbamazepine as the two drugs are used for different types of epilepsy.

Lamotrigine is considered an alternative to sodium valproate and has really grown in popularity in the UK. It is now considered to be one of the first-choice drugs for young women, but it has its drawbacks, namely that it is not easy to use: it has to be initiated slowly, and some people are allergic to it.
Epilepsy

Once you get past those parameters, it is generally well tolerated. However, there is evidence to suggest that blood plasma levels may drop quite precipitously, resulting in seizure breakthrough in some individuals during pregnancy. There is also evidence that it may affect and be affected by the pill, and that it may not be as effective as sodium valproate for some of the primary generalised epilepsies. Therefore, it also is not as direct an alternative to sodium valproate as was recently thought.

What about the choices available for partial epilepsy in terms of pregnancy?
Carbamazepine comes out very well with a relatively low major congenital malformation rate, but it has other problems. There is evidence in the literature to suggest that neurodevelopment delay may be associated with this drug. It also interferes with the contraceptive pill and is a hepatic enzyme inducer, so interactions are generally common. Hepatic enzyme inducers also pose a longer-term issue: they may be associated with an increased risk of osteoporosis.

In terms of drugs other than carbamazepine, lamotrigine ticks some of the boxes, but not all of them. Levetiracetam, which is one of the newest drugs, does look to be a very effective broad-spectrum AED. It does not seem to interfere with the pill and is generally well tolerated. Just last year we published some preliminary results for levetiracetam in pregnancy that are encouraging, but the numbers are not sufficient to be absolutely certain. Nevertheless, we have high hopes for this drug.

Are antiepileptics that are metabolised by the P450 system linked to an increased risk of osteoporosis?
There are papers that suggest that people with epilepsy in general have a higher risk of osteoporosis. The suspicion of osteoporosis has largely been on the older hepatic-enzyme-inducing drugs such as phenytoin, phenobarbital and, to a lesser degree, carbamazepine. However, there are other papers that suggest that osteoporosis is more common in women taking sodium valproate, which does not induce the P450 system.

Many of the papers are by necessity retrospective. A lot of them are compiled from people with epilepsy presenting with fractures, but fractures are not necessarily caused by osteoporosis. That will bring in biases within these papers. I think there is evidence to suggest that these particular AEDs may pose a risk with regard to bone health. The jury is still out on whether some are safer than others. From a theoretical point of view one might prefer not to use hepatic-enzyme-inducing drugs, but there is definitely a need for long-term controlled studies.

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What about catamenial seizures?
Catamenial seizures occur in certain parts of the menstrual cycle. There are a number of studies that have published on catamenial seizures, but they remain a little controversial.

Catamenial seizures certainly exist; however, more women believe they have catamenial epilepsy than actually do. It all depends on how you define exactly what catamenial seizures are: most people define them as occurring within a few days of the menstrual period, but depending on the time period included, you can potentially include a lot of people.

There is evidence to suggest that oestrogen is a convulsive agent and progesterone is an anticonvulsive agent, so there are hormone links. There may also be an effect of fluid retention or other psychological issues around that time. There are lots of contributory factors and there are various manipulations drug-wise that can be used to deal with it.

Once catamenial seizures have been diagnosed, one of the best approaches is to try to time additional antiepileptic therapy with the expected seizures. One of the common drugs that is used is clobazam, which is given for a few days around the time of expected seizure increase.

Is there a link between antiepileptic drug choice and polycystic ovary syndrome?
There has been a lot of work by Professor Isojarvi in Finland, who highlighted an apparent increase in the incidence of PCOS in women taking sodium valproate compared with women taking carbamazepine or lamotrigine. The link is controversial.

Many of the papers were retrospective and contained quite small numbers. And again there is the issue of definition of the syndrome as opposed to purely polycystic ovaries. I think there probably is a link, but how strong that link is I could not say. A lot more work needs to be done in this area.

What kind of strategies should a doctor consider to reduce the risk of birth defects?
The key is planning prior to conception. If the drug therapy needs to be altered to try to minimise or reduce risk, then that must be done well in advance of the pregnancy. All too often women present already in the early stages of pregnancy, but by that stage it is inadvisable to change AED therapy because it will probably only make things worse rather than better. Organogenesis occurs within the first trimester, so by the time the AEDs have been reduced or changed the
In Europe: Keppra® (levetiracetam) is indicated for:

— Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy

— Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy

— Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with myoclonic epilepsy

— Adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy

Please read full Summary of Product Characteristics (SmPC) before prescribing Keppra®.

*Keppra® achieved high seizure-freedom rates during the following Phase III trials: Monotherapy for partial onset seizures in newly diagnosed adults (≥16 years of age): 73% (173/237) ≥6 months; Adjunctive therapy for PGTC seizures in patients ≥4 years of age with IGE: 34% (27/79) during 20-week evaluation period; Adjunctive therapy for myoclonic seizures in adults and adolescents (≥12 years of age) with JME: 25% (15/60) during 12-week evaluation period; Adjunctive therapy for partial onset seizures in adults: 9% (23/269) during 16- to 18-week treatment period; Adjunctive therapy for partial onset seizures in children (4-16 years of age): 7% (7/101) during 14-week treatment period.

References:
3. Morrow J, L.E.V. N01057 Study Group. Efficacy and safety of levetiracetam as adjunctive treatment in adult and paediatric patients suffering from idiopathic generalised epilepsy with primary generalised tonic-clonic seizures. Abstract presented at: 10th Congress of the European Federation of Neurological Societies; September 2-5, 2006; Glasgow, UK.

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ABBREVIATED PRODUCT INFORMATION

NAME OF THE MEDICINAL PRODUCT
Kepro (levetiracetam) film-coated tablets, oral solution and 10 mg/ml concentrate for solution for infusion. QUALITATIVE AND QUANTITATIVE COMPOSITION: Each film-coated tablet contains 250 mg, 500 mg, 750 mg or 1000 mg levetiracetam. Each ml of oral solution contains 250 mg levetiracetam. Each ml of concentrate for solution for infusion contains 100 mg levetiracetam. Dosage form: Film-coated tablets, oral solution and concentrate for solution for infusion. Kepro contains a disaccharide, sodium, citrate, sodium, and levetiracetam.

CLINICAL PARTICULARS
Therapeutic indication: Kepro is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalization in adults and children from 12 years of age with newly diagnosed epilepsy. Kepro is also indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. Kepro is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy. Kepro concentrate is administered for patients when oral administration is temporarily not feasible. Novartis and Therapeutic: Kepro therapy can be initiated with either immediate or sustained-release preparations. Conversion to a form without immediate-release administration can be done directly without titration. The daily dose administered in two equally divided doses. The total daily dose and frequency of administration should be maintained. The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid, and taken without food. Each oral solution may be diluted in a glass of water or made up in infant or children’s food. A graduated oral syringe and instructions for use are supplied with the oral solution. In patients over 12 years of age the total daily dose should be divided into twice daily dosing. It is not necessary that the daily dose be divided into two equal doses. The dose may be titrated to a maximum of 10 mg/kg/day twice or 30 mg/kg/day divided thrice a day. The initial dose recommended in adults and adolescents is 10 mg/kg/day twice daily.

Microbiology: Adults and adolescents from 12 years of age The recommended starting doses are 25 mg/kg/day twice or 75 mg/kg/day twice daily (10 mg/kg/day divided thrice a day). The dose can be increased up to 1 mg/kg/day twice daily. The dose can be increased up to 1 mg/kg/day twice daily. The dose can be increased up to 1 mg/kg/day twice daily. The dose can be increased up to 1 mg/kg/day twice daily.

Adverse effects: Adults and adolescents 12 years and over (17 years or more, weighing 56 kg or more) The initial dose is recommended to be 5 mg/kg/day divided thrice a day. Dosage adjustment in children under 12 years of age is usually safe and efficacious.

Usage recommendations for children and adolescents

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Starting dose (mg/kg/day)</th>
<th>Maximum dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>10 mg/kg/day divided thrice a day</td>
<td>30 mg/kg/day divided thrice a day</td>
</tr>
<tr>
<td>20-29</td>
<td>20 mg/kg/day divided thrice a day</td>
<td>60 mg/kg/day divided thrice a day</td>
</tr>
<tr>
<td>30-39</td>
<td>30 mg/kg/day divided thrice a day</td>
<td>90 mg/kg/day divided thrice a day</td>
</tr>
<tr>
<td>40-59</td>
<td>40 mg/kg/day divided thrice a day</td>
<td>120 mg/kg/day divided thrice a day</td>
</tr>
<tr>
<td>60+</td>
<td>50 mg/kg/day divided thrice a day</td>
<td>150 mg/kg/day divided thrice a day</td>
</tr>
</tbody>
</table>

(1) Children 10 up age should be initially treated with Kepro 100 mg/ml oral solution.

(2) The maximum dosage of oral solution is 100 mg/kg/dose in children with no age restrictions.

(3) The maximum dosage of oral solution is 100 mg/kg/dose in children with no age restrictions.

(4) The maximum dosage of oral solution is 100 mg/kg/dose in children with no age restrictions.

CLINIC (2)<x> x weight (kg) = (2.5 x weight (kg))

Dosage adjustment for adult patients with impaired renal function

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;90</td>
<td>10 mg/kg/day divided thrice a day</td>
</tr>
<tr>
<td>Moderate</td>
<td>50-90</td>
<td>20 mg/kg/day divided thrice a day</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;50</td>
<td>30 mg/kg/day divided thrice a day</td>
</tr>
</tbody>
</table>

(1) A 30% dose reduction is recommended on the first day of treatment with levetiracetam.

(2) Following dialysis, a 250-500 mg supplementary dose is recommended.

(3) For children with renal impairment, the above adjustments should be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult and children patients with normal renal function for drug clearance in patients with mild to moderate impairment in patients with severe impairment, the creatinine clearance may underestimate the creatinine clearance. Therefore a 50% reduction in the daily maintenance dose is recommended when the creatinine clearance is <30 ml/min. Modifications: Increase the dose by 25% of the dose that is titrated to a maximum of 10 mg/kg/day (twice daily) every other day. Available data in children did not suggest impact on growth and puberty. Therefore a 25% increase in dose is recommended for children under 12 years of age, increased in adults aged 12 years or more. In adults aged 12 years or more, dosing adjustments do not increase in patients in whom renal impairment is severe. An increase in frequency of treatment is necessary for children whose renal function is decreased by more than 30%. The total daily dose should be adjusted according to renal function. In the event of chronic renal failure, discontinuation of treatment of adverse effects, including a 30% or 50% increase in dose every other day, until the dose is adjusted. In the event of chronic renal failure, discontinuation of treatment of adverse effects, including a 30% or 50% increase in dose every other day, until the dose is adjusted.

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Initial Therapy for Epilepsy – A Focus on Pre-menopausal Women

people who have epilepsy but who have not had a seizure for some considerable time may no longer need their drugs.

From my point of view, the first thing I would do would be to review the diagnosis because as many as 20% of people attending hospital with a diagnosis of epilepsy may ultimately turn out not to have it. Furthermore, in some cases there is an argument for saying that pregnancy will already have passed that period. Therefore, the key is pre-conception planning.

However, it is important to consider that the brain develops throughout the whole of the pregnancy. If one particular AED is found to be associated with neurodevelopmental delay, that would indicate a rethinking of this strategy and there would be a cause for changing a patient’s regimen during pregnancy – but we are not there yet.

At the pre-conception planning stage, is there much difference between new and old therapies?

The latest UK National Institute for Health and Clinical Excellence (NICE) guidelines indicated there was not. However, there is. All of the registries that have published and other preceding evidence would suggest that women taking sodium valproate have a higher risk of a major malformation in their child, particularly at higher doses. In these patients one would think about seeing if they can be withdrawn from the medication, have their AED switched or at the very least have their dose reduced.

And in summary?

We are living in an era in which information regarding AEDs – as well as the number of AEDs – is increasing all the time. Therapy and management of epilepsy for pre-menopausal women is improving. However, because of the increased number of AEDs and the gathering of huge amounts of information, it is an increasingly complex task. Many patients will benefit from the input of a specialist and/or a specialist epilepsy nurse to try to guide them through these issues and help them with their choices, many of which are likely to change over time.

All of the studies agree that polytherapy carries a much higher risk of foetal malformations than does monotherapy, so it is worth trying to reduce therapy to one drug. For some of the drugs – particularly sodium valproate and lamotrigine – it is worth considering dose as well, which may be relevant in the degree of relative risk.

For unplanned pregnancies where pre-conception planning has not been possible, what are the options?

At the present time, the general practice is that if somebody presents who is already pregnant, AEDs should not be changed because to do so would actually involve taking two drugs for a period of time, which carries an even greater risk. Furthermore, by the time the patient can come off the drug of concern, she would be through the first trimester and organogenesis.

It is also good practice to prescribe folic acid: studies carried out in the general population suggest that it may protect against neural tube defects, and we extrapolate this into the epileptic population. There is no direct evidence that folic acid actually protects our population group; moreover, the neural tube defects that are seen – particularly with sodium valproate – are slightly different from those in the general population: they tend to be lower and involve folding rather than canalisation, for example. Therefore, in terms of the question of whether folic acid protects the unborn child, we do not actually know. Initial results from our study hint that maybe it does not have this protective effect and maybe this is a special group, so we need to be looking at some other mechanism. I would advocate that, until evidence says completely the opposite, it is a good idea to prescribe folic acid.

In some cases there is an argument for saying that people who have epilepsy but who have not had a seizure for some considerable time may no longer need their drugs.

However, in some cases there is an argument for saying that:

- In cases where the patient is already pregnant, AEDs should not be changed because to do so would actually involve taking two drugs for a period of time, which carries an even greater risk. Furthermore, by the time the patient can come off the drug of concern, she would be through the first trimester and organogenesis.
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