Psychiatric Aspects of Epilepsy
Challenges in Diagnosis and Treatment

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Prevalence of psychiatric disorders in epilepsy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Epilepsy (range)</th>
<th>Population (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>11 - 44</td>
<td>2 - 4^1</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>15 - 25</td>
<td>2,5 - 6,5^2</td>
</tr>
<tr>
<td>Suicide</td>
<td>5 - 10</td>
<td>1 - 2^6</td>
</tr>
<tr>
<td>Psychoses</td>
<td>2 - 8</td>
<td>0,5 - 0,7^3</td>
</tr>
<tr>
<td>Dissociative seizures</td>
<td>1 - 10</td>
<td>0,1 - 0,2^4</td>
</tr>
<tr>
<td>ADHD</td>
<td>25 - 30</td>
<td>2 - 10^5</td>
</tr>
<tr>
<td>Personality disorders</td>
<td>20-60</td>
<td>5-13</td>
</tr>
</tbody>
</table>

All psychiatric disorders are 5 -10 times more common in epilepsy as compared to the general population.

^1Anthony et al. Epidemiol Rev 1995
^2Jacoby et al. Epilepsia 1996
^3Kessler et al. Arch Gen Psychiatry 1994
^5Costello J Am Acad Child Adolesc Psychiatry 1989
^6Barraclough Acta Psychiatr Scand 1987
Psychiatric aspects of epilepsy

Periictal Psychopathology
Depression
Psychosis
AED related disorders
Preictal Dysphoria

- Irritability, emotional lability, depression
- Prevalence: 13% of unselected cases

PTSD ?

17-year old boy with panic-attacks

- Experience of bomb attack during Chechen war
- Since then panic attacks
- Asylum seeker in Berlin
- Speaks no German
- Several attacks every day
The vegetarian who ate a sausage with curry sauce

Josef G Heckmann, Christoph JG Lang, Hermann Stefan, and Bernhard Neundörfer

A 61-year-old woman visited the canteen for lunch with a male colleague. The colleague was greatly astonished to see the woman, a passionate vegetarian, order a sausage with curry sauce. Furthermore, during conversation he noticed that she was a little confused, although she was able to walk and carry her tray without difficulty. Because of the woman’s changed behaviour, her colleague arranged a transfer to a hospital for her. On admission, the patient was slightly disorientated, but no focal neurological abnormalities were detected. She had no history of febrile convulsions or previous epileptic seizures and no relatives had epilepsy. EEG showed a pattern of continuous generalised 2–3 Hz spike and wave complexes consistent with a non-convulsive status epilepticus (figure). A dose of 6 mg clonazepam led to the disappearance of this pattern and disclosed predominant β-wave activity. Further examinations, including magnetic resonance tomography of the brain and analysis of CSF, were unremarkable. Treatment with seizure. However, it is essential to do a thorough examination because many structural frontal-lobe lesions can cause this subtype of non-convulsive status epilepticus.5

From our patient we learn three lessons. First, non-convulsive status epilepticus can manifest itself with slight or moderate signs and symptoms. It was the very phenomenon that our vegetarian patient ordered sausage with curry sauce that led to her transfer to the hospital. Thus it has to be assumed that a number of patients in a state of non-convulsive status epilepticus are not diagnosed or only diagnosed at a later stage.2 Second, the first clinical presentation with non-convulsive status epilepticus of our
Ictak Aggression in FLE
Neurology 2009

Jerry J. Shih, MD
Thabele Leslie Mazwi,

DIRECTED AGGRESSIVE BEHAVIOR IN FRONTAL LOBE EPILEPSY: A VIDEO-EEG AND Ictal SPECT daily at time of presentation, despite multiple medication trials to treat TS.

The electrographic ictal changes on a condensed transverse montage during a seizure. (B) Ictal SPECT showed focal areas of hyperperfusion in the right lateral and orbitofrontal cortex and left medial frontal cortex. Ictal SPECT scan was obtained using Technitium-99 and superimposed upon interictal SPECT scan and coregistered to MRI (SISCOM)
Depression in Epilepsy
often unrecognised and untreated

• 34% of 70 candidates for epilepsy surgery were diagnosed „significant Depression“. All were untreated (1)

• 63% of patients with spontaneous depression and 54% of patients with iatrogenic depression were symptomatic for longer than 1 year before treatment was started (2)

• 26% of 44 children with epilepsy were diagnosed with depression. All were so far undiagnosed and untreated (3)

1 Paradiso, Herman, Blumer et al., JNNP 2001
2 Kanner et al. The use of sertraline in patients with epilepsy: is it safe? Epilepsy Behav. 2000
3 Ettinger et al. Symptoms of depression and anxiety in pediatric epilepsy patients. Epilepsia. 1998
Why is depression in epilepsy often not recognized?

**Doctors:**
- no experience with antidepressants
- no psychiatric training
- no time

**Patients:**
- don’t complain about psychiatric symptoms
- don’t accept a psychiatric diagnosis

**Doctors and patients:**
- believe that depression is a normal reaction in epilepsy
Prevalence of „Major Depression“ correlates with severity of epilepsy

**General population:** 11 %\(^1\)
**Unselected patients with epilepsy:** 17 - 22 %\(^{1,2}\)
**Pharmacoresistent focal Epilepsy:** 44 - 55 %\(^{3,4}\)

\(^1\) Tellez-Zenteno et al. Epilepsia 2007
\(^2\) Edeh & Toone Neuropsychiatry, Neuropsychol Behav Neurol 1990
\(^3\) Blumer et al. J Neuropsychiatry Clin Neurosci 1995
\(^4\) Gilliam et al. Epilepsia et al. 2004
Depression is a predictor for quality of life in epilepsy

Gilliam and Kanner. Epilepsy Behav. 2002;3:S2-9
Depression is a predictor for poor prognosis

Patients with epilepsy + depression

- tolerate AED worse.\textsuperscript{1, 2}
- complain about memory problems.\textsuperscript{1, 2}
- are often pharamacoresistant.\textsuperscript{3}
- have poorer surgery results.\textsuperscript{4}

1 Cramer et al. Epilepsy and Behaviour 2003
2 Kanner et al. Epilepsia 2007
3 Hitiris et al. Epilepsia 2007
4 Kanner et al. Annals Neurology 2006
Interictal Dysphoric Disorder (IDD)  
8 key symptoms  
(described by Dietrich Blumer)

- **Labile depressive symptoms**  
  1. Depressive mood  
  2. Anergia  
  3. Pain  
  4. Insomnia  

- **Labile affective symptoms**  
  5. Fear  
  6. Anxiety  

- **Specific symptoms**  
  7. Paroxysmal irritability  
  8. Euphoric moods
Depression in epilepsy

The Blumer syndrome (IDD)

Does the Blumer syndrome exist? Is it specific for epilepsy? Is it specific for temporal lobe epilepsy?
Survey Among 67 Neurologists
Gillian et al. Epilepsia 2004

1. Do you routinely screen epilepsy patients for depression in your outpatient clinics?
   Yes: 18%

2. If a randomized controlled trial demonstrated that the treatment of depression improved compliance and health-related quality of life in epilepsy patients, would you systematically screen for depression in your outpatient clinic?
   Yes: 85%
NDDI-E
Neurological Disorders Depression Inventory for Epilepsy

1. Everything is a struggle.

2. Nothing I do is right.

3. Feel guilty

4. I’d be better off dead.

5. Frustrated

6. Difficulty finding pleasure

Advantage
Short, no confounder like side effects of AED

Cave
Screening not diagnostic tool

Rapid detection of major depression in epilepsy: a multicentre study
Frank G Gilliam, John J Barry, Bruce P Hermann, Kimford J Meador, Victoria Vahle, Andres M Kanner
Rapid detection of major depression in epilepsy: a multicentre study
Frank G Gilliam, John J Barry, Bruce P Hermann, Kimford J Meador, Victoria Vahle, Andres M Kanner

An NDDI-E Score > 15 supports the diagnosis Major Depression.

- Specificity 80%
- Sensitivity 81%
- Positive predictive value 62%
Depression in Epilepsy
The role of the mesial temporal lobe

Frequency and or severity of depression correlates with:

- Clinical diagnosis of TLE
  - Schmitz et al. Epilepsy Research 1999
- Hippocampus sclerosis
  - Quiske et al. Epilepsy Research 2000
- Amygdala-Volumetry
  - Richardson et al. Epilepsy Behav 2007
- Hippocampal spectroscopy NAA
  - Gilliam et al. Neurology 2007
- Temporal FDG PET hypometabolism
- Reduced 5HT1A PET hippocampal binding
Depression in epilepsy
Trigger

Plus
Psychoreactive problems
Seizure related anxiety
(loss of control),
Social discrimination
(learned helplessness),
Unprepared seizure freedom
(burden of normality)
Patients with depression have a 4-7x increased epilepsy risk.

- Forsgren & Nystrom Epilepsy Res 1990
- Hesdorffer et al. Epilepsia 1998
Mania in epilepsy

Three typical presentations

1. Brief euphoric episodes related to affective instability (Blumer syndrome)
2. Mania following epilepsy surgery
3. Postictal maniform psychosis

Interictal „endogenous“ mania is rare in epilepsy
History
Psychosis and epilepsy
20th century

1. Alternative psychoses  Landolt  1953
2. Interictal psychoses  Slater  1963
3. Postictal psychoses  Logsdail & Toone  1988
Psychosis and type of epilepsy

Relationship to TLE

1. Alternative psychoses  -
2. Interictal psychoses    +
3. Postictal psychoses     ++++
Epidemiology of psychoses in epilepsy

- **Incidence** 0,3 %\(^1\)
- **Prevalence**
  - General population 2 – 3 %\(^2\)
  - Hospitals 4 – 9 %\(^3\)
  - Surgery candidates 7 - 16 %\(^4\)

1 Onuma et al. Psychiatry Clin Neurosci 1995
4 Savard et al. in: Lüders: Epilepsy Surgery 1991
Interictale Psychoses in Epilepsy
Risk Factors

- Age of onset: Early
- Epilepsy syndrome: TLE / FLE
- EEG: Temporal foci
- Seizure types: Complex focal, multiple types
- AED Response: Pharmacoresistence
- Severity: Status epilepticus
- Laterisation: Left or bilateral
- Interval: ~ 14 years
- Seizure frequency: Low
- Personality: Paranoid
Psychoses and seizure activity: Relative frequency in two hospitals
Schmitz & Wolf 1995, Schmitz et al. 1999

- **Postictal Psychoses**
  - London: n = 26 (70%)
  - Berlin: n = 28 (60%)

- **Interictal Psychoses**
  - London: n = 26 (17%)
  - Berlin: n = 28 (20%)

- **Alternative Psychoses**
  - London: n = 26 (9%)
  - Berlin: n = 28 (10%)

- **Ictal Psychoses**
  - London: n = 26 (4%)
  - Berlin: n = 28 (10%)
Postictal Psychoses

Latency: Maximum 7 days
Duration: Hours, days
Psychopathology: Paranoid-halluzinatory, manic
EEG: „Epileptic“ (but no Status)
Therapy: Short time antipsychotics, benzos
Post-ictal (PiP) versus inter-ictal psychoses (IiP): Psychopathology

PiP: n = 45, IiP: n = 126

- Delusion of reference
- Delusion of persecution
- Religious delusion
- Acoustic hallucinations
- Visual hallucinations
- Delusion of grandiosity
- Logorrhea

Manic flavour

Kanemoto 2002
**PiP versus IiP: Aggression**

Kanemoto et al. 1999

<table>
<thead>
<tr>
<th></th>
<th>PiP</th>
<th>IiP</th>
<th>Postictal Confusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes</td>
<td>57</td>
<td>62</td>
<td>134</td>
</tr>
<tr>
<td>Aggression *</td>
<td>23 %</td>
<td>5 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Reactive Aggression</td>
<td>0 %</td>
<td>0 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Suicide attempts *</td>
<td>7 %</td>
<td>2 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

* p < 0.5
# Epidemiology of postictal psychosis

## Prevalence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected outpatients</td>
<td>2 %</td>
<td>Schmitz 95</td>
</tr>
<tr>
<td>Pharmacoresistant TLE</td>
<td>9 %</td>
<td>Kanemoto 96</td>
</tr>
<tr>
<td>TLE + hippocampus sclerosis</td>
<td>15 %</td>
<td>Kanemoto 96</td>
</tr>
<tr>
<td>TLE + HS + atrophy</td>
<td>56 %</td>
<td>Kanemoto 96</td>
</tr>
</tbody>
</table>

## Incidence

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Percentage</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>6 - 10 %</td>
<td>Kanner 96, 01</td>
</tr>
</tbody>
</table>
Psychotropic Effects of Anticonvulsants
Individuell unterschiedliche Therapieansprüche
How to choose the optimal anticonvulsant

1. Epileptic syndrome
2. Side effect profile
   - Psychotropic effects
   - Weight
   - Teratogenicity
3. Comorbidity
   - Psychiatric
   - Hepatic
   - Renal
4. Costs
### AED: Positive Psychotropic Effects
demonstrated in controlled trials

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Mania</th>
<th>Bipolar disorder</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>0</td>
<td>(+)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valproate</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Topiramate</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Pregabalinine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

+ = positive results, - negative results, 0 = no published data
Depression in AED trials
Synopsis of controlled and open trials

- High risk \( \geq 10\% \)
- Moderate risk 5-9\%
- Low risk < 5\%

Mula & Sander Drug Safety 2007
Inzidence of psychoses in controlled trials


<table>
<thead>
<tr>
<th>Medication</th>
<th>Psychosen (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigabatrin</td>
<td>2,5</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0,2</td>
</tr>
<tr>
<td>Felbamate</td>
<td>0,02</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>0,5</td>
</tr>
<tr>
<td>Topiramate</td>
<td>0,8</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>0,8 - 2</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>-</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0,3 - 0,7</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>1,9 - 2,3</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>0 - 0,6</td>
</tr>
</tbody>
</table>

Since Vigabatrin psychiatric patients are excluded from trials
## Psychiatric status and psychotropic AED effects

**Table 13.4** Potential psychiatric risks of antiepileptic drugs in patients with psychiatric comorbidity

<table>
<thead>
<tr>
<th>Patient’s pre-existing mental state</th>
<th>AEDs which should be used carefully</th>
<th>Possible side effect</th>
<th>AEDs which should be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional lability</td>
<td>PHB, VGB, TPM, TGB, ZNS, LEV</td>
<td>Major depression</td>
<td>LTG, CBZ, VPA</td>
</tr>
<tr>
<td>Anxious</td>
<td>LTG, LEV</td>
<td>Anxiety disorder</td>
<td>PGB, GBP, BZD</td>
</tr>
<tr>
<td>Paranoid</td>
<td>DPH, VGB, TPM, LEV</td>
<td>Schizophrenic psychosis</td>
<td>CBZ, VPA</td>
</tr>
<tr>
<td>Agitation</td>
<td>LTG</td>
<td>Insomnia, anxiety, hypomania</td>
<td>GBP, PGB, BZD</td>
</tr>
<tr>
<td>Hypermotor</td>
<td>LTG</td>
<td>Tourette’s syndrome</td>
<td>GBP, PGB, BZD, CBZ, VPA</td>
</tr>
<tr>
<td>Irritable</td>
<td>LEV, PRM, PHB</td>
<td>Aggression</td>
<td>GBP, PGB, BZD, CBZ, VPA</td>
</tr>
<tr>
<td>Learning disability</td>
<td>All AEDs</td>
<td>Behavior disorders</td>
<td>ALL AEDs: start low, go slow</td>
</tr>
</tbody>
</table>

PHB, phenobarbitone; PRM, primidone; LEV, levetiracetam; LTG, lamotrigine; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; DPH, phenytoin; ZNS, zonisamide; BZD, benzodiazepines; PGB, pregabalin.
Forced Normalisation is a phenomenon characterised by the fact that with the occurrence of psychotic states the EEG becomes normal or more normal as compared to previous recordings.

Heinrich Landolt (1917 – 1971)

Landolt 1959
Heinrich Landolt 1959: Forced normalisation

Figure 7. EEG of patient M.W., recorded postictally on 11 October 1951, when the patient was psychologically in his habitual state.

Figure 8. EEG of patient M.W., recorded on 17 October 1951, during a psychotic state.

Figure 11. EEG of patient M.W., recorded on 1 November 1951 after all AEDs had been discontinued (25 October–31 October 1951) which, with the exception of phenytoin, were reintroduced as from 31 October.
Alternative psychosis in Jean Christophe
Illustrated by his brother

During our stay, he suffers more paranoid breakdowns of this kind.

The new drug suppresses his epilepsy but makes him crazy!

His universe turns hostile, he envisions himself surrounded by bad omens.

David B. „Epileptic“
David B. "Epileptic"

"OK!
Mmm
DAD! TELL ME!
I don't want that you answer me!
Don't tell me!
DON'T TELL ME!
But know that SILENCE EQUALS DEATH!

I keep the piece of paper where he wrote down those numbers.

28 17
81 a 35

During his illogical, I realize that he's not doing well at all.

Why?
Why?

But... Christophe?

You don't want to know anything.

But there's no answer to give. Christophe, you're nothing.

Why why?

Why are you falling in?
Alternative psychosis in Jean Christophe
Illustrated by his brother

They stop giving him the new miracle drug.

His psychotic fits cease.

The epileptic seizures start up again.

When Jean-Christophe is not epileptic he suffers from something else.

It’s this other thing we ought to be taking care of.

But what is it?
Manifestations of Forced Normalisation

44 cases

Wolf 1984

- Paranoid-hallucinatory psychosis 19
- Prepsychotic dysphoria 9
- Hysterical episode 5
- Hypochondric episode 3
- Depressive episode 2
- Dysphoric episode 2
- Manic episode 2
- Twilight state 1
- Depersonalisation 1

Insomnia is a warning symptom.
FOR IMMEDIATE RELEASE
January 31, 2008

FDA News

FDA Alerts Health Care Providers to Risk of Suicidal Thoughts and Behavior with Antiepileptic Medications

The U.S. Food and Drug Administration today issued new information to health care professionals to alert them about an increased risk of suicidal thoughts and behaviors (suicidality) in patients who take drugs called antiepileptics to treat epilepsy, bipolar disorder, migraine headaches, and other conditions.

An FDA analysis of suicidality reports from placebo-controlled studies of 11 antiepileptic drugs shows that patients taking these drugs have about twice the risk of suicidal thoughts and behaviors (0.43 percent), compared with patients receiving placebo (0.22 percent). This risk corresponds to an estimated 2.1 per 1,000 more patients in the drug treatment groups who experienced suicidality than in the placebo groups.

"We want health care professionals to have the most up to date drug safety information," said Russell Katz, M.D., director of the Division of Neurology Products in FDA's Center for Drug Evaluation and Research. "This is an example of FDA working with drug manufacturers throughout products' lifecycles to keep health care professionals informed of new safety data."

Patients who are currently taking antiepileptic medicines should not make any changes without first talking to their health care provider. Health care providers should notify patients, their families, and caregivers of the potential for an increase in the risk of suicidal thoughts or behaviors so that patients may be closely observed for notable changes in behavior.

Following a preliminary analysis of data from several antiepileptic drugs that suggested an increased risk of suicidality, in March 2005 FDA requested this type of data from manufacturers of marketed antiepileptic drugs for which there were adequately designed controlled clinical trials. FDA received and reviewed data from 199 placebo-controlled studies of 11 drugs.

The analysis included 27,863 patients in drug treatment groups and 16,029 patients in placebo groups. There were four suicides among patients in the drug treatment groups and none among patients in placebo groups. There were 105 reports of suicidal thoughts or behaviors in the drug-treated patients and 35 reports in placebo-treated patients.

The higher risk of suicidal thoughts and behaviors was observed at one week after starting a drug and continued to at least 24 weeks. The results were generally consistent among all the different drug products studied and were seen in all demographic subgroups. There was no clear pattern of risk across age groups.
Analysis

• 199 Placebo-controlled trials with 11 AED

• Suicidal behavior (Suicide, attempt, suicidal ideation)

• Epilepsy, psychiatric disorders, migraine and pain

• 43.892 patients (27.863 AED, 16.029 Placebo)
<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events Per 1000 Patients</th>
<th>Drug Patients with Events Per 1000 Patients</th>
<th>Relative Risk Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
<th>Risk Difference Additional Drug Patients with Events Per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.8</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

4 suicides, all in the AED group
Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials.
Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials.
AED and suicidal behaviour
Andersohn et al. Neurology 2010

Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior

ABSTRACT

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453 Cases
8962 controls

4 AED-Groups:
Barbiturates
Old AED
New Low-Risk-AED: LTG, GBP, PGB, OXC
New High-Risk-AED: TGB, VGB, TPM, LEV

compared with no use of AEDs during the last year. Use of barbiturates (OR = 0.66; 95% CI 0.25-1.73), conventional AEDs (OR = 0.74; 95% CI 0.53-1.03), or low-risk newer AEDs (OR = 0.87; 95% CI 0.47-1.59) was not associated with an increased risk.
# AED and suicidal behaviour

Andersohn et al. Neurology 2010

## Table 2

Risk of self-harm or suicidal behavior associated with the use of different classes of AEDs

<table>
<thead>
<tr>
<th>Class</th>
<th>Cases (n = 453)</th>
<th>Controls (n = 9,962)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse</td>
<td>71 (15.7)</td>
<td>1,059 (11.8)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Current use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>5 (1.1)</td>
<td>180 (2.0)</td>
<td>0.35 (0.14–0.91)</td>
<td>0.66 (0.25–1.73)</td>
</tr>
<tr>
<td>Conventional AEDs</td>
<td>183 (40.4)</td>
<td>4,287 (47.8)</td>
<td>0.58 (0.42–0.80)</td>
<td>0.74 (0.53–1.03)</td>
</tr>
<tr>
<td>New AEDs (low risk)</td>
<td>16 (3.5)</td>
<td>372 (4.2)</td>
<td>0.61 (0.34–1.10)</td>
<td>0.97 (0.47–1.59)</td>
</tr>
<tr>
<td>New AEDs (high risk)</td>
<td>6 (1.3)</td>
<td>45 (0.5)</td>
<td>1.96 (0.76–4.59)</td>
<td>3.09 (1.22–7.77)</td>
</tr>
<tr>
<td>2 AEDs</td>
<td>52 (11.5)</td>
<td>1,354 (15.1)</td>
<td>0.52 (0.36–0.77)</td>
<td>0.76 (0.51–1.15)</td>
</tr>
<tr>
<td>≥3 AEDs</td>
<td>18 (4.0)</td>
<td>244 (2.7)</td>
<td>1.02 (0.59–1.77)</td>
<td>1.47 (0.82–2.61)</td>
</tr>
<tr>
<td>Recent use</td>
<td>82 (12.6)</td>
<td>1,104 (8.6)</td>
<td>1.03 (0.73–1.47)</td>
<td>1.18 (0.81–1.72)</td>
</tr>
<tr>
<td>Past use</td>
<td>20 (3.3)</td>
<td>317 (2.6)</td>
<td>0.91 (0.53–1.55)</td>
<td>0.95 (0.47–1.51)</td>
</tr>
</tbody>
</table>

Abbreviations: AED = antiepileptic drug; CI = confidence interval; OR = odds ratio.

*Adjusted for type of epilepsy (undefined, generalized, partial, partial and generalized), use of benzodiazepines, and psychiatric comorbidity (history of self-harm, depression with and without treatment with antidepressants, psychotic disorders, mania, anxiety disorder, borderline personality disorder, other personality disorders, alcohol dependence/abuse, and dependence on other substances).
## AED and suicidal behaviour

*Andersohn et al. Neurology 2010*

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 453)</th>
<th>Controls (n = 8,962)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonuse</strong></td>
<td>71 (15.7)</td>
<td>1,059 (11.8)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Barbiturates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>4 (0.9)</td>
<td>137 (1.5)</td>
<td>0.37 (0.13-1.04)</td>
<td>0.66 (0.23-1.90)</td>
</tr>
<tr>
<td>Primidone</td>
<td>1 (0.2)</td>
<td>42 (0.5)</td>
<td>0.31 (0.04-2.31)</td>
<td>0.68 (0.09-4.99)</td>
</tr>
<tr>
<td>Methylphenobarbitone</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td><strong>Conventional AEDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>85 (18.6)</td>
<td>1,768 (20.0)</td>
<td>0.65 (0.46-0.93)</td>
<td>0.83 (0.57-1.20)</td>
</tr>
<tr>
<td>Valproate</td>
<td>65 (14.4)</td>
<td>1,011 (11.6)</td>
<td>0.55 (0.36-0.81)</td>
<td>0.68 (0.46-1.01)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>32 (7.1)</td>
<td>669 (7.7)</td>
<td>0.49 (0.31-0.77)</td>
<td>0.67 (0.42-1.08)</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>1 (0.2)</td>
<td>16 (0.2)</td>
<td>0.80 (0.10-6.15)</td>
<td>1.31 (0.17-10.26)</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>0 (0.0)</td>
<td>3 (0.0)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td><strong>New AEDs (low risk)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>0 (0.0)</td>
<td>5 (0.1)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>13 (2.9)</td>
<td>327 (3.6)</td>
<td>0.58 (0.31-1.08)</td>
<td>0.93 (0.49-1.76)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>3 (0.7)</td>
<td>40 (0.4)</td>
<td>1.03 (0.31-3.45)</td>
<td>0.70 (0.18-2.75)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>0 (0.0)</td>
<td>(0.0)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td><strong>New AEDs (high risk)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levotracetam</td>
<td>2 (0.4)</td>
<td>8 (0.1)</td>
<td>3.54 (0.71-17.67)</td>
<td>6.42 (1.24-33.36)</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Topiramate</td>
<td>2 (0.4)</td>
<td>23 (0.3)</td>
<td>1.23 (0.28-5.38)</td>
<td>2.42 (0.54-10.77)</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>2 (0.4)</td>
<td>14 (0.2)</td>
<td>1.91 (0.43-8.59)</td>
<td>2.44 (0.52-11.48)</td>
</tr>
</tbody>
</table>
Antiepileptic Drugs Linked to Suicide

On January 31, 2008, the FDA warned that the most frequently used antiepileptic drugs (AEDs) may be linked to an increased risk of suicide. In a review of 199 studies comparing 11 epilepsy drugs to placebos, researchers found that patients taking the drugs had about twice the risk of suicidal behavior compared with patients taking a placebo. The drugs, included in the study and the subsequent FDA warning, are listed below:

- Carbatrol (Carbamazepine)
- Tegretol (Equetro)
- Felbatol (Felbamate)
- Neurontin (Gabapentin)
Conclusions

DEPRESSION

High impact on quality of life
Occurs in all age groups
Underrecognised, undertreated
Typical presentation: affective instability (IDD)
Risk factors: TLE and GABA-ergic drugs
Depression is a risk factor for epilepsy
Conclusions

**PSYCHOSIS**

Most common type: postictal transient psychosis with maniform psychopathology, risk for aggressive and suicidal behaviour, closely linked to mesial temporal lobe epilepsy, frequently seen during presurgical monitoring.
Conclusions

ANTIEPILEPTIC DRUGS

All AEDs may influence the mental state
Mechanisms: indirect (forced normalisation) or
direct (positive or adverse side effects)
Effects depend on preexisting mental state
Side effects profiles crucial for individual drug
choice
Psychiatric Comorbidity in Epilepsy

**Therapy**

1. Seizure control
2. Consider psychotropic profiles of AEDs
3. Antidepressants, antipsychotics

**Antidepressants**
- Escitalopram; Mirtazapine (sedation), Venlafaxin (somatoform complaints)

**Antipsychotics**
- Risperidone, Olanzapine (Sedation)

**CAVE**
- Start low, go slow
- Improve compliance
- Establish cooperation with psychiatrist
- Ask for suicidal ideation
- + Psychotherapy, patient education, social support
Psychiatric Aspects of Epilepsy
Challenges in Diagnosis and Treatment