Newest AEDs - new information and little known facts

Bassel Abou-Khalil, M.D.

Newest Generation AEDs
- Perampanel
- Eslicarbazepine
- Brivaracetam

Perampanel (PER)
- Approved in USA in 2012
- MOA: noncompetitive antagonism of AMPA glutamate receptor

PER - pharmacokinetics
- Oral absolute bioavailability: ~100%
- Protein binding: ~95%
- Extensively metabolized by primary oxidation mediated by CYP3A followed by glucuronidation
- Excretion: as inactive metabolites, 30% in the urine and 70% in the feces.
- $T_{1/2} = 105 \text{ hours}$ (average).

PER - interactions
- PER does not affect other AEDs
- PER dose of 12 mg (not 8 mg) reduces levonorgestrel by ~40%
- Enzyme-inducers decrease PER levels

PER - adverse effects
- Dizziness, somnolence, headache, fatigue, ataxia, blurred vision most common
- Aggression, hostility (black box warning-20% at 12 mg)
PER- efficacy and clinical use

- FDA indication
  - therapy for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older
  - adjunctive therapy for primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older

PER- generalized epilepsy

- Multicenter, double-blind study
- 162 patients ≥12 years with PGTC seizures and IGE randomized to placebo or perampanel (4-week titration from 2 to 8 mg/d, or highest tolerated dose) and 13-week maintenance period.
- Perampanel conferred greater median % change in PGTC seizure frequency (38.4% vs 76.5%) and greater 50% PGTC seizure responder rate (39.5% vs 64.2%).
- Seizure freedom during maintenance: placebo: 12.3%; perampanel: 30.9%

PER- generalized epilepsy

French et al, Neurology 2015

PER- progressive myoclonic epilepsy (PME)- Lafora disease (LD)

- 21-year-old woman with Lafora disease (EPM2A mutation) presenting at 14
- Daily myoclonus and GTCS every 3–4 days despite high doses of valproate, levetiracetam, clonazepam, piracetam, and zonisamide and ketogenic diet.
- Ataxia, disturbance of speech and gait, cognitive decline
- Adjunctive therapy with perampanel titrated up to 8 mg/day produced a sustained remission of myoclonus and GTCS for 3 months. Seizures recurred after dosage reduction to 6 mg/day, stopped again with titration to 10 mg/day.
- Patient regained ability to walk with help or walker.

PER- progressive myoclonic epilepsy (PME)- Lafora disease (LD)

Case report (Schorlemmer et al, 2013)

PER- PME- LD

- 15-year-old girl with onset of seizures at 12- GTCS then multifocal myoclonic jerks, with increasing frequency and intensity. EPM2B mutation.
- Progressive dysarthria, ataxia, and cognitive regression + frequent falls from myoclonus- wheelchair bound
- Failed valproate, lamotrigine, topiramate, levetiracetam, clonazepam- taken off all AEDs
- GTC every 2 days and near continuous multifocal spontaneous and action myoclonus
- Perampanel titration to 10 mg per day: one GTC in >1 month; striking improvement in myoclonus
- 7 months FU: able to run, write without myoclonus, and perform all activities of daily living independently.

PER- PME- LD

Case report (Dirani et al 2014)

PER in 10 patients with LD

- 10 patients with confirmed LD.
- Open-label adjunctive PER (mean dose of 6.7 mg/day).
- Assessed month before and at 3 and 9 months.
  - 3 patients withdrew because of inefficacy or side effects.
  - Four had significant reduction in seizures of greater than 74% from baseline. Seven had major improvement in myoclonus
- No significant improvement in disability and cognition.
- PER adjunctive therapy appears to confer particular benefit not commonly seen with other AEDs on

Goldsmith and Minassian 2016
Vanderbilt patient

- 20 year old man with GTC since age 13, myoclonic and absence seizures.
- EEGs showed 3.5-4 Hz SW discharges and PPR.
- Seizure frequency worsened despite multiple AED trials and VNS. He was having ~2 GTC clusters per week + disabling myoclonus.
- Genetic testing confirmed Unverricht Lundborg disease
- Addition of perampanel 4 mg per day produced dramatic response for myoclonus and GTCs

Perampanel for PME- ULD

Crespel et al, Epilepsia 2017

- 12 patients with Unverricht-Lundborg disease. Six had GTC and MYO seizures; all had action myoclonus
- PER was introduced by 2 mg steps at 2-4 week intervals until 6 mg/day, with a possible dose reduction or dose increase.
- Ten patients had a clear clinical response of myoclonus, and five were able to reduce concomitant therapy. Improvement was noted sometimes as soon as with 2 mg/day.
- Epileptic seizures stopped on PER in all six patients with seizures (100%).
- Some decrease in efficacy on myoclonus was seen in 2 patients.
- 6 had psychiatric adverse effects
- PER may show marked efficacy even in severe cases.

Other case reports/series

- Lance-Adam syndrome- complete cessation of jerks, recurrence with discontinuation, resolution at 4 mg per day
- Refractory hypoxic myoclonic status
- Epilepsia partialis continua- resolution with PER, recurrence with withdrawal
- Refractory and superrefractory status (12 patients)- 5 nonconvulsive SE (NCSE) with and 6 without coma. Two responded to PER (4 to 12 mg titration)

PER combinations

Kwan 2015

- Post hoc analysis conducted to assess impact of concomitant AEDs on PER efficacy and tolerability.
- As expected, efficacy was less in the presence of an enzyme-inducing AED.
- Efficacy was not affected by presence or absence of a non-enzyme-inducing sodium channel blocker.
- Efficacy was reduced in the presence of multiple AEDs, possibly reflecting more drug resistance rather than a pharmacodynamic interaction.
- Tolerability was not affected by concomitant AED mechanism or AED number.
Psychiatric adverse effects

- Analysis of pooled safety data from three phase III studies in patients with partial seizures.
- Overall rate of psychiatric TEAEs was higher in the 8 mg (17.2%) and 12 mg (22.4%) PER groups versus placebo (12.4%).
- Hostility/aggression were observed in 12.3% for 8 mg and 20.4% for 12 mg perampanel groups, versus 5.7% for placebo.
  - Resulting in discontinuation PER = 1.6% versus placebo = 0.7%.

PER psychiatric adverse effects

- Similar among PER-treated patients receiving or not receiving LEV, TPM or both. Severe/serious hostility and aggression were rare and occurred at a similar rate regardless of concomitant LEV/TPM.
- Seem more common in individual with intellectual disability (15 of 27), with aggressive behavior being the commonest effect.
- Behavioral AEs in 40.3% (62 pts- mean dose 5.4 mg). Most common were aggression, agitation, disruptive behavior, and mood symptoms.
- Hostility/aggression were observed in 12.3% for 8 mg and 20.4% for 12 mg perampanel groups, versus 5.7% for placebo.

PER cognitive effects

- 133 patients 12 to <18 years with focal seizures on 1-3 AEDs were randomized (2:1) to perampanel or placebo.
- Changes in neuropsychological outcomes were assessed at end of maintenance.
- In the full analysis set, there were no differences in CDR System Global Cognition Score, Quality of Working Memory, or Power of Attention.
- There were small differences with perampanel vs. placebo in other CDR System domains: improvements in Quality of Episodic Memory, and worsening in Continuity of Attention and Speed of Memory.
- Letter fluency, category fluency, and LGPT were not significantly different between groups.

Eslicarbazepine Acetate (ESL)

- Approved for marketing in the USA in 2014.
- A prodrug of eslicarbazepine- rapidly converted to the active metabolite (S)-licarbazepine by hydrolytic first-pass metabolism. (S)-licarbazepine is the active enantiomer of the monohydroxy derivative, which is the active metabolite for oxcarbazepine. The monohydroxy derivative from oxcarbazepine is a racemic mixture of the active (S)-licarbazepine and the inactive (R)-licarbazepine.
- Eslicarbazepine acts by blocking sodium channels and stabilizing the inactive state of the voltage gated sodium channel.

ESL- absorption, distribution

- Bioavailability >90%
- T max 1-4 hours post-dose.
- Food has no effect on absorption
- Protein binding <40%
- Vd= 0.87 L/Kg

ESL- metabolism, elimination

- Eslicarbazepine is metabolized to inactive compounds. It is not subject to autoinduction.
- Renal excretion, 60% unchanged, 30% glucuronide conjugate, 10% other metabolites.
- T1/2 ~ 13-20 hours in plasma, 20–24 hours in CSF.
ESL- interactions

- Moderate inhibitory effect on CYP2C19
  - can cause increased plasma concentration of phenytoin and other drugs metabolized by CYP 2C19
- Can induce CYP3A4, decreasing plasma concentrations of estrogen and drugs metabolized by CYP 3A4
- No apparent autoinduction
- Enzyme inducers may reduce level of eslicarbazepine

ESL- efficacy and clinical indications

- Effective against partial-onset (focal) seizures
  - FDA indication: treatment of partial-onset seizures (4 years and older)
  - Should be avoided in IGE
- Theoretical considerations suggest ESL could be considered as first-line monotherapy for focal seizures, with tolerability advantages over immediate-release oxcarbazepine (but financial considerations may be an obstacle).

ESL effect on lipids

- 36 adult patients with epilepsy
- Sodium level, total cholesterol (TC), low (LDL) and high (HDL) density lipoproteins and triglycerides measured before and 6-18 months after.
- TC and LDL values were significantly decreased already after at least six months of therapy with ESL (191.3 vs 179.7mg/dl, and 114.58 vs 103.11mg/dl).
- HDL values before and during ESL treatment were significantly increased (57.5 vs 63.9mg/dl).
- Triglycerides and sodium were unchanged

ESL and concomitant CBZ

<table>
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<th>TEAE event, n (%)</th>
<th>Placebo 400</th>
<th>800</th>
<th>1200</th>
<th>Total</th>
<th>+CBZ 400</th>
<th>800</th>
<th>1200</th>
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<tr>
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<td>n = 116</td>
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<td>3 (3)</td>
<td>5 (2)</td>
<td>11 (3)</td>
<td>4 (4)</td>
<td>4 (2)</td>
<td>11 (1)</td>
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<tr>
<td>Blurred vision</td>
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<td>0</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>5 (2)</td>
<td>1 (1)</td>
<td>7 (7)</td>
<td>12 (7)</td>
</tr>
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</table>

Pulitano 2017
ESL AEs +/- LTG

ESL- influence of titration rate and dose on AEs

- Data from three focal epilepsy placebo-controlled trials.
- 1447 patients randomized to ESL 400, 800, or 1200mg QD (dosing was initiated at 400 or 800mg QD) or placebo.
- During the double blind period, the incidence of common AEs were lower in patients who initiated ESL at 400mg vs 800mg QD. For the 800 and 1200mg QD maintenance doses, rates of TEAEs leading to discontinuation were lower in patients who began treatment with 400mg than in those who began taking ESL 800mg QD.
- Initiation of ESL at 400mg QD for 1 or 2 weeks is recommended.

ESL in elderly

- 29 patients >65 years (mean age 71.2)
- At 12 months, mean dose was 850mg/day, retention rate 69%, responder rate 62%; 24.1% were seizure-free.
- At 12 months, 16 patients (55.2%) had ≥1 adverse effect (AE), that led to discontinuation in 7 patients.
- Dizziness, nausea and ataxia were the most common AEs.
- Tolerability profile improved in 4/5 patients who switched from carbamazepine (CBZ) or oxcarbazepine (OXC) to ESL due to AEs.

ESL- elderly vs young adults

- A single-center, retrospective study of patients with focal epilepsy treated with ESL.
- 72 patients (14 were ≥60 years old); 59 (12 were ≥60 years old) treated for ≥6 months.
- Both groups achieved better seizure control from an average of 2 to 0.5 (young adults) and 3.5 to 0.65 seizures per month, respectively.
- AEs leading to discontinuation were more frequent in elderly (42.9%) than in young adults (17.2%).
- Hyponatremia is 4.3% of young adults vs 16.7 in

ESL transition from OXC

- 21 patients switched overnight from bid OXC to Qd ESL (1:1) as inpatients or outpatients due to persistent seizures and adverse effects.
- Assessments were performed immediately prior to and 5 days after switching from OXC to ESL.
- Significant improvements in mean scores for AEP (P<.001), QOLIE-10 (P=.001), and alertness (P<.05).
- Adverse Events Profile total scores improved for all patients, QOLIE-10 total scores improved for 17/21 (81.0%) patients, and alertness scores improved for 16/21 (76.2%) patients.
Brivaracetam (BRV)

- Approved in USA in 2016
- FDA indication: treatment of partial-onset seizures in patients ≥16 years of age with epilepsy
- MOA: binding synaptic vesicle protein 2A (SV2A) with ~20-fold higher affinity for than levetiracetam
- Higher brain permeability than levetiracetam
- Broad spectrum in preclinical models

BRV- Pharmakokinetics

- Bioavailability ~100%
- Weakly bound to plasma proteins (~17.5%)
- Half-life ~ 9 h
- Renally excreted following extensive metabolism, primarily by hydrolysis and to a lesser extent by CYP-dependent hydroxylation (main isoenzyme responsible for hydroxylation is CYP2C19)

BRV - Interactions

- Enzyme inducers (PHT, CBZ, PhB) reduce BRV levels
- BRV may increase CBZ-epoxide; may increase PHT concentration by up to 20%

BRV- Clinical Studies

- 100 and 200 mg doses more effective than placebo for all outcome measures; responder rates 38.9 and 37.8% (Klein et al, 2015)
- 20 and 50 mg efficacy inconsistent across studies
- Not effective in patients taking levetiracetam
- Efficacy numbers better in levetiracetam naïve patients that in patients who failed levetiracetam (but this may be due to greater drug resistance in patients who failed LEV)

BRV- adverse effects

- Somnolence, dizziness and fatigue most common AEs
- The incidence of irritability was 0.4% PBO; 3.2% BRV 100 mg/day, 2.8% BRV 200 mg/day

BRV - Clinical Use

- Wide spectrum agent (but only approved for partial-onset seizures)
- Available in oral tablets (10, 25, 50, 75, 100 mg), oral solution (10 mg/ml), injection (10 mg/ml) for oral replacement
BRV- Pooled data from 3 phase 3 studies
BenMenachem, Neurology 2016

- 409 pts- adjunctive PCB or BRV 50-200mg/day without titration
- Median % reduction in SGTCs frequency: placebo, 33.3%; BRV 50mg/day, 66.6% (p=0.001); BRV 100mg/day, 61.2% (p=0.002); and BRV 200mg/day, 82.1% (p<0.001).
- ≥50% responder rate for SGTCs : placebo, 33.0%; BRV 50mg/day, 61.3% (p=0.003); BRV 100mg/day, 55.0% (p<0.001); and BRV 200mg/day, 64.0% (p<0.001).
- Freedom from SGTCs: placebo, 14.8%; BRV 50mg/day, 22.6%; BRV 100mg/day, 31.0%; and BRV 200mg/day, 36.0% of patients.
- Almost one-third (30.4%) of patients overall were rendered completely free of SGTCs during the 12-week treatment period.

BRV- secondarily generalized tonic-clonic seizures
Moseley, 2017

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Efficacy against secondarily generalized tonic-clonic seizures- pooled data
Moseley et al, Epilepsy Res 2016

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BRV in older adults
Brodie 2016

- Pooled analysis from three trials of BRV in focal seizures
- 32 patients aged ≥65 years were randomized to placebo or BRV 50-200 mg/day; 30 patients (93.8%) completed.
- 87.5% placebo- vs 73.3% BRV-treated patients reported AEs
- Median percent reduction from baseline in focal seizure frequency was 14.0% for placebo vs 25.5, 49.6, and 74.9% for BRV 50, 100, and 200 mg/day, respectively.
- The ≥50% responder rate was 14.3% for placebo vs 25.0, 50.0, and 66.7% for BRV 50, 100, and 200 mg/day, respectively.
- BRV may be suitable for this age group

BRV in Unverricht Lundborg disease
Kalviainen, 2016

- Two prospective, multicenter, double-blind, phase III trials
- Patients with moderate-severe myoclonus randomized (1:1:1) to twice-daily BRV (N01187: 50 or 150 mg/day; N01236: 5 or 150 mg/day), or placebo.
- Primary efficacy end point was % reduction from baseline in action myoclonus score at last treatment visit.
- N01187: 50 patients randomized, 47 completed; N01236: 56 patients randomized, 54 completed.
- Effect of BRV on action myoclonus was not statistically significant.
- However, action myoclonus score showed wide intrapatient variability and may not have been the optimal tool to measure severity of myoclonus in EPM1.
Reduction of behavioral adverse events (BAEs) associated with LEV by switching to BRV

- 27/29 (93.1%) patients (≥16 years of age) switched overnight from LEV 1-3 g/d to BRV 200 mg/d had clinically meaningful reductions in BAEs.
- HRQoL scores improved.
- Patients experiencing BAEs associated with LEV may benefit from switching to BRV.

Yates et al. Epilepsy & Behavior 2015

BRV- Anger assessment

- Prospective open-label study of 17 pts treated with BRV compared with a control group (22 including 13 with LEV)
- State-Trait Anger with the Expression Inventory-2 (TAXI)
- BRV increased anger measures less than LEV in epilepsy patients.

Ortega, 2017