EVIDENCE REVIEW FOR NHS SURREY AND SUSSEX

PRESCRIBING CLINICAL NETWORK: ANTIEPILEPTICS FOR EPILEPSY

Prepared by: Jayesh Shah

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SUMMARY PAGE

- Epilepsy is the most common serious neurological condition in the UK but several high profile reports have consistently highlighted inadequacies in services and care, and on a population level there is evidence of waste of NHS resources.
- Correct diagnosis is essential, but can be very difficult.
- Most patients have potential to be seizure free but some patients will continue to have seizures.
- There is little evidence that newer AEDs offer benefits over older, more established medicines but prescribing costs are often higher.
- All patients with epilepsy should have a comprehensive care plan and regular review.

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1.1	23.5.13	Jayesh Shah	Part complete	• Sent for comments to secondary care and primary care
1.2	18.6.13	Jayesh Shah	Part Complete	• Comments from primary and secondary care included in paper. • Generic substitution documented as icon within document to reduce down 94 pages
1.3	7.8.13	Jayesh Shah	Final Version	• Additional comments since version 1.2 • Formulary decision recommendation for each medication • Statement for PCN to agree that they will adopt brand v generic guidelines as stated.
1.4	7.8.13	Jayesh Shah	Final version	• Perampanel submission entered as appendix
1.4	8.8.13	Victoria Overland	Final version	• Incorporation of MTRAC lacosamide review (Appendix 7.) and minor amendments to Section 5.6 to incorporate changes. • Reformatting
1.51	21.8.13	Jayesh Shah	Final version to panel members	• Comments added from Dr Stern and Dr Kimber and small amendments made to document • Additional options added to alternative to treatment section • Purpose of review clearly labeled A and B for primary and secondary reasons • New definition for seizures and epilepsy included which is under consultation • Tertitaty option changed so T = Tertiary/Third Line Option initiated and stabilized by specialist • Resource section and NICE Quality Standards in appendix 8 & 9

EVIDENCE REVIEW FOR NHS SURREY AND SUSSEX

PRESCRIBING CLINICAL NETWORK: ANTIEPILEPTICS FOR EPILEPSY

INTRODUCTION

Epilepsy is a common condition with up to 50 cases of new-onset epilepsy per 100,000 people each year (Kwan 2011). Seizures, of which there are many clinical manifestations, characterise epilepsy. The underlying cause may be neurological, neurovascular, neuroanatomical, metabolic, auto-immune or psychogenic so classifications can be controversial and misdiagnoses are common. Of those who are diagnosed with epilepsy, two-thirds are likely to become seizure-free on or off treatment (defined as no seizures in a 5-year period). Around 20-30% of epilepsy patients will develop drug-resistant epilepsy (Kwan 2011, Picot 2008, NICE CG137) often requiring multiple therapies to reduce the seizure frequency.

1. PURPOSE OF THE REVIEW

A. To provide recommendation on traffic light status of anti-epileptic medication in the treatment of epilepsy

B. To develop guidance and information that is supported by primary, secondary and tertiary care that is useful to prescribers and health care professionals involved in the care of epilepsy:

- to improve patient care
- to ensure access to appropriate treatment
- to improve selection and rationalization of treatment options
- to increase knowledge and confidence on antiepileptic medication
- to support audit of anti-epileptic prescribing

To provide information/recommendations when branded antiepileptic medication should be prescribe or when generic prescribing is acceptable. This will include guidance if switching is acceptable or not.

- NICE recommendations
- A consensus view from the: United Kingdom Clinical Pharmacists Association (UKCPA): Neurosciences Group **&** Pharmaceutical Market Support Group (PMSG): Generics Sub-Group

2. APPROPRIATENESS

PREVELANCE: Estimated to affect between 362,000 and 415,000 people in England. Estimated incidence is 50 per 100,000. Estimated prevalence of active epilepsy in the UK 5 -10 cases per 1000.

2.1 DEFINTION

Current Definition: Epilepsy is a condition characterised by recurrent, unprovoked seizures, rather than suffering one isolated seizure or being due to an underlying acute reversible medical problem such as meningitis or alcohol withdrawal. It should be viewed as a symptom of an underlying neurological disorder and not as a single disease entity.

An epileptic seizure is a brief disturbance of consciousness, behaviour, emotion, motor function, or sensation that is caused by an abnormal electrical discharge in the brain. The definition of epilepsy requires the occurrence of at least two unprovoked seizures more than 24 hours apart.

Definition Under Consultation: The International League of Epilepsies have commissinoned a task force to refine a new definition of seizures and epilepsy. This definition is in the box below and and clicking on the title below will give you access to the full paper. Useful or constructive comments on this definition need to be submitted to the ILAE by 1st October. I will be happy to collate all responses and submit on behalf of the organization.

Operational (Practical) Clinical Definition of Epilepsy

Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked seizures occurring more than 24 hours apart.
2. One unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (approximately 75% or more).
3. At least two seizures in a setting of reflex epilepsy.

Epilepsy is considered to be no longer present for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for at least 10 years off anti-seizure medicines, provided that there are no known risk factors associated with a high probability (>75%) of future seizures.

CLASSIFICATION

Classification of the type of epilepsy is controversial and has tended to focus on both the clinical presentation — the type of epileptic seizure, and on the underlying neurological disorder or syndrome.

Seizure type and epilepsy syndrome should be determined when epilepsy is diagnosed, because failure to classify the epilepsy syndrome correctly can lead to inappropriate treatment of the patient and persistence of seizures.

Epileptic seizures can be divided into **generalised seizures**, where the whole brain is involved and **focal (partial) seizures**, where the abnormal electrical discharge originates from one specific area of the brain.

GENERALISED SEIZURES**:** Generalised seizures affect all of the brain at once and can happen without warning. In all generalised seizures the person will be unconscious, even if just for a couple of seconds. Afterwards they will not remember what happened during the seizure.

TONIC-CLONIC (CONVULSIVE) SEIZURES (sometimes called grand mal) is often the type of seizure we think of when we think of epilepsy and are the most common type of seizure.

At the start of a tonic-clonic seizure:

- the person becomes unconscious
- their body goes stiff and if they are standing up they usually fall backwards
- they may cry out and may bite their tongue or cheek.

During the seizure:

- the muscles relax and tighten rhythmically, making their body jerk and shake (convulse)
- breathing might be affected and become difficult or sound noisy
- skin may change colour and become very pale or bluish
- there may be urinary incontinence.

After the seizure (once the jerking stops):

- the breathing and colour return to normal
- the person may feel tired, confused, have a headache and want to sleep.

Other less common generalised seizures include absence seizures, tonic seizures, atonic seizures and myoclonic seizures.

ABSENCES (sometimes called petit mal) are more common in children than adults, and can happen very frequently. During an absence seizure, a person becomes unconscious for a short amount of time. They may look blank and stare or their eyelids might flutter. They don't respond to what is happening around them. For example, if they are walking they may continue to walk, but will not be aware of what they are doing during the seizure.

In TONIC SEIZURES the person's muscles suddenly become stiff. If they are standing they often fall, usually backwards, and may injure the back of their head. Tonic seizures tend to be very brief and happen without warning. People usually recover quickly.

In ATONIC SEIZURES (sometimes called a drop attack) the person's muscles suddenly relax, and they become floppy. If they are standing they often fall, usually forwards, and may injure themselves. Like tonic seizures, atonic seizures tend to be very brief and happen without warning. People usually recover quickly.

MYOCLONIC SEIZURES involve the jerking of a limb or part of a limb. They are brief but can happen in clusters (many happening close together in time). They often happen shortly after waking up. They can happen on their own but it is more common that they happen as well as other types of seizures, such as tonic-clonic seizures.

FOCAL SEIZURES **(previously known as partial seizure)**. In partial seizures the seizure starts in, and affects, just part of the brain. The seizure might affect all of one hemisphere or just a small area in one of the lobes. Partial seizures are sometimes called 'focal' seizures because the seizure happens in just one area.

In **focal (simple partial) seizures** only a small part of the brain is affected. The person is conscious, aware and alert, and will usually know that the seizure is happening.

FOCAL SEIZURES EVOLVING TO SECONDARY GENERALISED SEIZURES **also known as complex partial seizure** (CPS) affects a bigger part of the brain than SPS. In a CPS the person's consciousness is affected and they may be confused and afterwards may have no memory of the seizure. They might be able to hear you if you talk to them, but they might not fully understand what you have said and might not be able to respond to you. During a CPS the person might make strange or repetitive movements that have no purpose (called 'automatisms').

STATUS EPILEPTICUS. When a seizure continues for more than 30 minutes or when one seizure follows another without recovery in between, it is known as status epilepticus or 'status'. When status epilepticus happens during a tonic-clonic (convulsive) seizure it is a medical emergency and needs urgent treatment

2.2 EFFECTS AND PROGNOSIS:

People with epilepsy may experience associated problems apart from the condition itself.

- Social stigmatization (perceived or experienced) may occur, affecting employment, education, driving, and social life.
- Psychosocial problems may occur, including lack of confidence (eg in work or leisure situations), poor self-esteem, dependence on others, anxiety, and depression. Social development may be a particular issue in children.
- Adverse effects of antiepileptic drugs (AEDs) are a significant problem for many people. Rash is the most common, occurring in up to 10% on carbamazepine, phenytoin, or lamotrigine.
- Physical trauma may occur as a result of having a seizure.
- There is an increased risk of fetal malformations for pregnant women taking AEDs.
- Developmental problems are common in some children with early onset seizures, such as infantile spasms (West's syndrome) and Lennox-Gastaut syndrome.
- Specific cognitive difficulties (eg with reading or arithmetic) can occur and may have a serious impact on a child's education if not recognised.
- Finally, there is a small but significant risk of sudden unexpected death in epilepsy, which is estimated to account for 500 deaths per year in the UK.

SEIZURE TYPES OCCUR WITH THE FOLLOWING FREQUENCY:

- 60% tonic-clonic
- 20% complex partial
- 12% mixed tonic-clonic and partial
- 3% simple partial
- Less than 5% absence, myoclonic, and other seizure types.

2.3 DIAGNOSIS:

Following a first seizure, referral to a specialist is recommended to ensure precise and early diagnosis and initiation of therapy as appropriate. Specialist is defined as a medical practitioner with training and expertise in epilepsy. For children this is a paediatrician with training and expertise in epilepsy.

Diagnosis can be difficult and it may not be possible to make a definite diagnosis when first assessed

NICE management guidelines state that all patients should have a regular structured review. Adult patients should have a review with their GP but, depending on their wishes, circumstances and epilepsy, the review may be carried out by the specialist. Children should have a regular review with a paediatric epilepsy specialist.

Maximum interval between reviews should be 1 year, but frequency will be determined by individual circumstances. For children a suitable review interval is likely to be between 3 and 12 months.

2.4 THE INTERVENTION:

NICE recommend initiation of AED therapy only when diagnosis is confirmed — generally after **second** epileptic seizure. It can be initiated after a first unprovoked seizure in the circumstances stated in NICE.

SO WHY NOT TREAT ALL PATIENTS WITH ANTI-EPILEPTIC DRUGS AFTER ONE SEIZURE?

70% of patients will not have a recurrence of seizure, so treating immediately with an AED may not give any benefit but exposes the patient to potential harm from the side effects of treatment.

Some patients will continue to have seizures despite treatment — some will have recognisable cerebral abnormalities and severe and persistent types of epilepsy.

Some patients may decide not to take drug treatment following a discussion with the clinician of the risks and benefits of 'treatment versus no treatment'.

When prescribing for epilepsy, monotherapy should be used wherever possible. Baseline biochemistry and full blood counts are needed.

Prior to initiating combination therapy, the clinician should consider reasons why monotherapy has failed. Some of the things to consider might include:

- is diagnosis correct?
- is adherence with treatment poor?
- is the choice and dose of AED appropriate for the epilepsy syndrome/seizure type.

Care setting: This depends on the medication chosen and the complexity of the patient.

HOW OFTEN SHOULD MONOTHERAPY BE ATTEMPTED BEFORE ADJUNCTIVE TREATMENT

NICE doesn't specifically state how many attempts at monotherapy should be made before combination therapy is tried, but SIGN guidelines from 2005 recommend that if two appropriate AEDs have failed independently as monotherapy, the chance of further monotherapy controlling seizures is low and combination therapy should be considered.

WHEN SHOULD MEDICATION BE WITHDRAWN?

NICE considered the timescale for withdrawal of AED treatment and concluded it should only be considered in those who have been seizure free for at least 2 years. Of importance is the need to consider individual circumstances of the patient and impact of seizure recurrence (for example on ability to drive) versus continued therapy (and possible adverse effects).

NICE guidance also contains a prognostic index which separates risk out by time since seizures, etc that should be consulted if withdrawal of AEDs is being considered.

CLINICAL REASONS FOR DISCONTINUATION OF FIRST AND SECOND LINE ANTI-EPILEPTIC DRUGS:

The following list is from Tertiary Epilepsy Specialist Opinion from Brighton and Sussex University Hospital approved in Sept 12

1. Lamotrigine, gabapentin and pregabalin have relatively weak anticonvulsant effects and are often stopped because they are ineffective. They are, however, often well tolerated and good for treating co-existing neuropathic pain and migraine. Each may aggravate myoclonus.

2. Tiagabine clinically lacks efficacy and is rarely initiated for treating seizures. It also exacerbates myoclonic seizures.

3. Sodium valproate is first line for all seizure types. However, it is unsuitable (except as a last resort) in any young woman of child bearing potential due to its high teratogenic potential and reduction of foetal IQ. It universally causes dose dependent weight gain and is associated with polycystic ovarian syndrome, menstrual irregularity (risking osteoporosis) and hair loss.

4. Vigabatrin is no longer initiated due to side-effects of irreversible visual field defects.

5. Older AEDs carbamazepine, oxcarbazepine cause cognitive sedation and drug-drug interactions through enzyme induction.

6. Levetiracetam and topiramate have good efficacy and broad spectrum of activity but cause potential unacceptable affective/psychiatric and behavioural side-effects.

7. Clobazam/clonazepam risk dependence and tolerance to their effect and unacceptable day time drowsiness in some patients.

Comments from Dr Stern, Frimley Park Hospital on 16th August 2013: this list is a bit idiosyncratic- I don't think that Lamotrigine is generally considered particularly inefficacious (? epileptologists…).

2.5 ALTERNATIVE TREATMENTS:

- Vagus Nerve Stimulation
- Deep Brain Stimulation
- Brain Surgery
- Ketogenic Diet
- Trigeminal Nerve Stimulation

3. EFFECTIVENESS

3.1 EXPECTED BENEFITS

After a first seizure recurrence varies greatly, and can be halved using AEDs. Remission is common.

It is often stated that 70% of people have potential to be seizure free. This figure is based on a study from the National General Practice study of epilepsy reported in the Lancet in 1995. This followed the outcome of 1091 patients registered with 275 GP practices throughout the UK who had a diagnosis of definite or possible epilepsy between 1987 and 1989. After 9 years from the first measured seizure across all patients, 87% had been seizure free for 3 years and 71% for 5 years. For those with a definite diagnosis of epilepsy, confirmed by 6 months following the initial event, 68% had been seizure free for 3 years, and 54% for 5 years.

3.2 OLDER AED OR NEWER AEDS

In addition to the NICE guideline on the management of epilepsy there is a NICE Technology Appraisal of newer AEDs from 2004 that concludes older AEDs should be used first-line, unless there are compelling reasons why they are not suitable.

Newer AEDs, within their licensed indications, are recommended in those who have not benefited from treatment with older agents or because of possible contraindications as given here.

The reason for this recommendation is that almost all studies comparing newer drugs with older drugs have found no statistically significant differences in terms of seizure-related outcomes eg proportion of people seizure-free, proportion with a 50% reduction in seizure frequency, or time to first seizure.

Additionally, the studies in the appraisal did not provide strong evidence of improved quality of life with the newer drugs, and there were limitations due to study design.

Epilepsy management can be described as the lock and key theory. The 9th choice may be the one medication that reduces patients seizure and improves quality of life and therefore all treatment should be made accessible in tertiary care.

4 BRANDS V GENERICS

NHS, Generics Sub Group of PMSG set up a working group to provide information on brands v generic substitution. Jayesh Shah was a member of this working group. Information in this section is directly from the working group. The full document is embedded as an appendix and this will give details so specific trials and looks at each medication individually. This is summarized in the excel table.

4.1 USE OF GENERIC AEDS

The majority of the classic first-line therapies in epilepsy are available from multiple manufacturers as brands and generic products (phenytoin, carbamazepine, sodium valproate, phenobarbital). Some of the second generation anti-epileptic drugs (AED) have generic versions available or coming soon. The awarding of generic AED medicines contracts for secondary and tertiary care in the NHS has been problematic for some time because of concerns about the benefits versus risks of using generic AEDs to treat epilepsy.

4.2 CONTROVERSY AROUND SWITCHING

The financial benefits of switching to less costly treatments are the most obvious drivers for changing patients' AED products. Generic drug prescribing can improve medication safety because consistency in prescribing the same drug name avoids confusion of multiple brand names. Hospital

contracts change infrequently so patients would seldom be exposed to a change of manufacturer in secondary care. Many medicines licensed for the control of seizures are also used for other indications. In practice it would be difficult to manage the use of two products; a generic for non-epilepsy indications and the brand for epilepsy.

There is some opposition to switching AEDs to generic versions because of concerns of inequivalence between the brands and generics. There are limited published papers investigating the risks of brand to generic prescribing with a wide range of findings. Increase in seizure frequency has been linked to natural variation in disease, low medication compliance, infection, nutrition status, hydration status, tiredness, and stress as well as changes between products that may have bioavailability or pharmacokinetic differences (National Society for Epilepsy 2010, Brain and Spine Foundation 2012, Sperling 2008). Existing evidence is unable to stratify these risks in order of importance. The incidence of seizure recurrence in previously seizure-free patients has been reported to be 30% with no known cause and another 10% with an identifiable cause such as omission of doses, sleep deprivation or fever (Schiller 2009). This confounds the determination of the impact of brand to generic switching and makes recommendations problematic.

4.3 RECOMMENDATIONS FROM EPILEPSY GROUPS AND GOVERNING BODIES

Many patient and other special-interest groups recommend prescribing certain AEDs by brand. (Epilepsy Action 2011, AAN 2006, Bialer 2010) In practice this is difficult and there is evidence that primary care epilepsy patients are switched from one generic or branded product to another without consultation more frequently than expected. (Rawnsley 2009, Wilner 2002). This may be as a result of many factors including a lack of awareness or information available to patients, carers, prescribers or community pharmacists. A survey of readers of Epilepsy Action's membership magazine 'Epilepsy Today' found that 36% of epilepsy patients who were given a different manufacturer's version of their AED refused to accept the product. The importance of shared decision-making is widely acknowledged and essential for improved adherence to medicines (DoH 2010). It is thought that 30 – 50% of medicines for long term conditions are not taken by patients as recommended (NICE CG76), and studies investigating AED adherence have demonstrated similar rates of compliance (Hovinga 2008, Ettinger 2009, Jones 2006) with some finding that non-adherent patients were significantly more likely to have seizures than adherent patients (Hovinga 2008, Jones 2006). Therefore any switching between brand and generic medicines must be in agreement with patients.

4.4 NICE STATEMENT ON AED

NICE (NICE CG137) has published a statement on AEDs which states:

"Consistent supply to the child, young person or adult of a particular manufacturer's AED preparation is recommended, unless the prescriber, in consultation with the child, young person, adult and their family and/or carers as appropriate, considers that this is not a concern. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side effects. Consult the summary of product characteristics (SPC) and British National Formulary on the bioavailability and pharmacokinetic profiles of individual AEDs, but note that these do not give information on comparing bioavailability of different generic preparations."

4.5 BIOEQUIVALENCE

Generic drugs are required to be bioequivalent to the reference branded formulation. Bioequivalence tests are carried out in small samples of healthy volunteers. The European Medicine Agency (EMEA) criteria for bioequivalence requires the upper and lower limits of 90% confidence intervals (CI) for a generic drug's area under the curve (AUC) and maximum concentration (Cmax) to be within 80% to 125% of the reference branded formulation. To fit the 90% confidence interval within these limits, the generic drug and the brand drug have to be almost identical and the only theoretical exception is if the generic drug formulation has a markedly lower variability than the brand formulation. However, concern has been raised that generic AEDs which are at the outer limits of these ranges may cause problems in some patients who are switched from branded drugs or from other generic drugs at the opposite end of the range. (EMEA 2010, Peterson 2011)

The EMEA has developed tighter criteria for drugs with a narrow therapeutic index and recommend these drugs have AUC and Cmax confidence intervals within 90.00 to 111.11% however they have not requested any AEDs are tested with these limits yet. (EMEA 2010)

4.6 BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

One reference suggests that there are three pharmacokinetic properties that predispose AEDs to problems with generics: low water solubility, narrow therapeutic range, and nonlinear pharmacokinetics.

A drug is considered to have high solubility when the highest dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1 to 7.5 at 37°C. A drug is considered to be highly permeable when the extent of absorption is 90% or higher.

The drugs are then classified into four Biopharmaceutics Classification System (BCS) classes: Class I: high solubility/high permeability; Class II: low solubility/high permeability; Class III: high solubility/low permeability; Class IV: low solubility/low permeability.

The BCS classification can provide an estimate for the likelihood of problems with generic substitution not predicted by in vitro dissolution testing. (Anderson 2008)

A value for BCS is included in the individual drugs' monographs where it is known.

4.7 PRINCIPLES FOR SWITCHING:

- Switching should only be considered where there is a significant clinical, logistical or financial benefit from switching. Risks involved in switching AEDs should be mitigated as far as possible.
- Patients should be asked whether they have previously experienced problems when switching between brands and generics or if they have been told by their doctor that they must not switch between brands or generics.
- Patients are encouraged to be involved in their own healthcare, with decisions made in partnership with clinicians, rather than by clinicians alone. (DoH 2010) Therefore, patients should be asked their views about switching between brands and generics after being informed of the benefits and risks.
- Patients should not routinely be switched from existing medicines without their consent unless urgent treatment is needed.
- Sustained or Modified Release products present a greater risk and should not be considered generic (see specific product recommendations below).
- Patients with highly labile seizure control should not be switched to generics and should be maintained on their usual brand or generic version for their AED therapy.
- Patients with optimal seizure control (i.e. seizure-free or their seizure frequency has been markedly reduced) should not be switched to generics and should be maintained on their usual brand or generic version for their AED therapy. This of highest importance where there is a history of good seizure control and where the recurrence of a seizure could lead to socio-economic harm (e.g. loss of a driving license).
- If there has been a recent loss of seizure control and additional or alternative AEDs are to be prescribed, even where products are not recommended to be switched this is an opportunity to move to a generic version where this is considered to be appropriate.

  - Risk factors for increased seizure frequency include (but are not exclusive to): head trauma, infections such as meningitis or encephalitis, cerebrovascular accidents, medicine interactions, lack of compliance with AEDs, high alcohol intake or illicit drug use, or where previously used routes or modes of administration become unavailable or unsuitable.

- Patients with allergies to certain excipients must only switch if it is known that the generic product does not contain those ingredients.
- Epileptic patients on a ketogenic diet should not be switched to generic formulations unless agreed by the patient's healthcare team as different products have different carbohydrate content.
- Non-epilepsy uses of AEDs do not generally have significant consequences following minor changes in dose so generic switching is unlikely to cause problems.

To ensure patients receive the most appropriate product, where differences exist between brands, most hospitals will stock a single product and a range of formulations within the branded product range.

An additional priniciple which was not included in the NHS sub group is the elderly population should not switch from brand to generic. This is because changes in metabolic functions in older people and also perhaps they are more sensitive to side effect which may be less noticeable in younger patients. Cognitvie decline and balance issues may occur. Recommended not to switch in the elderly.

4.8 SUMMARY OF BRANDS V GENERICS

Patients identified as suitable for switching from brand to generic are those who agree to try a generic version and are taking an AED which is significantly cheaper as a generic. They must not have any contraindications to switching such as: sensitivity to small dose changes, experience of previous unsuccessful attempts to switch, sustained release preparations, good seizure control, serious consequences from a change in seizures (e.g. loss of driving license) and they must not be on a ketogenic diet or have allergies to the excipients in the generic version.

5. SUMMARY OF KEY POINTS FOR CONSIDERATION

5.1 NATIONAL GUIDANCE: NICE CG Epilepsy January 2012

5.2 EFFICACY:

For those with a definite diagnosis of epilepsy, confirmed by 6 months following the initial event, 68% had been seizure free for 3 years,

5.3 POTENTIAL BENEFITS OVER EXISTING THERAPY

Little evidence to suggest that any anti-epileptic drug is more effective than another, although some drugs may be more effective than others for certain types of seizures (see Table)

5.4 BUDGETARY IMPACT

Inappropriate use of newer agents will adversely impact on expenditure. A number of antiepileptic drugs have recently become available generically and have fallen in price significantly.

Cost of each medication for pack size and formulation is in worksheet 2 of excel workbook. The newer antiepileptic medication are all approximately £4 to £6/ day

5.4.1 QIPP OPTIONS

Phenytoin: Note phenytoin tablets has increased from £3 to £68 for 28 days supply. Phenytoin is no longer routinely one of the first choice treatments. Current guidelines only place phenytoin as tertiary option in only focal seizures. Phenytoin may worsen the following types of seizures: absence, childhood and myclonic. The PCN would expect the number of units of phenytoin to be stabalised or decreasing than increasing.

Lamotrigine: The Department of Health issued a statement in 2005 that supported switching from Lamictal to the generic lamotrigine. Anecdotes from Surrey community pharmacists that have stated patients who have switched have had worsening of seizures

Levitracetam: NICE analysis showed that levetiracetam is the most cost effective adjunctive therapy, but when the analysis was undertaken in June 2011, it stated the additional cost of the medication compared to lamotrigine or oxcarbazepine is not justified by the additional benefit. NICE also stated

that with only a 30% reduction in unit cost, levetiracetam is likely to dominate oxcarbazepine and ne considered cost-effective compared to lamotrigine.

Cost of levitracetam in September 2011 was between £28 and £96 depending on strength. Current costs (August 2013) range between £2.28 and £7.78 for tablets but liquid is still at £66. If Keppra is prescribed or dispensed and endorsed on an FP10 then the cost will be between £28 and £86

Current price (June 2013) of the generic levetiracetam costs £2.34 for 60 tablets of 250mg and branded Keppra costs

5.5 PRECEDENT SETTING:

SIGN guidelines have similar recommendations to NICE.

The International League of Epilepsy have a number of guidelines and recommendations and these have been used as one of the evidences to develop the NICE guidelines.

5.6 CONCLUSIONS AND RECOMMENDATIONS (RECOMMENDATION WILL GO INTO POLICY STATEMENT)

a) To adopt the table of indications and appropriateness

b) To use generic medications where appropriate and support the principles of switching brand to generic medication as per NICE guidelines and guidelines from the NHS, Generics Sub Group of PMSG and add the inclusion that switching is not recommended in the elderly

c) Before prescribing unlicensed specials consult the local specials resource

d) It is recommended that:

- older antiepileptic drugs are given AMBER* status, i.e. these are drugs that require initiation by a specialist in secondary / tertiary care but due to more widespread experience in primary care GPs are generally happy to prescribe on specialist advice without the need for a formal shared care protocol
- newer antiepileptic drugs be given AMBER* status if minimal monitoring is required and safety of use is established.
- where additional monitoring is required the an AMBER status should be considered
- where safety concerns are highlighted, RED status is appropriate
- the table below shows the proposed status for AEDs

Older AEDs	Recommended Traffic Light Status	Newer AEDs	Recommended Traffic Light Status
Carbamazepine[1A]	Amber*	Eslicarbazepine[T]	Red (paediatrics) Amber (adults)
Clobazam[A T]	Amber*	Lacosamide[T]	Amber* (see Appendix 6. Evidence Review)
Clonazepam[T]	Amber*	Perampanel[T]	Amber* (see Appendix 7. Evidence Review)
Ethosuximide[1A]	Amber*	Retigabine[TL]	Amber
Felbamate[L]	Red	Rufinamide[T]	Amber
Gabapentin[A]	Amber*	Stiripentol[U]	Red
Lamotrigine[1A]	Amber*	Zonisamide[T]	Amber*
Levetiracetam[1A T]	Amber*	Buccolam (Buccal Midazolam)	Amber*
Oxcarbazepine[1A]	Amber*		
Phenobarbital[T]	Amber*		
Piracetam[T]	Red		
Phenytoin[T]	Amber*		
Pregabalin[T]	Amber*		
Topiramate[A T]	Amber*		
Sodium Valproate[1A]	Amber*		
Tiagabine[T]	Amber*		
Vigabatrin[T]	Amber*		

The medications listed in this table have all been reviewed by NICE and included in the clinical guideline or Technology Appraisal. Exception to this is Permapanel as this was licensed after the latest NICE guidelines. However NICE have looked at the evidence for the medication stiripentol although it is unlicensed at present.

Codes**
1 = First line option as per NICE guidelines
A = Adjunctive option as per NICE guidelines
T = Tertiary/Third Line Option initiated by specialist
L = Last-line tertiary options
U= Unlicensed

**Check appendix 1 to see if the medication above is included as first line, adjunctive or tertiary option for a particular seizure type or syndrome

e) Shared care documents to be developed for lacosamide and perampanel if PCN agrees to amber* status

f) Support the withdrawal of antiepileptics as per NICE guidance:

- The risks and benefits of continuing or withdrawing AED therapy should be discussed with children, young people and adults, and their families and/or carers as appropriate, who have been seizure free for at least 2 years.

- Withdrawal information should be obtained from a specialist (refer to Appendix H of NICE guideline)

g) Support the development and use of the Excel tool (Appendix 2) which provides the following information to prescribers (this tool has been sent to secondary and primary care specialists and its development is supported by them):

- Medication
- Traffic light status of medication
    - Adults
    - Children
- Formulation
- Brand Manufacturer
- Generic availability
- Patent expiry date if generic unavailable
- Cost of medication and cost effectiveness
- Licensed age
- Drug level monitoring requirements
- Monotherapy or adjunctive license
- Drug/Food Interactions
- Information on prescribing in the following groups:
    - Elderly
    - Cardiac
    - Pregnancy
    - Breast- feeding
    - Genetics
- Hypersensitivity cross reaction between medication
- Unlicensed use of medicine
    - Crushing or/and dispersing
    - Mixing with food
    - Using via feeding tubes
- Seizure type and classification
    - 1st line, adjunctive and tertiary medication and ranking within group if more than 1 option
    - Number of treatment options to be tried before moving to next step
    - Medication not licensed for indication but evidence available for the type of seizure
    - Specific information on the evidence for the medication for that type of seizure

- Additional Information
    - Blood monitoring
    - Vitamin or mineral supplementation

EVIDENCE REVIEW FOR NHS SURREY AND SUSSEX

PRESCRIBING CLINICAL NETWORK: ANTIEPILEPTICS FOR EPILEPSY

Appendix 1: THE EPILEPSIES: PHARMACOLOGICAL TREATMENT BY SEIZURE TYPE – ADAPTED FROM NICE CG

Anti-epileptic drug (AED) options by seizure type

The table that follows provides a summary reference guide to pharmacological treatment. NICE Clinical Guidelines for Epilepsy updated the table in 2011 and is found in Appendix K in the NICE clinical guidelines. Medicines listed below are placed in alphabetical order and not by preference within that group. This table has been adapted to include medication that was not currently licensed and therefore not reviewed in the guidelines published in 2011. These changes are highlighted in RED text. *Tertiary care can be interpreted as third line option initiated and stabilised by specialist

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary* care	Do not offer AEDs (may worsen seizures)
Generalised tonic–clonic	Carbamazepine Lamotrigine Oxcarbazepine[a] Sodium valproate **Levetiracetam tablets only**	Clobazam[a] Lamotrigine Levetiracetam Sodium valproate Topiramate		(If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy suspected) Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Tonic or atonic	Sodium valproate	Lamotrigine[a]	Rufinamide[a] Topiramate[a]	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine[a] Sodium valproate	Ethosuximide Lamotrigine[a] Sodium valproate	Clobazam[a] Clonazepam Levetiracetam[a] Topiramate[a] Zonisamide[a]	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

EVIDENCE REVIEW FOR NHS SURREY AND SUSSEX

PRESCRIBING CLINICAL NETWORK: ANTIEPILEPTICS FOR EPILEPSY

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Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary* care	Do not offer AEDs (may worsen seizures)
Myoclonic	Levetiracetam[a] Sodium valproate Topiramate[a]	Levetiracetam Sodium valproate Topiramate[a]	Clobazam[a] Clonazepam Piracetam Zonisamide[a]	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Focal	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam[a] Gabapentin[a] Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate[a] Lacosamide **Perampanel** Phenobarbital Phenytoin Pregabalin[a] **Retigabine – Last option** Tiagabine Vigabatrin Zonisamide[a]	
Prolonged or repeated seizures and convulsive status epilepticus in the community	Buccal midazolam – Buccolam Brand Rectal diazepam[b] Intravenous lorazepam			

EVIDENCE REVIEW FOR NHS SURREY AND SUSSEX

PRESCRIBING CLINICAL NETWORK: ANTIEPILEPTICS FOR EPILEPSY

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Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary* care	Do not offer AEDs (may worsen seizures)
Convulsive status epilepticus in hospital	Intravenous lorazepam Intravenous diazepam Buccal midazolam	Intravenous phenobarbital Phenytoin		
Refractory convulsive status epilepticus	Intravenous midazolam[b] Propofol[b] (not in children) Thiopental sodium[b]			

[a] At the time of publication (January 2012) this drug did not have UK marketing authorisation for this indication and/or population (please see table 3 in appendix E of the NICE guideline for specific details about this drug for this indication and population). Informed consent should be obtained and documented.
[b] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (please see table 3 in appendix E of the NICE guideline for specific details about this drug for this indication and population). Informed consent should be obtained and documented in line with normal standards in emergency care.

APPENDIX 2 THE USE OF GENERIC ANTI-EPILEPTICS DRUGS IN PATIENTS WITH EPILEPSY

Final Generic Antiepileptics Final Ve

This has been sent out as a separate pdf for those unable to open the embedded document.

APPENDIX 3: EPILEPSY MEDICATION INFORMATION FOR IMPROVED MEDICINES OPTIMISATION AND REVIEWS. A LEARNING TOOL.

2013 06 19 Epilepsy Table version 7.xlsx

This has been sent out as a separate Excel Spreadsheet for those unable to open the embedded document.

APPENDIX 4: NEWER AED, BSUH TERTIARY EPILEPSY SPECIALIST OPINION, COST AND ANTICIPATED NUMBER OF PATIENTS

NICE Guidance and BSUH Tertiary Epilepsy Specialist Opinion	Cost/28days	No. of pts
1. ZONISAMIDE 1. Zonisamide can be considered as an adjunct: a) for treating absence seizures or myoclonus where the 1st line and adjunct AEDs have failed clinically. *NB: there are a smaller number of drugs effective for these seizure types* b) for patients who suffer cognitive side effects to the 1st line and adjunct AEDs. Zonisamide is more selective and therefore causes less incidence of cognitive sedation than the 1st line AEDs.	Usual maintenance dose 300mg – 500mg daily = £94.08 - £156.80 Cost offset by other AEDs that are stopped	30 – 50 new patients initiated a year

c) for overweight patients who don't tolerate topiramate. 2. Zonisamide can be considered as monotherapy In July 2012 the European Medicines Agency approved zonisamide **monotherapy** for the treatment of partial seizures (with or without secondary generalisation) in newly diagnosed epilepsy. There is a draft NICE technology appraisal (Nov 2011) to appraise the clinical and cost effectiveness of zonisamide monotherapy for the treatment of partial onset seizures in epilepsy.		
2. PIRACETAM should be available for treating patients with uncontrollable myoclonus e.g Lance-Adams syndrome. This is extremely rare.	At max dose of 24g = £102.38	1 new patient every 5 years
3. ESLICARBAZEPINE (note this has been reviewed in Surrey and PAD status is RED in paediatrics and Amber in adults) Eslicarbazepine can be considered for patients whose seizures respond well to carbamazepine or oxcarbazepine but for whom the side effects at a clinically effective dose are intolerable e.g. in young adults in work or college who are seizure free on carbamazepine or oxcarbazepine but who suffer cognitive sedation. Eslicarbazepine is more selective and there is a lower incidence of cognitive sedation. Advantages No auto induction; once a day; rapid dose titration; well tolerated ***Nb*** *Low dose carbamazepine or oxcarbazepine remain the drugs of choice for frontal lobe seizures, trigeminal neuralgia and paroxysmal symptoms in MS and other neuro- inflammatory conditions*	At max dose of 1.2g daily = £215.88 Cost offset by other AEDs that are stopped.	10 – 20 new patients initiated a year for all indications
4. RUFINAMIDE is an orphan drug used for Lennox Gaustaut syndrome. It has demonstrated efficacy in treating drop attacks that result in significant injuries for the patient (tonic/atonic seizures).	Max dose: Bodyweight over 70kg = 1.6g twice daily = £384.38 Bodyweight 50-70kg = 1.2g twice daily = £144	1 – 3 new patients year
5. LACOSAMIDE is very useful in patient with a psychiatric history,	Max dose 200mg	50 new patients

behavioural or learning difficulties, or affective disorders (depression, anxiety). It has a neutral side effect profile which does not worsen behaviour or mood. ***Nb*** *Levetiracetam, topiramate and possibly zonisamide should be avoided in this group since they are known to worsen psychiatric and behavioural symptoms* It has probable efficacy in mycoclonic and other generalised seizures (not yet licensed for this indication)	twice daily = £144.16 Cost offset by other AEDs that are stopped.	initiated a year

APPENDIX 5: CONSULTATION

SECONDARY CARE

From: Hargreaves Lynne (ROYAL SURREY COUNTY HOSPITAL NHS FOUNDATION TRUST)
Sent: 19 June 2013 11:46
To: Shah Jayesh (NHS SURREY AND SUSSEX COMMISSIONING SUPPORT UNIT)

Please find attached the Pharmacy Evaluations for lacosamide and zonisamide. The minuted outcomes were as follows:

Extract from DTC minutes 0312
4.3 Zonisamide (Zonegram ®) Capsules (Dr G Warner) Request to have this anti-epileptic drug available in pathway for Consultant Neurologist initiation only. No more expensive than other anti-epileptics. NICE guidance covers 1st line and 1st line adjuvant options but nothing beyond – i.e. not the setting in which this drug is used (subsequent line). **Action: Formulary status granted; Consultant Neurologist initiation only. Amber* drug.**

Zonisamide was audited post DTC at the November 12 meeting and its formulary status was confirmed as above.

Lacosamide was added onto formulary for a 6 month appraisal in Feb 2009.

I am currently awaiting a Consultant Application for Perampanel.

Regards, Lynne
Lynne Hargreaves
Formulary Pharmacist

Attachments embedded: RSCH 4 3 - Zonisamide Pharmacy; RSCH 0812012 - lacosamide.docx

CONSULTANT OPINION

Conversation with: JohnPhilip O'Dwyer , Neurologist, Frimley Park
Sent: 18 June 2013

General positive on excel table and will look in more detail with nurse Jan and comment back. Access to medication is essential as it may be that very last medication that is the lock and key to treat the patients seizures. Therefore all medication with evidence should be available at hospital level. Side effects, others risk v benefit for each individual patient.

Email from Graham Warner, Royal Surrey County Hospital on 4th July 2013

Handwritten notes on pdf copy therefore key points summarized below:

- Although little evidence for new drugs, each new drug will cure 5% of intractable epilepsies and therefore essential for access to these medicines.
- Deep Brain Stimulation is not standard but VPN is.

CARE PROVIDER AND CHARITY

From: Sandra Bale [mailto:sbale@youngepilepsy.org.uk]
Sent: 17 June 2013 17:21
To: Shah Jayesh (NHS SURREY AND SUSSEX COMMISSIONING SUPPORT UNIT)
Subject: RE: Epilepsy Table

Have had a quick look through. I think it would be very useful. I'll run it by our doctors here and will let you know their thoughts. Will give some thought to any other info that might be useful and will get back soon.

COMMUNITY PHARMACIST

From: Ray Bunn [mailto:ray.bunn@kamsons.co.uk]
Sent: 13 June 2013 13:07
To: Shah Jayesh (NHS SURREY AND SUSSEX COMMISSIONING SUPPORT UNIT)
Well done for this!!!! I know only too well how long these things take.

I think what you have included is all needed and useful.

An issue that crops up frequently in clinical practice is the difference between and when to use the immediate release and when to use the slow release preparations, particularly valproate and carbamazepine. Therefore clarification of this somehow would be useful.

Ray, Ray Bunn BPharm MBA MRPharmS, Community and Palliative Care Pharmacist, Kamsons Pharmacy & St Catherine's Hospice, Crawley, West Sussex RH11 9BA

CLINICAL COMMISSIONING GROUP

Discussions took place with the following GPs and positive feedback regarding excel tool. All stated choice of medication tends to be directed by secondary care.

Dr Raj Sekon, Medwyn Surgery Dorking, Surrey Downs CCG

Dr Chris Issac; Jenner House Surgery, North East Hampshire CCG

Dr Gardener, Lingfield Surgery, East Surrey CCG

Dr Andreas Pitsiaeli on 23 Jun 2013 wrote:

> *Hi Jayesh*
>
> *Speaking as a GP this sort of information is very useful for those drugs that we prescribe regularly*
>
> *On the whole the data is all relevant and crucially the need to measure drug levels, monitor other bloods and ability to crush etc are very practical*
>
> *It looks a detailed piece of work but could be worth it for GPs in the end*
>
> *I don't think this is a waste of time but I think that it was probably quite a lot for GPs to take on board and perhaps they then don't bother which is a pity*
>
> *Andreas*

PRIMARY CARE PHARMACIST

> *This is an amazing amount of work!*
>
> *Personally I would love to have the table as a resource with the background of the headings eg description of seizures. Not sure whether I would personally value the generic info but I'm sure others would.*
>
> *I will pass on to a couple of community pharmacists and to Steve who looks after The Meath in* Godalming.

Kim
Kim Jany
Primary Care Pharmacist

PROVIDER SERVICES

From: collins sarah (virgin care ltd)
sent: 19 june 2013 11:57
to: shah jayesh (nhs surrey and sussex commissioning support unit)

We discussed the table at our team meeting (dr irwin and dr hill at asph and myself) and below is a summary of our thoughts based on your original questions:

1. Is the table useful? - generally no, although information about whether medication can be crushed or given via peg could be helpful.

2. Is the table needed? No - because we use other documents

3. Is there anything missing in the table? No (and the comment was that it is very in-depth)

4. Is there anything that is not required in the table? Blood monitoring - we were interested to see that blood monitoring was included as nice does not recommend routine blood monitoring, and this is something that we definitely do not do in paediatrics (nice specifically say this is not necessary in most circumstances). This actually causes our parents a lot of confusion and distress as they do frequently get told by gps their child should be having regular blood tests and they won't get a repeat prescription unless the child does have bloods taken, but the child's paediatrician tells them they bloods are not needed. Continuity of care is important and this issue causes a lot of problems for our families, so there needs be clearer guidance within the table that blood monitoring is the exception not the rule in paediatrics (but i also thought this applied to adults as well).

5. Do prescribers who change epilepsy medication follow the steps 1.0, 1.1, 2.0, 3.0 as is recommended by nice or do you use an alternative method?

Would individual shared care be required for the newer medicine or will this table cover the key areas ? We use nice guidance and the bnfc for starting and changing medication in paediatrics. For newer medications it is under advice from tertiary neurology teams and bnfc. Shared care is required for paediatrics anyway.

Is there a document similar to this already on the market? Bnfc/ nice

Generally we felt this has limited use in paediatrics as it is always a specialist initialising treatment usually at secondary level, and as the prescriber taking responsibility for initialising treatment, dr irwin and dr hill said they would be extremely unlikely to look at the table and would refer to the bnfc. They also raised concerns about who takes responsibility for ensuring this table is kept up to date and accurate.

We felt that this table may be helpful for gps initialising treatment in adults, but for paediatrics it would be more useful to provide gps and pharmacies with basic advice to include things like not changing brands at each repeat prescription, not changing formulation (i.e. Liquid to tablets) at each repeat prescription, and providing 3 months supply of medication on repeat prescriptions (instead of 2-4 weeks) which would be of more benefit for our paediatric patients as these little things are more of a problem/ concern for our client base, and cause families huge amounts of unnecessary distress and anxiety. Changing from brand/ generic preparations has actual caused huge changes in seizure control and side effects for a number of patients recently (even aeds such as carbamazepine) and based on this and previous experience we never recommend changing preparation of any aed - this is something that we feel strongly needs to be highlighted within the table, and isn't.

I hope that makes sense!

With regards to audit of aeds, i do have a database that i started, looking at diagnosis and aed choice of the children we see at asph (the aim is we can then audit in the future). I don't know whether the information is what you had in mind, but if you let me know more specifically what you want, i can tell you if i can help!

COMMENTS FROM CONSULTATION 2: 7TH AUGUST 2013 TO 21ST AUGUST 2013

NEUROLOGY CONSULTANTS

From: Jeremy Stern, Neurologist
Sent: 16th August 2013

I am not sure of the purpose of the “epilepsy 101” section- there is nicely presented basic information, but the structure is patchy and so missing important areas of an overview like enzyme induction, polypharmacy and contraception that are important for non-specialist prescribers.

To enable auditing of prescribing against recommendations is given as a bullet point in the introduction. The conclusions/recommendations could be more explicit about this- I can’t see it being very useful for that in the current form.

P11 clinical reasons for discontinuation, this list is a bit idiosyncratic- I don’t think that Lamotrigine is generally considered particularly inefficacious (? epileptologists…).

There’s probably lots out there that uses this terminology but “Third-line” might be a better term than “tertiary” as that can have connotations of referral to a regional centre which often isn’t needed, and also changes over time as newest drugs become more familiar.

P19 The traffic lights look fine to me except:

- Perhaps vigabatrin sits better in Amber.
- Lacosamide seems fairly trouble-free and I am sure could stay in Amber * without a formal document, I can’t see a need for it- hasn’t caused problems so far.

P22- Carbamazepine is listed first for generalised seizures, but not usually chosen first by neurologists- it goes further than the Do not Offer AEDs box on the right.

Not sure what was meant by Keppra in red type, "tables only"- maybe I missed it somewhere in the text. Keppra is currently used more than carbamazepine for first line generalised epilepsy and like valproate has the advantage of not being an enzyme inducer.

Comments from Jayesh Shah on 21st August 2013:

Unclear if consultant is referring to the introduction text as "101" or the excel table. Additional information can be added if it is of use to those that will use it. The primary purpose of the paper is to agree the traffic light status of the antiepileptic medication.

In regards to audit the wording for this has slightly been amended to state "to support audit of anti-epileptic prescribing" once traffic light status agreed for each medication rather then "to be able to audit". NICE audits are places in the appendix below titled resources.

Happy to change tertiary to third line hospital initiated.

Your comment for lamotrigine has been noted and added to p11

Your comment regarding Vigbatrin will be discussed at PCN. Any reason why?

Comment on carbamazepine – please can you tell me when carbamazepine is used

Fianl comment. "tables only" should have been "tablets only". NICE stated evidence for levetiracetam is good and it will be cost effective when generic and until then the options were other medication as per table. Tablets is written here as this is cost effective as generic available but not for liquid. Any medicines in red in this table are changes we have made to the NICE original table.

From: Dr Jeffery Kimber, Consultant at SASH
Sent on: Tue 13th August 2013

I would make the following comments concerning the discussion document about AEDs

First I think it will not help patients ultimately if they can only access some drugs by travelling to a tertiary centre – this model is not repeated for any other neurology treatment (with perhaps the exemption of some MS drugs)

We know that 20% of epilepsy is intractable but can be improved by these newer AEDs and one cannot predict which patient will respond to which drug

I disagree that all patients with epilepsy need to see a consultant annually – those on stable medicine doses without side effects and with 2 year remission from seizures (and if female with no pregnancy

Comments from Jayesh Shah on 21st August 2013: Tertiary can be changed to third line inititated by a professional with specialist interest in epilepsy.

P9 of the document is from NICE regarding reviews. This states annually for adults and this is by GP unless patient wishes otherwise.

APPENDIX 6: PERAMPANEL

Perampanel Review by Jayesh Shah, Primary Care Pharmacist

1. Purpose of the Review

- To agree that the new medicine perampanel is positioned as Amber

2. Appropriateness

2.1 The patient: Patients over the age of 12 years with partial seizures with or without secondary generalisation who require adjunctive treatment.

2.2 The problem:

Definition: see main paper

Effects and prognosis: Despite the availability of several anti-epileptic drugs (AEDs) there continues to be unmet needs with existing AEDs, in terms of both efficacy and tolerability. Moreover, the rates of non-adherence to AEDs are high, ranging from 26% to 50%[1,2], leading to increased burden of disease.

Where seizure control has not been obtained with initial adjunctive therapies it is important that physicians have a choice of AEDs to allow a combination to be selected which can provide benefits in these highly refractory patients.

References:

1. Manjunath R, Davis KL, Candrilli SD, Ettinger AB. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. Epilepsy Behav 2009;14(2):372-8.
2. Zeber JE, Copeland LA, Pugh MJV. Variation in Antiepileptic Drug Adherence Among Older Patients with New-Onset Epilepsy. Annals of Pharmacotherapy 2010;44:1896-904.

2.3 The Intervention:

Perampanel is an anti-epileptic drug which is indicated for the adjunctive treatment of patients over the age of 12 years with partial seizures with or without secondary generalisation.

How does it work: Perampanel is a first-in-class Anti-Epileptic Drug (AED) that acts by blocking AMPA glutamate receptors in the brain. Activation of these receptors plays a critical role in seizure generation and spread.

Care setting: Initially secondary care and when stable primary care.

Frequency: As epilepsy is a chronic condition, treatment is continuous.

Recommended starting dose is 2mg orally once daily. Based on clinical response and tolerability, dose may be increased to maintenance dose of 4mg/day to 8mg/day. Depending upon individual clinical response and tolerability, dose may be increased to 12mg/day.

2.4 Alternative treatments:

Multiple alternative but would expect if on perampanel to have tried the common ones.

4. Summary of Key Points for Consideration

4.1 National guidance: Is there any national guidance relating to this topic e.g. NICE guidelines.

NICE guidance:

Perampanel has not been reviewed by NICE, but they have published an evidence summary: new medicine which suggests that it is an option for use within its licensed indication. (http://www.nice.org.uk/mpc/evidencesummariesnewmedicines/ESNM7.jsp)

SMC guidance:

Perampanel has been reviewed by the Scottish Medicines Consortium (SMC) and is accepted for restricted use within NHS Scotland.

Indication under review: Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

SMC restriction: use as a second-line adjunctive treatment in patients with refractory partial onset epilepsy. Treatment should be initiated only by physicians who have appropriate experience in the treatment of epilepsy.

(http://www.scottishmedicines.org.uk/SMC_Advice/Advice/819_12_perampanel_Fycompa/Briefing_Note_perampanel_Fycompa

4.2 Efficacy: For patients who are persistently drug resistant (refractory), perampanel once daily represents an effective option as second adjunctive therapy.

Three global, phase III, double-blind, placebo-controlled, randomised studies were conducted to investigate the clinical efficacy and safety of perampanel.[1-3] An open-label extension (OLE) to these studies is ongoing (study 307).[4]

- The primary efficacy endpoint was a 50% responder rate. The 50% responder rate was significantly higher in the perampanel 4 mg/day, 8 mg/day and 12 mg/day groups than the placebo groups. Other endpoints included the percent change in seizure frequency per 28 days during treatment relative to baseline, and the percent change in the frequency of complex partial plus secondarily generalised seizures.

- A statistically significant effect on the reduction in 28-day seizure frequency compared to placebo was observed with perampanel at doses of 4 mg/day (study 306)[3], 8 mg/day (studies 304, 305 and 306)[1-3], and 12 mg/day (studies 304 and 305).[1,2]

- These studies show that once-daily administration of perampanel at doses of 4 mg/day to 12 mg/day was significantly more efficacious than placebo as adjunctive treatment in this population.

- The majority of adverse events reported in the phase III studies were mild to moderate. The only very common adverse events were dizziness and somnolence, the prevalence of which decreased with treatment duration.[1-3] The rate of treatment discontinuation as a result of an adverse reaction was 1.7%, 4.2% and 13.7% in patients randomised to receive perampanel at the recommended doses of 4 mg, 8 mg and 12 mg daily, respectively, and 1.4% in patients randomised to receive placebo. The adverse events most commonly leading to discontinuation were dizziness and somnolence.[5] For expected adverse events please refer to the perampanel SPC.[5]

References:

1. French J A et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 2012; 79: 589–596.
2. French J A et al Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305. Epilepsia 2013; 54(1): 117-125
3. Krauss G L et al.Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 2012; 78: 1408–1415.
4. Krauss G L et al. Perampanel, a selective, noncompetitive a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: Interim results from phase III, extension study 307. Epilepsia 2013; 54(1): 126-134
5. Fycompa (perampanel) Summary of Product Characteristics (SPC)

4.3 Potential Benefits over existing therapy

Perampanel demonstrated similar safety and efficacy in adolescents as in adult patients.

Patients with a history of secondarily generalised seizures achieved an even greater seizure frequency reduction and response rate.

Quality of life was significantly improved for patients receiving perampanel versus placebo suggesting that the benefit of perampanel treatment decreases the human burden associated with partial-onset epilepsy.

Perampanel is a once-daily tablet, which may help facilitate adherence to treatment.

Perampanel is formulated in a range of dose strengths to allow dosing flexibility - as 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg film-coated tablets. Patients are initiated on 2 mg/day, then the dose should be titrated according to the individual patient response.

4.5 Budgetary Impact

No additional monitoring is required for perampanel recipients other than that normally expected with AEDs.

A flat-pricing scheme for NHS acquisition cost has been implemented, which equates to a cost of £5 per patient per day across all tablet strengths so should a patient require a dose increase there is no associated increase in cost.

There are no perceived additional service costs associated with the use of perampanel over and above those allied with routine management of side effects and regular patient assessment.

4.5.1 Cost: As above, a flat-pricing scheme for NHS acquisition cost has been implemented, which equates to a cost of £5 per patient per day across all tablet strengths

4.5.2 Precedent setting: The cost of newer antiepileptics is fairly standard.

EVIDENCE REVIEW FOR NHS SURREY AND SUSSEX

PRESCRIBING CLINICAL NETWORK: ANTIEPILEPTICS FOR EPILEPSY

Evidence retrieved

Study	Design	Numbers	Results	Safety and tolerability
Title: Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. **Citation:** Neurology 2012; 79: 589–596. **Author(s):** French J A et al.	Randomised, double-blind, placebo-controlled, dose-escalation, multi-centre, parallel-group Duration: 19 weeks (6-week dose titration, 13-week dose maintenance) Treatment groups: perampanel 8mg/day perampanel 12mg/day placebo	N=388	Primary Efficacy 50% responder rate perampanel 8mg/day: 37.6% (P=0.0760) perampanel 12mg/day:36.1% (P=0.0914) placebo: 26.4% Secondary median % change in seizure frequency per 28 days: perampanel 8mg/day: -26.3% (P=0.0261) perampanel 12mg/day: -34.5% (P=0.0158) placebo: -21.0% median % change in frequency of complex partial plus secondarily generalised seizures: perampanel 8mg/day: -33.0% (P=0.0020) perampanel 12mg/day:	Incidence of TEAEs: perampanel 8mg/day: 117 (88.0%) perampanel 12mg/day: 123 (91.8%) placebo: 100 (82.6%) Most frequently (≥10%) reported TEAEs: perampanel 8mg/day: dizziness, somnolence and headache perampanel 12mg/day: dizziness, somnolence, irritability, headache, fall and ataxia placebo: somnolence and headache Incidence of SAEs: perampanel 8mg/day: 8 (6.0%) patients perampanel 12mg/day: 9 (6.7%) patients placebo: 6 (5.0%) patients

			-33.1% (P=0.0081) placebo: -17.9%	
Title: Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305. **Citation:** Epilepsia 2013; 54(1): 117-125 **Author(s):** French J A et al.	Randomised, double-blind, placebo-controlled, dose-escalation, multi-centre, parallel-group Duration: 19 weeks (6-week dose titration, 13-week dose maintenance) Treatment groups: perampanel 8mg/day perampanel 12mg/day placebo	N=386	Primary Efficacy 50% responder rate: perampanel 8mg/day: 33.3% (P=0.002) perampanel 12mg/day:33.9% (P<0.001) placebo: 14.7% Secondary median % change in seizure frequency per 28 days: perampanel 8mg/day: -30.5% (P<0.001) perampanel 12mg/day: -17.6% (P=0.011) placebo: -9.7% median % change in frequency of complex partial plus secondarily generalised seizures:	Safety and tolerability Incidence of TEAEs: perampanel 8mg/day: 112 (86.8%) perampanel 12mg/day: 104 (86.0%) placebo: 93 (68.4%) Most frequently (≥10%) reported TEAEs: perampanel 8mg/day: dizziness, fatigue and somnolence perampanel 12mg/day: dizziness, somnolence, fatigue and headache placebo: headache Incidence of SAEs: perampanel 8mg/day: 10 (7.8%) patients perampanel 12mg/day: 12 (9.9%) patients placebo: 7 (5.1%) patients

			perampanel 8mg/day: -32.7% (P<0.001) perampanel 12mg/day: -21.9% (P=0.005) placebo: -8.1%	
Title: Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. **Citation:** Neurology 2012; 78: 1408–1415. **Author(s):** Krauss G L et al.	Randomised, double-blind, placebo-controlled, dose-escalation, multi-centre, parallel-group Duration: 19 weeks (6-week dose titration, 13-week dose maintenance) Treatment groups: perampanel 2mg/day perampanel 4mg/day perampanel 8mg/day	N=706	Primary Efficacy 50% responder rate: perampanel 2mg/day: 20.6% (P=ns) perampanel 4mg/day: 28.5% (P=0.013) perampanel 8mg/day: 34.9% (P<0.001) placebo: 20.6% Secondary median % change in seizure frequency per 28 days: perampanel 2mg/day: -13.6% (P=ns) perampanel 4mg/day: -23.3% (P=0.003) perampanel 8mg/day: -30.8%% (P<0.001) placebo: -10.7%	**Safety and tolerability** Incidence of TEAEs: perampanel 2mg/day: 111 (61.7%) perampanel 4mg/day: 111 (64.5%) perampanel 8mg/day: 121 (71.6%) placebo: 101 (54.6%) Most frequently (≥10%) reported TEAEs: perampanel 2mg/day: dizziness and somnolence perampanel 4mg/day: dizziness and headache perampanel 8mg/day: dizziness, somnolence and headache placebo: dizziness Incidence of SAEs: perampanel 2mg/day: 6 (3.3%) patients perampanel 4mg/day: 6 (3.5%) patients perampanel 8mg/day: 6 (3.6%) patients placebo: 9 (4.9%) patients

	placebo		median % change in frequency of complex partial plus secondarily generalised seizures: perampanel 2mg/day: -20.5% (P=ns) perampanel 4mg/day: -31.2% (P=0.007) perampanel 8mg/day: -38.7% (P<0.001) placebo: -17.6%	
Title: Perampanel, a selective, noncompetitive a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: Interim results from phase III, extension study 307. **Citation:** Epilepsia	Open-label extension phase of the double-blind, placebo-controlled, dose-escalation, parallel-group studies to evaluate the efficacy and safety of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures Duration: up to 5	N=1218	Primary Efficacy median % change in seizure frequency per 28 days 50% responder rate: weeks 1-13: 31.1% weeks 14-26: 41.4% weeks 27-39: 45.3% weeks 40-52: 46.9% weeks 53-65: 50.7% weeks 66-78: 51.1% weeks 79-91: 51.7% weeks 92-104: 62.7% Safety and tolerability	

2013; 54(1): 126-134 **Author(s):** Krauss G L et al.	years or until product becomes available commercially Except ion: UK and India, where total duration is 272 weeks (16-week blinded conversion period and 256-week maintenance period) >90% of patients received perampanel >8-12mg/day		Incidence of TEAEs: perampanel <4mg/day (n=1): 1 (100%) perampanel 4mg/day (n=15): 13 (86.7%) perampanel >4-8mg/day (n=86): 83 (96.5%) perampanel >8-12mg/day (n=1,084): 940 (86.7%) Incidence of SAEs: perampanel <4mg/day (n=1): 0 perampanel 4mg/day (n=15): 2 (13.3%) perampanel >4-8mg/day (n=86): 11 (12.8%) perampanel >8-12mg/day (n=1,084): 144 (13.3%)	

APPENDIX 7. MIDLANDS THERAPEUTICS REVIEW AND ADVISORY COMMITTEE LACOSAMIDE EVIDENCE REVIEW

MTRAC EVIDENCE REVIEW Lacosamide.

This pdf has also been sent as a separate attachment for those unable to open the embedded document.

This review recommends:
Treatment with lacosamide should be initiated and stabilised within secondary care. It is then appropriate for GPs to prescribe lacosamide over the longer term.

Summary of evidence:

Category B*: suitable for restricted prescribing under defined conditions*

Q3 rating: The evidence for the efficacy of lacosamide was considered to be relatively strong, based on three double-blind, randomised controlled trials (RCTs) comparing lacosamide with placebo. Compared with placebo, treatment with lacosamide 400 mg/day was associated with a greater decrease in seizure frequency, with a higher proportion of patients experiencing at least a 50% decrease in seizure frequency; evidence for efficacy was weaker for the 200 mg/day dose. As a number of established alternative therapies exist, lacosamide is considered to have a relatively low place in therapy.

The Q rating relates to the drug's position on the effectiveness indicator grid.
The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.

APPENDIX 8: RESOURCES

1. NICE Web-based Pathway This pathway covers the diagnosis and management of the epilepsies in children, young people and adults in primary and secondary care. This pathway assumes that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

   This pathway recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.

2. Epilepsy Online Education Tool This module has been produced by BMJ Learning in collaboration with NICE. This module should help you know:
   - How best to care for patients with epilepsy
   - How best to communicate with patients with epilepsy so they can help to manage their condition
   - When you should refer patients to a specialist
   - How best to care for women of childbearing potential with epilepsy.

3. Classification
   - Diagram to Explain Classification with 2010 Terminology.
   - ILAE Organization of Epilepsies – New 2010 classification

4. Clinical Guidelines:
   - ILAE How Evidence Based Guidelines Developed for the Treatment of Epilpetic Seizures with AEDs
   - NICE 2012 Epilepsy Clinical Guidelines

5. Care Planning:
   - Care Planning Tool for System One GP Clinical Systems. Epilepsy Action has been working closely with NHS Yorkshire and the Humber to develop a patient care planning template within SystmOne. The template guides clinicians through the annual review with an aim to improving the health and healthcare of a patient with epilepsy.
   - Epilepsy Care Action Plan

5. Audits NICE Clinical audit tools are developed to support the implementation of NICE guidance. The aim is to assist organisations with the audit process, thereby helping to ensure that practice is in line with the NICE recommendations. These audits can be amended to match the traffic light agreement for antiepileptics.
   - CG137 Epilepsy: pharmacological treatment by seizure type
   - CG137 Epilepsy: pharmacological treatment by syndrome

APPENDIX 9: LIST OF NICE QUALITY STANDARDS IN EPILEPSY

Statement 1. Adults presenting with a suspected seizure are seen by a specialist in the diagnosis and management of the epilepsies within 2 weeks of presentation.

Statement 2. Adults having initial investigations for epilepsy undergo the tests within 4 weeks of them being requested.

Statement 3. Adults who meet the criteria for neuroimaging for epilepsy have magnetic resonance imaging.

Statement 4. Adults with epilepsy have an agreed and comprehensive written epilepsy care plan.

Statement 5. Adults with epilepsy are seen by an epilepsy specialist nurse who they can contact between scheduled reviews.

Statement 6. Adults with a history of prolonged or repeated seizures have an agreed written emergency care plan.

Statement 7. Adults who meet the criteria for referral to a tertiary care specialist are seen within 4 weeks of referral.

Statement 8. Adults with epilepsy who have medical or lifestyle issues that need review are referred to specialist epilepsy services.

Statement 9. Young people with epilepsy have an agreed transition period during which their continuing epilepsy care is reviewed jointly by paediatric and adult services.

In addition, quality standards that should also be considered when commissioning and providing a high-quality epilepsy service are listed in related NICE quality standards.