Emerging Pharmacotherapy in Down Syndrome

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Down Syndrome

1 in 691 births
400,000 Americans have Down syndrome
6000 children are born with Down syndrome annually

Important Historical Milestones in Down Syndrome

1838 Esquirol describes the appearance of a child with DS
1866 Down describes the clinical features of DS in the medical literature
1959 Lejeune et al. in France and Jacobs et al. in England find a third chromosome in patients with DS

Physical Features Associated with Down Syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upward slanting palpebral fissures</td>
<td>82%</td>
</tr>
<tr>
<td>Loose skin on nape of neck</td>
<td>81%</td>
</tr>
<tr>
<td>Brachycephaly</td>
<td>75%</td>
</tr>
<tr>
<td>Hyperflexibility</td>
<td>73%</td>
</tr>
<tr>
<td>Flat nasal bridge</td>
<td>68%</td>
</tr>
<tr>
<td>Gap between first and second toes</td>
<td>68%</td>
</tr>
<tr>
<td>Epicanthal folds</td>
<td>59%</td>
</tr>
<tr>
<td>Clinodactyly</td>
<td>57%</td>
</tr>
<tr>
<td>Transverse palmar crease</td>
<td>53%</td>
</tr>
<tr>
<td>Protruding tongue</td>
<td>47%</td>
</tr>
</tbody>
</table>

Down syndrome: Medical Issues

<table>
<thead>
<tr>
<th>Medical Concern</th>
<th>% affected</th>
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<tbody>
<tr>
<td>Congenital heart disease</td>
<td>50%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>66-89%</td>
</tr>
<tr>
<td>Ophthalmic conditions</td>
<td>60%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5%</td>
</tr>
<tr>
<td>Endocrine (ie. Hypothyroid)</td>
<td>15-40%</td>
</tr>
<tr>
<td>Dental conditions</td>
<td>60-100%</td>
</tr>
<tr>
<td>Orthopedic anomalies</td>
<td>15%</td>
</tr>
<tr>
<td>Seizures</td>
<td>5-10%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Cognitive Features

- Global Developmental Delay
- Problems with learning
- Problems in speech/language skills
- Learning gets harder with age
- Problems in short and long-term memory
- Well-documented risks of early onset Alzheimer’s disease (~30 years)

Rich in history in cognitive, language, behavioral studies

But, treatment has not progressed at the same pace
Current Treatments is Helpful Down syndrome
- Targets symptoms, but not the underlying mechanism causing these deficits
  - Speech therapy
  - Physical therapy
  - Occupational therapy
  - Special education and resources

So treating the underlying disorder would be better...

Developing Therapies for Cognitive Impairment Caused by Down Syndrome
- Define the problem that we want to target in humans
- Explore animal models that reflect the problems
- Discover the underlying mechanisms or cause of these problems
- Develop rationale drug therapies to fix the problems

Hippocampus and Prefrontal Cortex important for learning and memory
- Learning is normal in infants with DS less than 6 months of age, but becomes more difficult within the 1st year
- A decline may occur in adulthood as Alzheimer onset begins

The Ts65Dn mouse model of Down syndrome
- Short stature
- Flat facie
- Flat nasal bridge
- Protruding tongue
- High arched palate (roof of mouth is high)
- Intellectual disability
  - Learning and memory problems

Cognitive and Behavioral Deficits in Ts65Dn mice
- Hyperactive
- Impaired in performance tasks
  - Morris water maze tests
  - Spatial memory (working, short-term, long-term memory)
- Alteration in the T-maze
Learning and Memory Improvement with GABA-A Blockers

- Ts65Dn (Down syndrome) mice vs. Wild type (normal mice)
- GABA-A Blockers: Picrotoxin, Bilobalide, Pentylentetrazole (PTZ)

GABA (inhibition) vs Glutamate (excitation)

Pathway to Drug Approval

Basic Research
- Ideas and Learning
- Does it Work in Animals?

Preclinical Research
- Is it Safe in Humans Both With & Without Disease?

Phase I
- Does it Work in Humans?

Phase II
- New vs. Old Treatment in Humans, Data for FDA Decision

Phase III
- Ideas and Learning
- Does it Work in Animals?

GABA-A Blockers in Development for Down Syndrome

- Roche Pharmaceuticals R04938581 (GABA-A blocker compound)
  - Ts65Dn
    - Improved learning and memory
    - No observable increased anxiety or seizures

- Martínez-Cué et al. J of Neuroscience, 2013

GABA-A Blockers in Development for Down Syndrome

- Roche Pharmaceuticals R04938581, Phase I
  - 129 healthy volunteers
  - Good safety profile

- RG1662 Phase II trial in Down syndrome
  - Safety profile
  - Placebo controlled (2 groups: drug vs sugar pill)
  - 6 weeks treatment, twice a day dosing
  - 33 patients with DS, 18-30 years
  - 2011-2013; Data Pending

- RG1662 Phase III trial (start September 2013)
  - 10 US Centers (Emory, Duke, Johns Hopkins, etc.)
  - Placebo-controlled (2 groups: drug vs sugar pill)
  - 26 weeks treatment, twice a day dosing
  - 230 patients with DS, 12-30 years
    - 12-30 years in Europe
    - 18-30 years in US
  - Outcome anticipated: Cognitive, working memory, adaptive behavior, language, sleep, parenting stress
Combing Targeted Treatments with Education Intervention

- Medications alone will not reverse the Down syndrome learning problems
- Important for adults with Down syndrome
- Example of learning programs combined with targeted treatment studies
  - Computer learning program
  - Reading program
  - Cogmed working memory program

Challenges in Trial Design to Show New Drugs Work

- Lack of clinical trial experience in Down syndrome
- No template from any developmental disability about how to demonstrate treatment of cognition or underlying disorder
- Dosing, safety, length of treatment
- Side effects in cognitively impaired
- Outcome measures
- Timing