Professor Carole Longson, Director of the Health Technology Evaluation Centre at NICE said:

“Seizures can be extremely debilitating as they can interfere with a person's social life, employment and other daily activities. While there are a number of effective anti-epileptic drugs already widely available on the NHS, people can have different responses to them. It's therefore very important for doctors to have a broad range of options so that they can find the right combination for their patients.”
Prophylactic treatment is not a guarantee that seizures will be prevented

The benefit of seizure prevention must be weighed against the potential for anticonvulsant drug toxicity.

Seizures occur as part of acute illnesses
Metabolic disorders
--hypoglycemia
--hyponatremia

Neurosurgical conditions Risk(%)  
--stroke 6-12 
--subarachnoid hemorrhage >10 
--brain tumor 45-50 
--closed head injury 4-10 
--intracranial surgery 17
The prevention and early treatment of seizures is important following neurosurgery, because

- seizures can precipitate serious complications
  secondary intracranial bleeding
  hypoxia
  aspiration
  raised intracranial pressure

- seizures can be provoked by
  Hyponatremia
  Acidosis
  Alcohol withdrawal
  Hypoxemia
  Sepsis
  Steroid therapy
  Postoperative hematoma
Found 150 studies with search of: levetiracetam

Hide studies that are not seeking new volunteers.
Hide studies with unknown recruitment status.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study Description</th>
</tr>
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<td>1</td>
<td>Unknown</td>
<td>Levetiracetam (Keppra) Tolerability in Chronic Abusing Methadone-Maintained Patients.</td>
</tr>
<tr>
<td>2</td>
<td>Completed</td>
<td>Safety Study Of Intravenous Levetiracetam.</td>
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<tr>
<td>3</td>
<td>Completed</td>
<td>A Bioequivalence Study Of Levetiracetam Versus Keppra.</td>
</tr>
<tr>
<td>4</td>
<td>Completed</td>
<td>Long Term Follow-up Study Of Keppra XR (Levetiracetam XR) for Partial Seizures.</td>
</tr>
</tbody>
</table>

U.S. Food and Drug Administration

Search for levetiracetam in all of FDA

Keppra (levetiracetam) Tablets and Oral Solution and Keppra ...
Levetiracetam is licensed for the combination treatment of partial seizures with or without secondary generalization.

It is not recommended for children younger than 16 years.
It has no reported drug interactions.
Overview

- Introduction
- Mechanism of action of AED
- The SV2A Ligands
- Application & Evidence in Neurosurgery
- Future Outlook

Introduction

- Epilepsy is a complex phenotype with multiple etiologies.
- Loscher and Schmidt, 1988: seizures induced by electrical stimulation
- Bouilleret et al., 1999: seizures induced by chemical treatment
Introduction

- Two traditional models employed in routine screening and identification of new AEDs are:
  - the maximal electroshock (MES)
  - subcutaneous pentylenetetrazol (PTZ or Metrazol) tests

Pathophysiology of the form of Acquired Epilepsy:

- Massive release of the excitatory amino acid neurotransmitter glutamate
- Excessive activation of postsynaptic glutamate receptors

The neurons that survive in the penumbra region are the underlying substrates for ischemia-induced epileptogenesis.
Mechanism of action of AED

- Three major classes of molecular targets are believed to be relevant for limiting seizure activity including:
  - (1) voltage-gated sodium and calcium channels
  - (2) GABA receptors
  - (3) ionotropic glutamate receptors (i.e., NMDA or N-methyl-D-aspartate, AMPA, or a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptors.

SV2A Ligands

synaptic vesicle protein 2 (SV2), was originally identified with a monoclonal antibody generated against cholinergic vesicles from the electric organ of the electric ray.
Three forms of SV2 are expressed in all brain regions.

SV2 is a 12-transmembrane protein incorporated in the membrane of synaptic vesicles, present in the presynaptic terminal.

SV2A is the most widely distributed in the brain and also present on many neuroendocrine cells.

Approximately 12,000 compounds were screened in vitro for SV2A binding affinity, 900 compounds were examined for seizure protection in audiogenic susceptible mice, and 30 compounds were characterized more widely in animal models of seizures and epilepsy.
The overall postoperative epilepsy incidence is 17% with a wide range from 3 to 92% during a follow-up period of 5 years.


1/5 of patients undergoing aneurysm surgery will develop postoperative seizures.

Operations for MCA aneurysms are associated with a 38% risk of epilepsy.

Operations for Acom A aneurysms have a 21% risk of epilepsy.

Arteriovenous malformations have a 20% risk of postoperative epilepsy.

Cerebral abscess is associated with a 72% incidence of epilepsy.


TRAUMATIC BRAIN INJURY

Early epilepsy; in post traumatic brain injury, is an indication for anticonvulsants because two thirds of these patients have more than one fit and 10% develop status epilepticus.

Three factors increase the risk of late epilepsy

1) Intracranial haematoma (35%);
2) Early epilepsy (25%);
3) Depressed fracture (3–70%).

AED Prophylaxis indication in Neurosurgery

- 1) be at significant risk for seizures,
- 2) have some expectation that the seizures might cause harm,
- 3) be at low risk of an adverse drug reaction from the AED.

Nathan B.F. Epilepsy Currents, Vol. 9, No. 3 (May/June) 2009 pp. 71–72
An American Academy of Neurology clearly suggests that AED prophylaxis is useful for severe traumatic brain injury but does not recommend it for newly diagnosed brain tumors


RCT study in add-on phenytoin of supratentorial neurosurgery did not find AED prophylaxis to be beneficial


Under Pubmed search engine for “levetiracetam and seizure prophylaxis” since Dec, 2011 with limitation including Humans, Randomized Controlled Trial, English, and published in the last 10 years, there is only one RCT study


The study of levetiracetam add-on for drug-resistant localization related (partial) epilepsy with medication-resistant partial seizures.


**Application & Evidence in Neurosurgery**

-The newer AED

- Promising ideal drug that will be an alternative AEDs for prophylaxis and seizure control