**Pharmacoresistant epilepsy:**

"Unmet needs in solving the puzzle(s)"

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**Introduction**

- Despite the availability of > 25 antiepileptic drugs,
- 30% of people with epilepsy do not respond to conventional agents, exhibiting pharmacoresistance (PR)—a high percentage not changed significantly in decades
- Two prevailing hypotheses of pharmacoresistance, target hypothesis and transporter hypothesis, can only partially explain the complexity and diversity of PR
- PR as complex puzzle in which target and transporter hypotheses represent a very small piece of the whole

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**Unknown physiopathology**

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**Pharmacoresistance (PR)**

- International League Against Epilepsy (ILAE) recently defined pharmacoresistance (PR) in epilepsy as a

  "Failure of an adequate trial of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al., 2010)

  "If the patient has had no further seizure for three times the interseizure interval (of the relapsed seizures) or 1 year, whichever is longer, the epilepsy is redefined as drug responsive"
Pharmacoresistance (PR)

- >10 years of research on PR focused on two prevailing hypotheses:
  - "Transporter hypothesis" with reduced drug target sensitivity in epileptogenic brain tissue (Schmidt & Loscher, 2005)
  - "Target hypothesis" with reduced drug target sensitivity in epileptogenic brain tissue (Schmidt & Loscher, 2005)
- Hypothesis of "intrinsic epilepsy severity" (IES)
  - Assumes inherent properties of epilepsy syndrome including genetic traits to be most responsible for drug refractoriness

Role of Multidrug Transporters in Pharmacoresistance to Antiepileptic Drugs

Changes in known AED targets or drug efflux transporters in experimental epilepsy models and human epileptic tissue

- Voltage-gated sodium channels
  - Overexpression of auxiliary subunits
  - Increased expression levels

- Voltage-gated calcium channels
  - Overexpression of auxiliary subunits
  - Increased expression levels

- Calcium influx
  - Increased expression levels

- Hypersensitive (HS)
  - Overexpression
  - Reduced expression

- Multidrug resistance proteins
  - Overexpression
  - Reduced expression

- Active defense mechanisms
  - restricting the penetration of lipophilic substances into the brain

Pharmacoresistance (PR)

- Predictors for PR extensively analyzed with assumption reflect underlying neurobiologic processes
  - Glasgow group (Brodie, 2013) studied largest prospective cohort of newly diagnosed epilepsy demonstrated
    - Localization-related epilepsies higher risk for PR / idiopathic epilepsies (Hitiris et al., 2007)
    - Univariate and multivariate logistic regression analyses revealed
      - Positive family history of epilepsy
      - Previous failed seizures
      - Traumatic brain injury
      - Interictal recreational drug use
      - Prior or current psychiatric comorbidity, particularly depression, as predictors

- Phenomenology important to understanding PR evolves, appears critical to assess predictors on basis of prospective, longitudinal studies
  - 21% of patients with 1st seizure diagnosis or newly diagnosed epilepsy and imaging verified localizations remained drug refractory after 1 year, with or without treatment (Hitiris et al., 2007)
  - Epilepsy analysis perspective from frequently cited cross-sectional MRI study in focal refractory epilepsy (Semah et al., 1998)
  - IED described to indicate a poor treatment prognosis
  - Current dilemma of PR by observation that the temporal pattern of drug response varied significantly in a prospective cohort of 1,098 patients with newly diagnosed epilepsy:
    - 27% had prompt initial response
    - Some with initial response required additional treatments with further AEDs and dosage adjustments before responding
    - < 20% never controlled at any time
    - 30% fluctuated between periods of seizure freedom sometimes lasting more than a year (Brodie et al., 2013)
Pharmacoresistance (PR)

- To overcome these diverse obstacles in explaining PR, an integrative concept introduced, incorporating multifactorial process, including:
  - Severity of the disease,
  - Structural brain lesions
  - Network disturbances with ongoing neural reorganization
  - Genetic/metabolic abnormalities

- Need to move from research approach focusing exclusively on drug mechanisms and targets (sodium channels and GABA receptors) to research concept deepens our understanding of epileptogenesis by analyzing molecular pathways and gene expression mechanisms.

Seizure-free rates with successive antiepileptic drug regimens in patients with newly diagnosed epilepsy

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>No. of patients</th>
<th>Seizure-free monotherapy</th>
<th>Seizure-free combination therapy</th>
<th>Total seizure-free</th>
<th>Total without AED</th>
<th>Total without AED or PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>1,098</td>
<td>148</td>
<td>6</td>
<td>196</td>
<td>13.2</td>
<td>26.3</td>
</tr>
<tr>
<td>Second</td>
<td>100</td>
<td>18</td>
<td>15</td>
<td>45</td>
<td>13.2</td>
<td>24.6</td>
</tr>
<tr>
<td>Third</td>
<td>88</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>1.6</td>
<td>14.7</td>
</tr>
<tr>
<td>Total</td>
<td>322</td>
<td>24</td>
<td>20</td>
<td>44</td>
<td>8.4</td>
<td>12.1</td>
</tr>
<tr>
<td>Total without AED</td>
<td>320</td>
<td>11</td>
<td>11</td>
<td>22</td>
<td>8.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Total without AED or PR</td>
<td>310</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0.6</td>
<td>4.4</td>
</tr>
</tbody>
</table>

1,098 patients undertaken 10 years after the first; Overall seizure-free rate had risen to 68.4%. More patients did well on more than one AED, with the percentage rising from the initial 7% to a current 6.4%.

Genetic studies are unlikely to result in a reliable prediction of drug resistance in individual patients.

Various factors and putative drug-resistance mechanisms correlation with pharmacosensitivity

- Epidemiology and severity of epilepsy
- Disease and network-associated disturbances
- Genetic factors
- Individual drug response

Unmet needs of pharmacoresistant epilepsy

- Comprehensive description of natural history
- Comprehensive description of complications and comorbidities
- A rigorous delineation of epidemiology and socioeconomic impact
- Clinically meaningful diagnostic and prognostic physiologically based electroencephalography (EEG) biomarkers

Unmet needs of pharmacoresistant epilepsy

- Clinically meaningful for biomolecular/biochemical mechanistic understanding of etiopathogenesis
- Representative animal models of pharmacoresistant epilepsy;
- New and effective drugs or other novel treatments
- Promote continuing research and research funding
Need for a Comprehensive Description of the Natural History of Pharmacoresistant Epilepsy

- 70 million people in the world have epilepsy, between 34 and 76 new cases diagnosed per 100,000 every year. More than 30% have drug-resistant seizures.
- What is the natural history of newly diagnosed adult epilepsy?
- What is the natural history of newly diagnosed pediatric epilepsy?
- Do patients develop refractoriness to pharmacotherapy or is some drug resistance do novo?
- What factors predict a poor outcome to treatment?

Need for a Comprehensive Description of Complications and Comorbidities of Pharmacoresistant Epilepsy

- Uncontrolled seizures and exposure to high doses of multiple, ineffective medications result in considerable comorbidity, including:
  - Intellectual disability
  - Seizure-related problems
  - Systemic complications in epilepsy
  - Psychiatric problems such as depression, anxiety disorders, failure to achieve or loss of independence, and poor quality of life
- Cognitive impairment: common and often devastating comorbidity of pharmacoresistant epilepsy
- The cognitive comorbidity can be:
  - Chronic, due primarily to underlying etiology of epilepsy
  - Dynamic or evolving because of recurrent seizures or interictal spikes

Need for a Comprehensive Description of Complications and Comorbidities of Pharmacoresistant Epilepsy

- Effective treatment of pharmacoresistant epilepsy needs to target not only overt seizures but
  - Interictal abnormalities
  - Risk ofSUDEP
  - Full spectrum of comorbidities, from both prophylactic and therapeutic perspective

Need for a Rigorous Delineation of Epidemiology and Socioeconomic Impact of Pharmacoresistant Epilepsy

- Uncontrolled seizures may debilitating psychosocial consequences and carry significant risk of injury and/or death
- It is not uncommon for patients with pharmacoresistant epilepsy to also experience feelings of significant depression and/or anxiety
- Pharmacoresistant epilepsy often chronic, lifelong problem and associated with significant disease-related costs both treatment and social.
Need for a Rigorous Delineation of Epidemiology and Socioeconomic Impact of Pharmacoresistant Epilepsy

- Accurate prediction of cost of pharmacoresistance (at personal and societal level, and financial and emotional level)
- Population-based studies suggest that many people who develop pharmacoresistance do so relatively early in their epilepsy course.
- Various predictors of pharmacoresistance have been identified; however, accurate prediction is still challenging.

Need for Clinically Meaningful Diagnostic and Prognostic Biomarkers: Physiologically Based (EEG)

- Now clear evidence that interictal spikes in animals and humans can result in cognitive impairment (Holmes, 2013).
- In patients with frequent interictal spikes occurring 24 h per day, interictal spikes themselves may play a significant role in cognitive function.
- In young children in whom activity-driven mechanisms drive neuronal connectivity, interictal spikes may have persistent adverse effects on brain development that extend beyond the time of interictal spike.
- Future therapeutics need to consider not only overt seizures but the EEG abnormalities as well.

Need for Clinically Meaningful Diagnostic and Prognostic Biomarkers: Anatomically Based (MRI Imaging)

- Most commonly used neuroimaging method is structural imaging (MRI), but functional images as functional MRI (fMRI) and positron emission tomography (PET) improved the searching for biomarkers.
- MRI quantification analysis to identify subtle structural abnormalities.
- Recent improvements in MRI hardware, software, helping to put cases of “MRI-negative” epilepsy on the decline.
- Need to extend and exploit these technical advancements in pharmacoresistance, enabling insights to diagnosis, prognosis and response to treatment.

Table 2. Distribution of epilepsy syndromes

<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>Status- Free patients with EEG (n, %)</th>
<th>Patients with ongoing seizures and with EEG (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>4 (31)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Dravet syndrome</td>
<td>4 (7)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>West syndrome</td>
<td>1 (4)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy syndrome</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4 (7)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>30</td>
</tr>
</tbody>
</table>

Need for Biomolecular/Biochemical Mechanistic Understanding of Etiopathogenesis for Pharmacoresistant Epilepsy

- Proposed pathoetiologic mechanisms include:
  - Altered expression of drug targets (i.e., receptor or ion channel modifications)
  - Endothelial drug transporter activation (i.e., increasing drug clearance)
  - Intrinsic severity factors (Holtkamp & Meierkord, 2007)
- The ultimate understanding of clinical phenomenology of pharmacoresistance lies within molecular level conceptualization of proepileptogenic cascade.
Need for Biomolecular/Biochemical Mechanistic Understanding of Etiopathogenesis for Pharmacoresistant Epilepsy

- Seizures cause excessive neuronal membrane depolarization, which can influence cellular nucleus.
- Seizures may mediate epigenetic modifications resulting in:
  - Persistent genomic methylation
  - Histone density
  - Posttranslational modifications
  - Non-coding RNA–based changes?
- Addressing such epigenetic mechanisms may be successful strategy to increase brain’s sensitivity to AEDs and may even act as disease-modifying treatment.

Need for Representative Animal Models of Pharmacoresistant Epilepsy

- Although exploiting maximal electroshock and pentylenetetrazole models of seizures profitable in the past, it is probably time to move on.
- Maximal electroshock and pentylenetetrazole are models of seizures (ictogenesis).
- Kindling and pilocarpine–induced spontaneous recurrent seizure models have been put forward as animal surrogates for pharmacoresistance and epileptogenesis.
- Need for relevant models of epileptogenesis can be used screening of new chemical entities.

Features that should prompt antibody search in epilepsy patients

- The detection of antineural autoantibodies in patients with epilepsy led to the concept of "autoimmune epilepsy.
- Patients with antibodies to potassium channel complex have high chance of becoming seizure-free within days to months upon immunotherapy.
- Seizures in setting of antibodies to NMDA receptor have high likelihood to remit, again especially with rapid institution of immunotherapy.

Need for New and Effective Drugs or Other Novel Treatments for Pharmacoresistant Epilepsy

- Although targeting voltage-gated sodium channel and GABA_A ligand–gated ion channel as drug targets profitable in past
- All traditional therapeutics are antictogenic, not anti-epileptogenic
- Future of AEDs development lies in the discovery of anti-epileptogenic

Need for New and Effective Drugs or Other Novel Treatments for Pharmacoresistant Epilepsy

- Ictogenesis (the initiation and propagation of a seizure in time and space) is a rapid electrical/chemical event occurring over seconds or minutes.
- Epileptogenesis (gradual process whereby normal brain transformed into a state susceptible to spontaneous, episodic, time-limited recurrent seizures through initiation and maturation of an "epileptogenic focus"
- Ictogenesis and epileptogenesis have unique differences. However, if we embrace such conceptual changes, will this lead to effective new therapies?
Need for New and Effective Drugs or Other Novel Treatments for Pharmacoresistant Epilepsy

- >100 billion neurons in human brain (with the associated trillions of synaptic connections) capacity for change and plasticity
- Brain will be able to "work around" any new drug, invariably leading to seizure recurrence and pharmacoresistance in a subset of people with epilepsy
- Just as there is no perfect antibiotic
- However, this fear is speculation at present, and need for new and effective drugs for pharmacoresistant epilepsy
- Need for new and effective receptors against to target antiepilepsy agents important

Need to Promote Continuing Research and Research Funding Targeting Pharmacoresistant Epilepsy

- There are many people with pharmacoresistance whose lives could be significantly improved by better therapeutic approaches
- Such improvements benefit to physical and socioeconomic health of society
- Need for continuing research to enable improvements lives of people with pharmacoresistant epilepsy
- Need to actively promote the fact that targeting pharmacoresistant epilepsy is worthwhile goal