Optimizing therapy of seizures in adult patients with psychiatric comorbidity

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동아의대신경과
Optimizing therapy of seizures in adult patients with psychiatric comorbidity

Eylert Brodkorb, MD, PhD; and Marco Mula, MD

Abstract—This article provides an overview of appropriate antiepileptic treatment in adult patients with chronic epilepsy and concomitant psychiatric disorders. It highlights the influence of various treatment options for epilepsy on psychiatric symptoms. Six specific topics are discussed: psychosocial aspects and treatment compliance; positive and negative psychotropic effects of antiepileptic drugs (AEDs); pharmacokinetic and pharmacodynamic interactions between AEDs and psychoactive drugs; risks and benefits of resective surgery; the effect of vagal nerve stimulation; and recommended strategies for optimizing epilepsy therapy in patients with psychiatric disorders. Given the multitude of epilepsy treatment options with various CNS effects, it is crucial to select treatments according to the clinical profile of each individual patient.

NEUROLOGY 2006;67(Suppl 4):S39–S44
Contents

- Risks and benefits of AEDs
  - positive and negative psychotrop effect
  - pharmacokinetic and pharmacodynamic interactions between AEDs and psychoactive drugs
- Risks and benefits of resective surgery
- Effect of VNS
- Recommended strategies for optimizing epilepsy therapy in patients with psychiatric disorders
Introduction

- Prevalence rates of mental illness are significantly higher in people with TLE and/or refractory epilepsy
  - Depression: 30%
  - Anxiety disorders: 10% ~ 25%
  - Psychosis: 2% ~ 7%
  
  Gaitatzis A. Acta Neurol Scand 2004;110:207–220

- AEDs may exert various psychotropic effects (negative or positive)
  

- Psychotropic drugs may influence the propensity to have seizures
  
  Pisani F. Drug Saft 2002;25:91–110
analyze and identify the various elements that may contribute to psychiatric symptoms

- psychosocial issues
- adverse treatment effects
- neurobiological factors directly related to epileptic disorder

How are psychopathologic features related to factors associated with epilepsy?

How can management of seizures positively influence coexisting psychiatric symptoms?

Which precautions should be kept in mind to avoid negative effects?
Introduction: Epilepsy patients should be educated appropriately

- nature of their epilepsy
- value of treatment
- risks posed by noncompliance
- difficult life events, social problems, and vocational problems
- seizure-provoking situations
- seizure precipitants
  - emotional stress, anxiety, and sleep deprivation
- interictal depression, anxiety, or psychosis may be connected to seizure-related stresses
  - anticipatory fear of attacks may develop into incapacitating phobia
Treatment compliance: How may nurses contribute to the improvement of epilepsy care

- recent RCT of the effect of a nurse-led intervention program in uncontrolled epilepsy
  - telephone contacts, counseling, and teaching
  - significant improvements in epilepsy inventory (QOLIE-89)
  - strong correlation between QOLIE 89 scores and depression scores

- treatment compliance is fundamental for seizure control
- comprehensive and multidisciplinary epilepsy service is a common platform in patients with comorbidities and special needs
  Ramaratnam S. Cochrane Database Syst Rev 2003;4:CD002029
2 categories of AEDs on psychotropic profile

1. sedating effects
   - potentiation of GABAergic neurotransmission: PB, BDZ, VPA, GBP, TGB,
   - anxiolytic and antimanic properties
   - fatigue, cognitive slowing, weight gain

2. activating effects
   - attenuation of glutamatergic neurotransmission: FBM, LTG * TPM: 1+2
   - anxiogenic and antidepressant properties
   - activation, weight loss

Psychotropic effects of AEDs are related to direct and indirect mechanisms
Mood stabilizing?

(1) GABA-ergic
   - Sedating
   - Anxiolytic
   - Antimanic

(2) Anti-glutamatergic
   - Activating
   - Anxiogenic
   - Antidepressive

Levetiracetam?

Barbiturates
Benzodiazepines
   - Valproate
   - Vigabatrin
   - Tiagabine, Gabapentin

Topiramate

Felbamate
Lamotrigine
# Psychotropic properties of AEDs

<table>
<thead>
<tr>
<th>Antiepileptic drug</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Barbiturates</strong></td>
<td>Depression, hyperactivity</td>
<td>Anxiolytic, hypnotic</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Behavioral abnormalities, psychosis</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine-Oxcarbazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Valproate</strong></td>
<td>Encephalopathy</td>
<td>Mood stabilizing, antimanic</td>
</tr>
<tr>
<td><strong>Felbamate</strong></td>
<td>anxiety, irritability</td>
<td>Mood stabilizing, <strong>antimanic</strong> (anxiolytic)</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>Insomnia, agitation</td>
<td>(Increased attention and concentration)</td>
</tr>
<tr>
<td><strong>Vigabatrin</strong></td>
<td>Depression, aggression, psychosis</td>
<td><strong>Mood stabilizing, antidepressant</strong></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Depression, psychomotor slowing, psychosis</td>
<td>Antibulimic in binge eating disorders</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>Behavioral problems in children</td>
<td>(Mood stabilizing)</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Agitation, depression, psychosis</td>
<td>(Anxiolytic)</td>
</tr>
<tr>
<td><strong>Tigabine</strong></td>
<td>Depression (Non-convulsive status epilepticus)</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Irritability, emotional lability</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td></td>
<td>Anxiolytic</td>
</tr>
</tbody>
</table>
Depression is more severe in Epilepsy than Asthma, Healthy Controls

Chi square p<0.001; Epilepsy Vs. Asthma p<0.05

Ettinger et al. Epilepsia (EIP abstract) 2003
Moderate-Severe Depression: More Common Among Women with Epilepsy

Gibson et al. Epilepsia 2002 (EIP abstract)
Correlation Between QOL and Depression

(R=0.67, N=776) Depression = Lower QOL

Cramer et al. Epil & Behav, 2003
Subsyndromal depressive symptoms, detected in up to 80% of epilepsy patients in some samples

Kanner AM. Epilepsy Behav 2000;1:37–51

Depressive symptoms are stronger predictors of QOL than seizure reduction in patients with active epilepsy

- 87 TLE patients, impact of depression on HR-QOL exceeded and was independent of impact of frequent, severe, chronic seizures
  
  Johnson EK. Epilepsia 2004;45:544–50

- 122 refractory epilepsy patients, depression was present in 54%, strongly predicted QOL impairment whereas frequent seizures did not

Boylan LS. Neurology 2004;62:258–61
Diagnosis and treatment of mood disorders in persons with epilepsy

Frank G. Gilliam  Curr Opin Neurol 18:129–133. 2005

Purpose of review
Epilepsy is a common, disabling neurological disorder associated with increased rates of comorbid psychiatric disorders as compared with the general population.

Recent findings
Mood disorders, especially major depression, appear to be more prevalent in persons with epilepsy than in those with the other chronic disorders and the general population.

Depression may have more influence on quality of life than do cognitive and seizure factors. Although psychological, social, and vocational disabilities contribute to mood dysfunction in epilepsy, functional neuroimaging studies have consistently shown correlation of presence of cerebral abnormalities with increased severity of symptoms of depression. Most persons with epilepsy are not routinely screened for depression, and depression is subsequently treated in only a minority of patients. Although serotonin receptor density is greatest in brain regions commonly associated with epilepsy, such as the mesial temporal and prefrontal areas, no controlled trials have investigated the efficacy of serotonin reuptake inhibitors in persons with epilepsy. Optimal methods to identify and treat depression in epilepsy require substantial further research.

Summary
Depression is a common comorbid condition with significant negative effects on health status in persons with epilepsy, but additional understanding of the disorder is needed to improve diagnosis and treatment.
Improved mood states with lamotrigine in patients with epilepsy

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Abstract

Lamotrigine (LTG) was added to other antiepileptic drugs (AEDs) in a study of adjunctive therapy. In addition to seizure control and adverse effects, patients were evaluated for changes in mood states and quality of life. The Profile of Mood States (POMS) and 31-item Quality of Life in Epilepsy (QOLIE-31) instruments were administered at baseline (N = 196), after addition of LTG as adjunctive treatment (N = 155), and after withdrawal of other drugs to LTG monotherapy (N = 51). POMS scores correlated highly with the QOLIE-31 Emotional Well-Being subscale, a known measure of mood. All POMS subscales were significantly improved (all P < 0.0001) at the end of the adjunctive therapy phase. POMS scores remained significantly better than baseline among patients completing the conversion to monotherapy (all P < 0.003). Minimal clinically important changes were determined for POMS scores. These data indicate that LTG improves mood states to a clinically important degree, even in the presence of other AEDs. The improvement likely was not a synergy but attributable only to LTG because it remained stable after withdrawal of the other AEDs.

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Effect of lamotrigine on depressive symptoms in adult patients with epilepsy

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Available online 27 October 2006

Abstract

In this investigation, the effects of lamotrigine versus placebo on depressive symptoms in patients with epilepsy were prospectively assessed. This investigation was a secondary analysis of a randomized, double-blind, placebo-controlled, parallel-group study in which adult patients received adjunctive lamotrigine (n = 32) or placebo (n = 38) for a 7-week dose escalation phase, followed by a 12-week maintenance phase, for primary generalized tonic-clonic (PGTC) seizures. Mood symptoms were assessed with the Beck Depression Inventory, second edition (BDI-II), the Profile of Mood States (POMS), and the Cornell Dysthymia Rating Scale—Self-Report (CDRS). Mean (SD) BDI-II scores at screening reflected mild depressive symptoms and were similar between groups (lamotrigine 18.3 (12.1), placebo 16.8 (12.0)). At the end of the maintenance phase, mean (SD) improvement from baseline was greater with lamotrigine than placebo with respect to BDI-II score (lamotrigine 8.9 (7.6), placebo 1.7 (8.5), P = 0.01) and POMS total score (lamotrigine 32.0 (30.4), placebo 6.5 (32.3), P = 0.03) and numerically greater with lamotrigine than placebo for CDRS score (lamotrigine 7.3 (7.8), placebo 4.1 (13.9), P = 0.50). Among the subset of patients with at least mild depression (BDI-II score ≥ 10), mean improvement from baseline was numerically, but not statistically significantly, greater with lamotrigine (11.5, n = 13) than placebo (3.1, n = 18) (P = 0.054). Median percentage reductions in seizure frequency were significantly greater with lamotrigine than placebo during the escalation phase, the maintenance phase, and the escalation and maintenance phases combined for PGTC seizures and all generalized seizures. However, improvement in seizure frequency was not correlated with improvement in mood (r = 0.1, P = ns). Compared with placebo, lamotrigine improved mood symptoms independently of seizure reduction in patients with generalized seizures. Lamotrigine may be useful in treating patients with epilepsy and comorbid depressive symptoms.

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The Role of Hippocampal Sclerosis in Topiramate-related Depression and Cognitive Deficits in People with Epilepsy

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Summary: Purpose: To clarify the role of hippocampal sclerosis (HS) in developing psychiatric and cognitive adverse events during therapy with topiramate (TPM) in patients with temporal lobe epilepsy (TLE).

Methods: We analyzed the data of 70 patients with TLE and HS and 128 patients with cryptogenic TLE matched for age, sex, starting dose, and titration schedule of TPM. They were selected from the first consecutive 431 patients started on TPM between 1995 and 1999.

Results: Patients with HS were more likely to develop cognitive adverse events (CAEs; p = 0.002) and depression (p = 0.018) and to be receiving a polytherapy regimen (p = 0.007). However, regression analysis demonstrated that only HS was a predictive factor for the occurrence of CAEs (OR = 2.4; p < 0.001) and depression (OR = 2.3; p = 0.02).

Conclusions: Patients with TLE and HS were more prone to develop CAEs and depression than were patients with cryptogenic TLE, during TPM therapy, despite the same titration schedule. The presence of HS and not duration of epilepsy or polytherapy regimen represented the main risk factor. Key Words: Epilepsy—Depression—Topiramate—Hippocampal sclerosis—Adverse events.
Effects of lamotrigine compared with levetiracetam on anger, hostility, and total mood in patients with partial epilepsy

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*Department of Neurology, University of Arizona, Tucson, Arizona, U.S.A.; †North Shore-LIJ Comprehensive Epilepsy Centers, New Hyde Park, New York, U.S.A.; ‡Department of Neurology, University of Kentucky Medical Center, Lexington, Kentucky, U.S.A.; ¶Barrow Neurological Institute, Phoenix, Arizona, U.S.A.; §Department of Neurology, Ohio State University, Columbus, Ohio, U.S.A.; #Tampa General Hospital, University of South Florida, and Willsley Research, Inc., Tampa, Florida, U.S.A.; and **GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.

SUMMARY

Purpose: To assess anger/hostility during treatment with lamotrigine adjunctive therapy versus levetiracetam adjunctive therapy in patients with partial seizures.

Methods: This randomized, double-blind, parallel-group study in adults with partial seizures included an 8-week escalation phase, during which adjunctive lamotrigine (n = 112) or adjunctive levetiracetam (n = 116) was titrated to a target dose, and a 12-week, double-blind maintenance phase, during which dosages of study medication and concomitant antiepileptic drugs were maintained. The primary endpoint was change from baseline to the end of the maintenance phase (week 20) in the Anger-Hostility subscale score of the Profile of Mood States (POMS).

Results: Improvement with lamotrigine relative to levetiracetam was observed for mean ± SD (standard deviation) change from baseline to the end of the maintenance phase (week 20) on the Anger-Hostility subscale (lamotrigine −2.0 ± 8.2, levetiracetam −0.3 ± 8.4; p = 0.024) (the primary endpoint); the Anger-Hostility subscale on weeks 5, 6, 7, 8, 9, 11, 12, 14, 16, 18, and 19; and the Total Mood Disturbance score on weeks 6, 7, 8, 9, 11, 12, 17, 19, and 20. Improvement (p < 0.05) with lamotrigine relative to levetiracetam was also observed on the POMS subscales Depresion-Depression, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. No difference in seizure frequency was observed between groups. The most common adverse events with both medications were headache and dizziness.

Discussion: Adjunctive lamotrigine significantly improved Anger-Hostility subscale scores relative to adjunctive levetiracetam in patients with partial seizures at the end of 20 weeks. This difference was consistently observed throughout the treatment period. Similar improvement with lamotrigine versus levetiracetam was observed for other mood symptoms.

KEY WORDS: Epilepsy/seizures, Antiepileptic drugs, Partial seizures, Clinical trials.
“forced normalisation is the phenomenon characterised by the fact that, with the occurrence of psychotic states, the EEG becomes more normal, or entirely normal, as compared with previous and subsequent EEG findings.”

- Patients with uncontrolled seizures with history of episodic psychosis
  - aim of complete seizure control should be carefully approached
  - recent change (within 30 days) of AEDs (felbamate, lamotrigine, tiagabine, topiramate, vigabatrin, and zonisamide)
# Neurotransmitters and forced normalization

## TABLE 1. Relationship between seizures and psychosis

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Seizures</th>
<th>Psychosis</th>
<th>Tentative relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Anticonvulsant</td>
<td>Propyschotic</td>
<td>Antagonism</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Proconvulsant</td>
<td>?Antipsychotic</td>
<td>Antagonism</td>
</tr>
<tr>
<td>Peptides</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Serotonin</td>
<td>?Proconvulsant</td>
<td>?Propyschotic</td>
<td>Unclear</td>
</tr>
<tr>
<td>GABA</td>
<td>Anticonvulsant</td>
<td>Propyschotic</td>
<td>Antagonism</td>
</tr>
</tbody>
</table>
Interactions between AEDs and psychotropic drugs: *Pharmacokinetic*

- enzyme-inducer AEDs (PHT, PB, CBZ)
  - reduce plasma concentration of psychotropic medications
- enzyme inhibitor (VPA)
  - safely be used with a wide range of antidepressants (ADs) and antipsychotics (APs)
- New AEDs
  - Pregabalin, Gabapentin, Levetiracetam
    - have a better and more selective pharmacokinetic profile
    - can be safely prescribed in combination
  - Lamotrigine
    - biotransformed in the liver, not by the cytochrome P450 system, but almost exclusively by uridindiphosphate glucuronyltransferase (UDPGT)
    - can be safely combined with most psychotropic drugs

Table 2 Relevant interactions between antiepileptic and psychotropic drugs

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>CBZ</th>
<th>PB</th>
<th>PHT</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↓</td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td></td>
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<tr>
<td>Imipramine</td>
<td>↓</td>
<td></td>
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<td>↑</td>
</tr>
<tr>
<td>Desipramine</td>
<td>↓</td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>=</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Sertraline</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td></td>
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<tr>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
<td></td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>CBZ</th>
<th>PB</th>
<th>PHT</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
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<tr>
<td>Thioridazine</td>
<td>↓</td>
<td></td>
<td>↑</td>
<td></td>
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<tr>
<td>Haloperidol</td>
<td>↓</td>
<td>=</td>
<td>↓</td>
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</tr>
<tr>
<td>Clozapine</td>
<td>↓</td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>↓</td>
<td></td>
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</tr>
<tr>
<td>Risperidone</td>
<td>↓</td>
<td>=</td>
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<td></td>
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<tr>
<td>Ziprasidone</td>
<td>↓</td>
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<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>↓</td>
<td></td>
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</tr>
</tbody>
</table>

Symbols at left refer to the psychotropic drug and symbols at right to the anticonvulsant drug, when prescribed in combination (blank fields = data not available).

↑, increased plasma concentration; ↓, decreased plasma concentration; =, unchanged plasma concentration; CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; VPA, valproate.
Interactions between AEDs and psychotropic drugs: **Pharmacokinetic**

- **Antidepressants (ADs)**
  - Older, such as the tricyclics (TCAs)
    - have a complicated metabolism, with active metabolites and inhibiting properties affecting different isoforms of CYP
  - Newer-generation drugs, such as SSRIs, SNRIs, NRI
    - better pharmacokinetic profile without marked influence on the metabolism of AEDs

- **Antipsychotics (APs)**
  - Clozapine
    - characterized by a large variability in its PK
  - Olanzapine
    - dose adjustments rarely necessary even when EI-AEDs are co-prescribed

1. Add-on effects
   - common CNS side effects shared by these classes of drugs
   - CBZ with clozapine (agranulocytosis) is not recommended
     Koch-Stoecker S. Epilepsia 2002;43(suppl 2):19–24

2. Adverse effects on seizure thresholds of APs and ADs
   - at standard doses, should not be overestimated
   - low doses may even improve seizure control, possibly by
     - suppressing emotional seizure precipitating factors
     - direct serotonergic influence of ADs
   - high dose levels, rapid dose increments, drug combinations
     - tendencies to lower the seizure threshold
Interactions between AEDs and psychotropic drugs: Pharmacodynamic

- Clozapine and chlorpromazine
  - the most proconvulsant APs
- Seizure-aggravating effect of atypical APs is usually modest
  - Risperidone: less associated with seizure exacerbation than olanzapine

- Causes of acute exacerbations are often complex
  - drugs may only represent one of several subthreshold factors (emotional factors, lack of sleep, and stress)
  - concomitant withdrawal from benzodiazepines and the neurotoxic effects of APs or ADs may enhance the risk of seizures
Resective epilepsy surgery

- chronic interictal psychosis has been considered as a contraindication to epilepsy surgery
  - Psychotic symptoms usually do not improve after the operation
  - exacerbations of psychosis after seizure remission are a concern

- schizophrenia-like psychosis can arise de novo after temporal lobectomy (phenomenon of forced normalization)
Resective epilepsy surgery

Surgical treatment of temporal lobe epilepsy with interictal psychosis: results of six cases

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Received 6 September 2002; revised 27 November 2002; accepted 21 January 2003

Abstract

We describe the postsurgical outcome of six patients with medically intractable temporal lobe epilepsy and interictal psychosis who underwent temporal lobe resection. All patients were submitted to a comprehensive presurgical investigation, including prolonged video-EEG monitoring. Despite their psychotic disorders, all patients were able to provide informed consent and we were able to complete the investigation of all cases. Surgical complications occurred in two cases. Seizure outcome was Engel class I (free from incapacitating seizures) in all except one patient. There was no worsening of their psychoses. Until now, there has been relative improvement in the mental conditions of five patients. Although psychosis has been considered by some authors as a contraindication to epilepsy surgery, with appropriate psychiatric intervention, patients with refractory epilepsy and chronic interictal psychosis may be submitted to prolonged presurgical investigation and undergo surgery successfully.

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POSTICTAL PSYCHOSES
- Onset in the late postictal period (hours or days after) of an isolated or cluster of CPS, with or without secondary generalization
- Prevalence
  - 4% in cases of apparently controlled epilepsy
  - 7–18% in refractory epilepsy
- Good outcome for postictal psychotic episodes after temporal lobectomy

INTERICTAL PSYCHOSES
- Chronic and/or recurrent
- Progress with persistence of psychotic symptoms
- Prevalence is variable
  - 2 to 7.1% in general population
  - 0.8 to 9.2% in general clinics
  - 8.8 to 27% in epilepsy clinics
- Epilepsy surgery programs reject patients with interictal psychosis

Prevalence is variable
- 2 to 7.1% in general population
- 0.8 to 9.2% in general clinics
- 8.8 to 27% in epilepsy clinics
- Good outcome for postictal psychotic episodes after temporal lobectomy
Surgical treatment for patients with refractory epilepsy and interictal psychosis is worthwhile due to:

- Better psychosocial functioning
- Better integration into psychiatric treatment
- Reductions in AEDs
  - Better adherence to psychopharmacological treatment
  - Lower risk of drug interactions and neurotoxicity
- Less influence of neuroleptics on epileptogenic threshold and seizure control
- Diminished mortality rate
- Lower cost
- Surgery should not be contraindicated because of stigma against mental disorders
Resective epilepsy surgery

- study of 320 patients, Shaw P. J Neurol Neurosurg Psychiatry 2004;75:1003–1008
  - new-onset psychosis in the first month after surgery: 3.5%
    - risk factors: congenital or developmental defects and bilateral EEG abnormalities
- New-onset depression after temporal lobectomy: 4% to 8%, Gaitatzis A. Acta Neurol Scand 2004;110:207–220
- recent controlled study, however,
  - pre-existing depressive symptoms responded better to successful resective surgery than to pharmacologic treatment, Reuber M. Seizure 2004;13:29–35
- Anxiety
  - may develop after epilepsy surgery
  - recognized as the most common psychiatric postoperative problem, Naga AA. Cogn Behav Neurol 2004;17:57–61
Vagal nerve stimulation (VNS)

- VNS has potential for the treatment of various CNS disorders other than epilepsy, including depression and anxiety
- Sustained mood improvements
  - in epilepsy patients in several trials, regardless of seizure outcome
  - isolated mood disorders
- now available as treatment for chronic or recurrent depression

Schachter S. Epilepsy Behav 2004;6(suppl 1):6–9
  - Recent FDA approval (for patients not responded to > 4 adequate ADs
- Strong antianxiety effects of VNS in depressed patients
  - Further studies in anxiety disorders are ongoing
### Table 3 Treatment considerations in epilepsy with psychiatric comorbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Antiepileptic drugs</th>
<th>Resective surgery</th>
<th>Vagal nerve stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Avoid: barbiturates, VGB, TGB, TPM</td>
<td>May be helpful in the long term, but watch for postoperative aggravation</td>
<td>Positive effect</td>
</tr>
<tr>
<td></td>
<td>Consider: LTG</td>
<td></td>
<td></td>
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<tr>
<td>Anxiety</td>
<td>Caution with: LTG, FBM, LEV</td>
<td>No known specific effect, but may be a major part of postoperative psychosocial difficulties</td>
<td>May have positive effect</td>
</tr>
<tr>
<td></td>
<td>Consider: BZD, GBP, PGB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>Avoid: VGB, TPM, ESM</td>
<td>May aggravate interictal psychosis</td>
<td>No known specific effect</td>
</tr>
<tr>
<td></td>
<td>Caution with: LEV</td>
<td>Postictal psychosis may improve</td>
<td></td>
</tr>
</tbody>
</table>

BZD = benzodiazepines; ESM = ethosuximide; FBM = felbamate; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; TGB = tiagabine; TPM = topiramate; VGB = vigabatrin.
comprehensive treatment of people with epilepsy requires that their psychiatric pathologies are recognized and taken into account in their overall management.

Successful AED therapy in patients with psychiatric comorbidities is a comprehensive epilepsy care package:
- psychosocial support
- patient education about the principles of treatment
- be aware of the various effects of the many treatment alternatives
- possess a thorough knowledge of the individual clinical profiles.
감사합니다