Thirty Years of 'New' Antiepileptic Drugs: What Did We Achieve, and What is Next?

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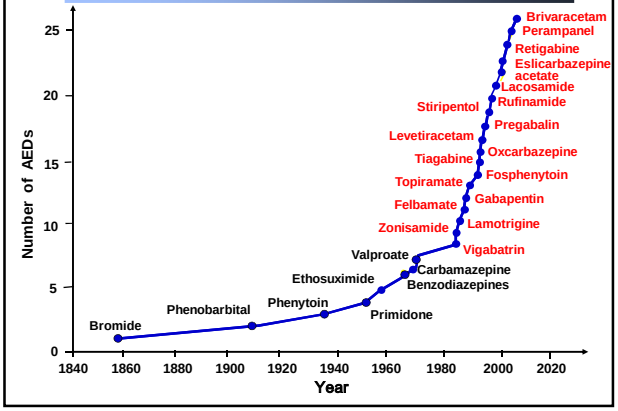
Introduction of AEDs over the Years



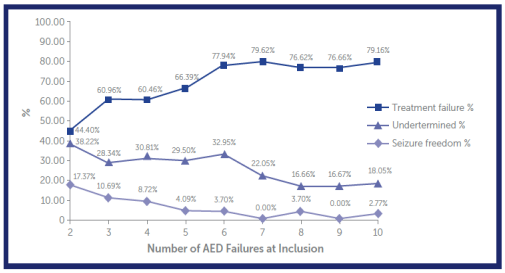
Treating Epilepsy in 2017: The Bright Side

- Two thirds of patients achieve seizure freedom with available AEDs, usually with little or no side effects
- Available drugs differ in efficacy spectrum, side effects and impact on comorbidities – opportunities to tailor treatment choices have never been greater
- We learnt how to combine AEDs more effectively in difficult-to-treat patients
- There have been advances in identifying patients eligible for epilepsy surgery

Treating Epilepsy in 2017: The Dark Side

- About one third of patients are pharmacoresistant – the same as in 1938!
- None of existing drugs is ideal in terms of ease of use and tolerability profile
- Currently available drugs suppress the symptoms, but do not affect the underlying disease
- Using at best an armamentarium of 25 drugs is a challenge, and the risk of suboptimal use is significant

Response Status (ILAE Criteria) after Adding another AED in1,053 Adults with Pharmacoresistant Epilepsy as a Function of Previous AED failures (Physician's Assessment)



Perucca et al. Presented at the XII European Congress of Epileptology, Prague, 11-15-September 2016

Has the Introduction of New AEDs Reduced the Burden of Drug Resistance?

Results from an Expanding Single-Center Cohort

Percentage of newly diagnosed patients achieving seizure freedom (minimum FU of 2 years):

Kwan and Brodie, 2000[1]	63.4% (333/525)
Mohanraj and Brodie, 2005[2]	64.6% (504/780)
Brodie et al, 2012[3]	68.2% (749/1098)

[1]New Egl J Med 200; 342:314-09; [2]Epilepsy and Beahavior 2005;6:382-7; [3]Neurology, 2012;78:1548-54; [4]Brodie et al, Istanbul IEC, Sept 2015

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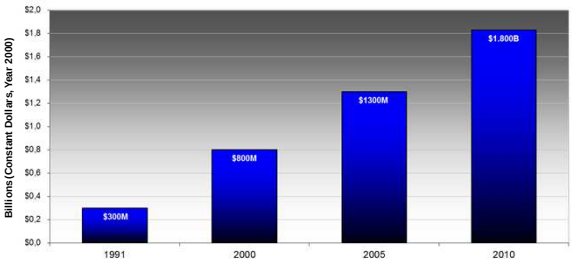
Major Unmet Needs in Epilepsy Treatment

- More efficacious treatments for patients who are currently pharmacoresistant
- Predictors of responses to individual drugs - would allow avoidance of trial-and-error approach
- Safer treatments for certain patient groups (e.g. women with generalized epilepsies)
- Treatments targeting the underlying disease, rather than merely symptomatic drugs

The Increasing Cost of Drug Development

Cost to Develop One New Drug[1]



Sources: [1]J. DiMasi and H. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics*, 2007; J. DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 2003; Paul et al Nature Rev Drug Discovery 2010

Underestimated Incentives to Develop New AEDs

- A new AED with good efficacy/tolerability can still be very profitable, despite modest impact on drug resistance
- Opportunities for orphan indications – small market compensated by fast track development and premium prices
- Value can be enhanced by biomarker-guided AED development, and the advent of precision medicine
- Other advances made possible by better models, new paradigms, and new indications, incuding disease modification (and non-epilepsy indications)

Potential AEDs in Clinical Development (2017)

- Allopregnanolone
- Beprodone (VLB-01)
- Cannabidiol
- Cannabidivarin
- Cenobamate (YKP3089)
- Cerliponase α (BMN 190)
- CNN 1014802
- CPP 15
- 2-Deoxy-glucose
- Ganaxolone
- JNJ-26489112
- Huperzine A (INS001)
- Naluzotan (PRX 0023)
- PF-04895162 (ICA-105665)
- Pitolisant
- Selurampanel (BGG492)
- SAGE 217
- TAK 935
- Tonabersat

*List excludes compounds registered for other indications and now being tested as potential AEDs

Targets of Potential AEDs in Development

'Traditional' targets	'Novel' Targets
AMPA receptors (selurampanel)	CB receptors (cannabidiol, cannabidivarin)
$GABA_A$ receptors (allopregna-nolone, ganaxolone)	AchE (huperzine A)
GABA transaminase (CPP 115)	Gap junctions (tonabersat)
Potassium channels (ICA105665)	Glycolysis (2-deoxy-glucose)
Sodium channels (cenobamate, CNN 1014802)	H_3 receptors (pitolisant)
	$5\text{-}HT_{1A}$ receptors (naluzotan)
	Melatonin receptors (VLB-01)
	Cholesterol 24S-hydroxylase (TAK935)

Future Epilepsy Therapies - Where Will the Next Breakthrough Come From?

- Gene or microRNA silencing (e.g., antagomirs)
- Gene therapy (e.g., studies with neuropeptide Y)
- Stem cell therapy
- Biosensor-mediated focal drug delivery to the brain (closed loop technology, including seizure prediction)
- Optogenetics and DREADD technology
- Drug delivery via nanoparticles / nanotherapeutics
- Neuromodulation

A Common Denominator of Future Therapies: Precision Medicine

- Identification of reliable predictors of response to specific treatments will allow truly rational drug selection
- Tests are becoming available to identify the molecular cause of epilepsy in the individual
- Treatments can then be selected (or developed) to correct the molecular defect, or its consequences

Examples of Precision Medicine Applied to Epilepsy

- Ketogenic diet for epilepsies caused by GLUT1 deficiency – established
- Everolimus for focal epilepsy associated with tuberous sclerosis - established