# Psychiatric Comorbidity in Epilepsy

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## Psychiatric Disorder in Epilepsy

- First organized description from Falret&Morel(1860)
- " The periodicity of mental changes and prominence of outbursts of anger&fury"

## Psychiatric Comorbidity of PWE

- Negative impact on response to treatment
- Risk factor for poor quality of life
- Increase burden and cost on healthcare services
- Remained underrecognized and undertreated by the majority of clinician

## Prevalence of Psychiatric Comorbidity

| DSM-defined diagnosis | Prevalence rate ( range ) |
|---|---|
| Mood disorder | 24 – 75 % |
| Anxiety disorder | 10 – 25 % |
| Psychosis | 2 – 7 % |
| Personality disorder | 1 – 2 % |

Jones R et al Functional Neurology 2010

## Relationship between Psychiatric disorder and Epilepsy

- Psychiatric disorders caused by the seizures : Ictal , postictal, and interictal disorders
- Epileptic and psychiatric disorders caused by common brain pathology
- Epileptic and psychiatric disorders coexist in the same patient but are not causally related

## Mechanism of Comorbidity

- Common neuropathology or genetic predisposition
- Developmental disturbance
- Ictal or subictal neurophysiologic effects
- Alteration of receptor sensitivity
- Secondary endocrinologic alterations
- Primary, independent psychiatric illness
- Consequence of medical or surgical treatment
- Consequence of psychosocial burden of epilepsy

## Classification of Psychiatric Disorders Associated with Epilepsy by Fenton (1981)

1. **Disorders clearly attributable to the brain disorder causing the epilepsy**
   - Learning disability
   - Chronic organic brain syndromes
   - Focal brain disease
2. **Disorders strictly related in time to seizure occurrence**
   - Preictal - prodrome
   - Ictal - psychiatric manifestations of seizure activity (aura, automatisms, nc status, FLE)
   - Postictal - psychiatric abnormalities occurring in the immediate postictal period
3. **Interictal psychiatric disorders**
   - Childhood disorders
   - Neuroses
   - Psychoses
   - Personality disorder
   - Dementia

## Classification of Neuropsychiatric Disorders in Epilepsy ILAE Commission on Psychobiology of Epilepsy (2006)

1. **Psychopathology as a presenting feature of epileptic seizures**
2. **Interictal psychiatric disorder that are specific to epilepsy**
   - Cognitive dysfunction
   - Psychoses of epilepsy
   - Affective-somatoform ( dysphoric ) disorders of epilepsy
3. **Personality disorder**
4. **Other relevant conditiond**
   - Relate to EEG change : forced normalization
   - AED induced psychiatric disorders

## Effects of AED

| Antiepileptic drug | Negative psychotropic symptoms | Positive psychotropic symptoms |
|---|---|---|
| Barbiturates | Depression, hyperactivity | Anxiolytic, hypnotic |
| Carbamazepine/ oxcarbazepine | Irritability | Mood stabilizer, antimanic |
| Ethosuximide | Behavioral abnormalities, psychosis | None identified |
| Felbamate | Depression, anxiety, irritability | None identified |
| Gabapentin | Behavioral problems in children | None identified |
| Lamotrigine | Insomnia, agitation | Mood stabilizer, antidepressant |
| Levetiracetam | Irritability, emotional lability | Possible antimanic |
| Phenytoin | Encephalopathy | Possible antimanic |

| Antiepileptic drug | Negative psychotropic symptoms | Positive psychotropic symptoms |
|---|---|---|
| Pregabalin | Unknown Depression | Anxiolytic |
| Tigabine | (nonconvulsive status epilepticus) | Possible anxiolytic |
| Topiramate | Depression, psychomotor slowing, psychosis | Mood stabilizer |
| Valproate | Encephalopathy | Mood stabilizer |
| Vigabatrin | Depression, aggression, psychosis | None identified |
| Zonisamide | Agitation, depression, psychosis | Possible antimanic |

Garcia CS. Epilepsy Research and Treatment 2012

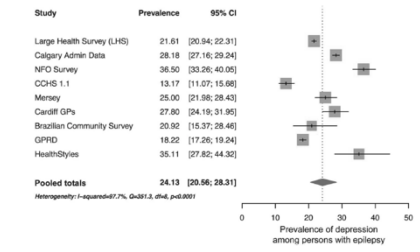
## Depression in Epilepsy

- Prevalence ranged from 20-55% in recurrent seizure, 3-9% in controlled epilepsy
- Jacody ( 1996) reported lifetime prevalence = 29% , comparing to 16% in DM, 17% in asthma, 8.7 % in healthy respondents
- Impacts : Used more health resources, poor QoLs, 5 time greater risk of suicide

Seethalakshmi R et al Epileptic Disord. 2007

## Prevalence of Depression among PWE

Figure 2 **Overall prevalence of active depression among persons with epilepsy**




CCHS = Canadian Community Health Survey; CI = confidence interval; GP = general practitioners; GPRD = General Practice Research Database; NFO = National Family Opinion.

Fiest KM. et al Neurology 2013

## A Bidirectional Relation

- Traditional view : Consequence or Complication
- Recent finding : Epilepsy increase risk for depression,

  Depression increase 3-7 fold risk for epilepsy.
- Animal model

- Increase anxiety& depressive behavior preceding seizure in Transgenic rats
- Worsening seizure with substances interfere with synthesis or release of NE, 5 HT
- Treatment with NE , 5HT agent blocked seizure

Kanner AM. Epilepsia 2011

## A Bidirectional Relation

- Recent finding : Human studies
- Decrease binging 5-HT1A of PET scan in both disorder
- Significant drop in seizure in 3 trial of SSRIs in patients with treatment-resistant epilepsy.
- Serotonin's anticonvulsant effect mediated via inhibition of voltage-gated ion channels, effect on GABA and glutamate receptors, neurosteriod synthesis.

Kanner AM. Epilepsia 2011

## Dysphoria in epilepsy

- Kraepelin(1923) stated "Periodic dysphorias represent the most common psychiatric dis. in epilepsy, characterized by irritability with or without outbursts of fury. Accompanied by depressed mood, anxiety, headache& insomnia"
- ❖ Mulder&Dally ( 1952 ) - reactive depression
- ❖ Bett ( 1974) - endogenous presentation
- ❖ Mendez( 1986) - fewer anxiety, guilt, hoplessness, low self-esteem ; but more psychotic symptoms

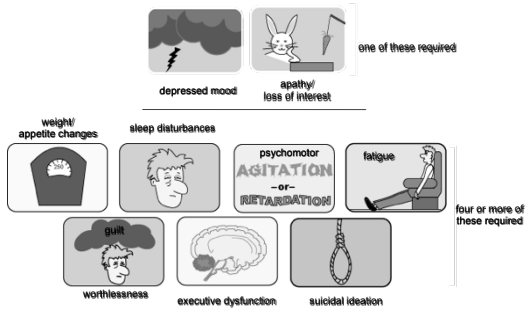
## Etiology of Depression in epilepsy

- Forced normalization
- AED induced depression: vigabatrin, tiagabine, topiramate, phenobarbital , levetiracetam
- Laterality hypothesis: connectivity of mesial temporal lobe to frontal lobe ; left TLE ( consequence of seizure)
- Endocrine& metabolic consequence fromseizure
- Psychological factors: Unpredictability& uncontrollability learned helplessness , burden of normailty

## Risk factors for depression

- Gender : Male > female
- Sinistrality: left-handed PWE ( indicated early brain injury)
- Related neurological condition: MS , CVD, dementia, head injury
- Genetic Family history of depression, suicide
- Amygdala enlargement and hippocampal atrophy
- Past history of behavioral disturbance in childhood, neurosis
- Patients with learning disability , low IQ
- Late-onset epilepsy , CPS , MTS , TLE

DSM-IV Symptom Dimensions of a Major Depressive Episode




Duration = 2 weeks

## Depression in PWE

- > 50 % have atypical manifestation : depression, irritability, anxiety Anhedonia is the better marker for depression
- Symptoms may confound with physical s&s, medication SE
- Classified as : interictal vs periictal(preictal, ictal, post-ictal
- Depression can be iatrogenic effect associated with the introduction or discontinuation of certain AEDs, complication of surgery
- Some patients have subsyndromic form of depression
- Some patients have comorbid anxiety : predicted higher risk of suicide and treatment-resistant depression

# Post-ictal depression

| Posticta symptom of depression | Frequency ($N = 100$) | Duration (h) |
|---|---|---|
| Poor frustration | 36 | 24 (0.5–108)[a] |
| Anhedonia | 33 | 24 (0.1–148) |
| Hopelessness | 25 | 24 (1.0–108) |
| Helplessness | 31 | 24 (1.0–108) |
| Crying bouts | 26 | 6 (0.1–108) |
| Suicidal ideation | 13 | 24 (1.0–240) |
| Irritability | 30 | 24 (0.5–108) |
| Guilt | 23 | 24 (0.1–240) |
| Self-deprecation | 27 | 24 (1.0–120) |

a = Median ( Range)

Kanner Am et al. Epilepsy&Behavior 2010

# Dietrich Blumer's interictal dysphoric disorder

- Patients with refractory epilepsy ; esp. TLE
- Short duration, last hours - 2 to 3 days, attenuated in premenstrual period
- Increase risk of sudden, unexpected suicide attempts , interictal psychosis
- 3 of the followings:(Depressive-somatoform symtoms, affective symptoms)

| Labile depressive symptoms | Labile affective symptoms | Specific symptoms |
|---|---|---|
| - Depressive mood<br>- Anergia<br>- Pain<br>- Insomnia | - Fear<br>- Anxiety | - Paroxysmal irritability<br>- Euphoric moods |

Blumer D et al Harv Rev Psychiatry 200

# Assessment

- Structured interviews :

- The Structured Clinical Interview for DSM IV Axis I Disorder ( SCID)
- The Mini International Neuropsychiatric Interview ( MINI)
- Hamilton Rating Scale for Depression ( HRSD, HAM-D)

- Screening psychometric test :

- Beck Depression Inventory ( 21 items)
- Center for Epidemiology Studies-Depression Scale ( CES-D)
- The Neurological Disorders Depression Inventory for Epilepsy(NDDI-E)

## Neurological Disorders Depression Inventory in Epilepsy (NDDI-E)

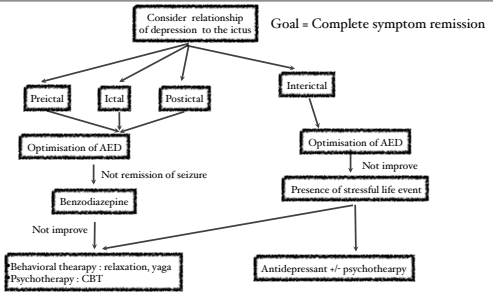
**For the statements below, please circle the number that best describes you over the last two weeks including today.**

| | Always or often | Sometimes | Rarely | Never |
|---|---|---|---|---|
| Everything is a struggle | 4 | 3 | 2 | 1 |
| Frustrated | 4 | 3 | 2 | 1 |
| Nothing I do is right | 4 | 3 | 2 | 1 |
| Feel guilty | 4 | 3 | 2 | 1 |
| Difficulty finding pleasure | 4 | 3 | 2 | 1 |
| I'd be better off dead | 4 | 3 | 2 | 1 |

NDDI-E > 15 Sensitivity = 0.8 , Specificity = 0.9 , PPV = 0.62, NPV = 0.96

Gilliam FG. et al Lancet Neurol 2006

# Managment of Depression




Seethalakshmi R et al Epileptic Disord. 2007

# Management of depression in epilepsy

- Pre-ictal and ictal depression : reduce seizure frequency
- Benzodiazepine , behavior intervention may abort or prevent the development of the symptoms
- Treatment with antidepressants involves 3 major issues
  - - Effect of antidepressants on seizure threshold
  - - Antidepressant-anticonvulsant interaction
  - - Efficacy of antidepressant in PWE

Seethalakshmi R et al Epileptic Disord. 2007

| Antidepressant | Drug dose | Seizure prevalence (%) |
|---|---|---|
| Amitriptyline | < 200 mg<br>> 200 mg | 0.1<br>0.6 |
| Imipramine | 50 – 600 mg | < 0.1 – 0.9 |
| Clomipramine | > 200 mg | 0.5 |
| Maprotiline | 150 – 200 mg | 0.4 |
| Fluoxetine | 20 – 60 mg | 0.2 |
| Fluvoxamine | < 100 mg | 0.2 |
| Sertraline | 50 – 100 mg | < 0.1 |
| Paroxetine | 20 – 60 mg | 0.1 |
| Bupropion | 300 mg SR<br>300 – 450 mg IR<br>> 450 mg IR | 0.1<br>0.4<br>> 0.6 |
| Mirtazapine | 30 mg | < 0.1 |

Mula M. et al . Expert Opin Pharmacother. 2008

## Prevention of depression

- Iatrogenic depressive episodes are common
- Psychiatric adverse events of AED related with past psychiatric history and/or family psychiatric history.
- Prevention strategy:

1. Avoid introduce of an AED with negative psychotropic properties
2. Monitor the discontinuation of an AED with mood-stabilizing properties : valproate , carbamazepine, lamotrigine .
3. Adjust doses of antidepressants when introducing AED with enzyme-inducing properties
4. Assess psychiatric premorbidity of PWE before epilepsy surgery to avoid depression in the first 6 months ( 20-30%)

Kanner AM. Epilepsia 2013

## AED with psychotropic effects related to the premorbid mental state

| Mechanism | GABA-ergic drugs | Antiglutamatergic drugs |
|---|---|---|
| Psychotropic effects | Seadting , anxiolytic, depressogenic , antimanic , | Activating, anxiogenic, antidepressive |
| Drug | gabapentin , benzodiazepine, valproate, barbiturates ,vigabatrin, tiagabine , | Felbamate, Lamotrigine |
| Effect in activated patients | Positive | Negative |
| Effect in sedated patients | Negative | Positive |

*Ketter TA et al. Neurology 1999.*

## Psychiatric risk of AED

| Patient's preexisting psychopathology | AED | Possible SE |
|---|---|---|
| Dysthymia | phenobarbitone, vigabatrin, topiramate, tiagabine | Major depression |
| Paranoia | phenytoin, vigabatrin, topiramate | schizophrenic psychosis |
| Agitation | Lamotrigine | Insomnia, anxiety, hypomania |
| Hypermotor | Lamotrigine | Tourette syndrome |
| Dysphoric | Levetiracetam | Aggression |
| LD | All AED | Behavior disorders |

Schimtz B. Epilepsia 2006

## Effects of ATD in PWE

| Study group | Antidepressants | Follow up | Seizure frequency in treatment group | Reference |
|---|---|---|---|---|
| 9 PWE | FLX | 3 months | 4 Px increase in seizure frequency by >50%; 5 Px not increased | Gigli *et al.* (1994) |
| 36 PWE and MDD | SRT, FLX | 1 year | 2 Px increase in seizure frequency; 34 Px not increased (number of Px with *reduced* seizures not mentioned) | Thome-Souza *et al.* (2007) |
| 100 PWE and depression or OCD | SRT | 1 year | 6 Px increase in seizure frequency; 94 Px not increased (number of Px with *reduced* seizures not mentioned) | Kanner *et al.* (2000) |
| 39 PWE and depression | CIT | 4 months | 2 Px had 50% increase in seizures; 37 Px with 50% decrease in seizures | Specchio *et al.* (2004) |
| 11 PWE | CIT | 8–10 months | All Px showed improvements: 64.1% mean reduction in seizure frequency | Favale *et al.* (2003) |
| 17 PWE | FLX | 14 months | Seizures disappeared in 6 Px; in others, seizure frequency reduced by 30% | Favale *et al.* (1995) |
| 43 PWE and HAMD score >15 | CIT | 2 months | No change in seizure frequency | Hovorka *et al.* (2000) |
| 75 PWE and HAMD score >15 | MIR, CIT, REB | 7.5 months | No change in seizure frequency | Kuhn *et al.* (2003) |
| 28 PWE | FLV | 29–444 days | No change in seizure frequency | Harmant *et al.* (1990) |
| 121 PWE | Various 1st and 2nd gen. drugs | 1 year | No change in seizure frequency compared to non-treated Px | Okazaki *et al.* (2011) |

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## Efficacy of ATD in PWE

| Drug class | Examples in clinical use | Proposed mechanism of action | References to studies of use in patients or epilepsy models |
|---|---|---|---|
| Selective serotonin reuptake inhibitor (SSRIs) | Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline | Blockade of SERT, plus some with additional pharmacological actions | Favale *et al.* (1995); Kanner *et al.* (2000); Specchio *et al.* (2004) |
| Serotonin and noradrenaline reuptake inhibitors (SNRIs) | Venlafaxine, Desvenlafaxine, Duloxetine | Selective SERT and NET blockade | Santos *et al.* (2002); Ahern *et al.* (2006); Borowicz *et al.* (2011) |
| Tricyclics (TCAs) | Imipramine, Desipramine, Doxepin, Dothiepin, Amoxapine | Blockade of SERT and NET, also acting on histaminergic and cholinergic receptors. Negligible DAT affinity | Dessain *et al.* (1986); Preskorn and Fast (1992) |
| Monoamine oxidase inhibitor (MAOIs), *reversible* | Moclobemide | Reversible inhibition of MAO-A (and others MAO-B also) | Trimble (1978); Bonnet (2003); Krishnan (2007) |
| Monoamine oxidase inhibitor (MAOIs), *irreversible* | Tranylcypromine, Phenelzine | Irreversible inhibition of MAO-A and MAO-B | Pisani *et al.* (2002) |
| Noradrenaline reuptake inhibitors (NRIs) | Reboxetine | Blockade of NET | Kuhn *et al.* (2003) |
| Noradrenaline dopamine reuptake inhibitor (NDRI) | Bupropion | Not well defined, but shown to be a noradrenaline and dopamine reuptake inhibitor | Settle *et al.* (1999) Mainie *et al.* (2001) |
| Serotonin-2 receptor antagonist and reuptake inhibitors (SARIs) | Trazodone, Nefazodone | Antagonist of 5-$HT_{2A}$ receptor and blockade of SERT | Vanpee *et al.* (1999) |
| Noradrenaline and specific serotonergic antidepressant (NaSSA) | Mirtazapine | Blockade of 5-$HT_2$ receptors, 5-$HT_3$, $H_1$ and $\alpha_2$ adrenergic receptor antagonist | Kuhn *et al.* (2003) |
| Others | Agomelatine | Melatonergic ($MT_1$ and $MT_2$) receptor agonist, $5HT_{2C}$ antagonist | No reported use in PWE |

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## Other treatment

- AED - as mood stabilizer ( lamotrigine , valproate,carbemazepine )
- US FDA alert for increase risk of suicide with AEDs as a class in 2008 , based on meta-analysis
- Vagus nerve stimulation (VNS) , ECT and rTMS - limited data in epilepsy
- Physical activity for mild depression
- Psychological treatment : Relaxation therapy, CBT, yoga

## Anxiety Disorder in PWE

- Anxiety may be more common than depression and equally disabling
- 11 -25 % in generally, > 50% in some specialist setting
- Significant predictor of reduced health-related QoL
- Relative frequent in treatment resistant epilepsy
- Associated with a poor response to pharmacotherapy
- Tend to comorbid with depressive disorder
- PWE can experience more than 1 anxiety disorder
- Increase risk of suicide

## Anxiety Disorder in PWE

- **Generalized anxiety disorder** : fear of future seizure, disease progression, complication
- **Panic attack and panic disorder** : ictal anxiety /fear
- **Phobia** : agoraphobia , social phobia
- **Obsessive-compulsive disorder**: aura(forced thinking)

## Panic Attack vs. focal seizure

| | **Primary panic attack** | **Focal seizure with ictal fear** |
|---|---|---|
| Consciousness | Alert | Alert but may progress to impaired |
| Duration | 5-10 min | 0.5 – 2 min |
| Déjà vu, hallucination | very rare | > 5 % |
| Automatism | very infrequent | common with progression to CPS |
| Agoraphobia | Common | Not unless comorbid interictal anxiety |
| Depressive symptoms | Common, severity associated | Not uncommon, severity not associated |
| Anticipatory anxiety | very common | not common |
| Interictal EEG | Normal | Often abnormal |
| Ictal EEG | Normal | Usually abnormal |
| MRI of temporal structure | Usually normal | Often abnormal |

Vazquez B et al Epilepsy Behav 2003

## Risk Factors for Anxiety

- Seizure frequency and perception of danger
- Late life onset
- Focal ( TLE , Left ) > generalized epilepsies
- Chronic refractory seizure disorders

## Neurobiology Mechanism

- Amygdala → anxiety , panic disorder , ictal fear
- Seizure arising in ant. cingulate, orbitofrontal cortex
- Abn function of GABA-A receptors

(some AED have anxiolytic properties )

## Anxiety symptoms and seizure

- Comorbid anxiety disorder
- Ictal phenomenon
- Postictal phenomenon
- Interictal phenomenon

## Anxiety Symptoms and AED

- AED can exacerbate anxiety / have anxiolytic effects
- History of psychiatric disorder increased vulnerability to psychiatric side effects of AED
- AEDs with glutamatergic mechanism cause activation

AEDs enhance GABAergic alleviate anxiety.

## Treatment of Anxiety in PWE

- Psychoeducation and support
- Counselling , CBT
- Medication : antidepressant ( SSRIs, TCA ) , BZD
- AED with anxiolytic potential : barbiturate, CBZ, gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabin, valproate,

Risk of seizures with drugs prescribed for anxiety disorders

| Drug | Approximate risk (%) |
|---|---|
| High risk (5% or higher risk of seizure) | |
| Chlorpromazine (high dose) | 9 |
| Medium risk (0.5% or higher risk of seizure) | |
| Olanzapine | 1 |
| Quetiapine | 1 |
| Bupropion | 0.5 |
| Clomipramine (high dose) | 1 |
| Low risk (0.5% or lower risk of seizure) | |
| Risperidone | 0.3 |
| Imipramine | 0.5 |
| SSRIs | 0.1 |
| Venlafaxine | 0.3 |
| Mirtazepine | 0.05 |

## Psychosis in PWE

Categorized in relation to seizures or treatment:

- Ictal psychosis
- Postictal psychosis
- Interictal psychosis
- Forced normalization/ alternative psychosis
- De novo psychosis following epileptic surgery

## Logsdail& Toone Operational Criteria for PIP

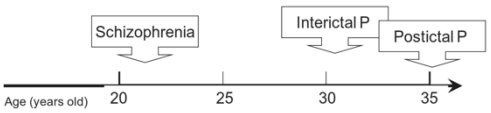
1. Onset of confusion or psychosis within 1 week of the return of apparently normal function
2. Duration of 1 day to 3 months
3. Mental state characterized by :
   a. Clouding of consciousness, disorientation, delirium
   b. Delusion or hallucination ,in clear consciousness
   c. A mixture of a and b
4. No evidence of factors,which may contribute to the abnormal mental state:
   a. AED toxicity
   b. A previous history of interictal psychosis
   c. EEG evidence of status epilepticus
   d. Recent history of head injury or alcohol/drug intoxication

## Annual Incidence of new cases of psychosis

| | | |
|---|---|---|
| Schizophreniform psychosis in patients with epilepsy | | |
| Lindsay *et al.* [1979] | 0.75% | Temporal lobe epilepsy; child) |
| Onuma *et al.* [1995] | 0.30% | General epilepsy outpatient; adult |
| Bredkjaer *et al.* [1998] | 0.38% | General epilepsy patient |
| Tadokoro *et al.* [2007] | 0.42% | General epilepsy outpatient; adult (ours) |
| Schizophrenia in general population | | |
| World Health Organization [1992] | 0.22% | (median value) (15-54 years old) |

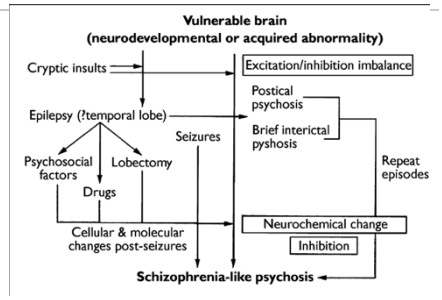
Kanemoto K. et al Ther Adv Neurol Disord. 2012

## Age at psychosis onset on PWE and Schizophrenia




Kanemoto K. et al Ther Adv Neurol Disord. 2012

## Pathophysiology of Psychosis in PWE




Sachdev . Epilepsia 2007