Psychiatric Treatments in Children

Challenges of Psychiatric Treatments

- Psychiatric medications do not treat the causes and mechanisms of psychiatric disorders.
- The etiology and pathophysiology of psychiatric disorders is still unknown
- Psychiatric medications were invented based on random clinical observations.

Challenges of Psychiatric Treatments in Children

- Psychiatric medications in children are generally—
  - less effective than in adults
  - associated with more severe side effects

Antipsychotic Medications

Chlorpromazine was developed in 1950 for "artificial hibernation"

Antipsychotic Medications: Use in Children

<table>
<thead>
<tr>
<th>Evidence Based</th>
<th>Non-evidence based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Other psychotic disorders</td>
</tr>
<tr>
<td>Tourette disorder</td>
<td>ADHD</td>
</tr>
<tr>
<td>Bipolar affective disorder</td>
<td>Oppositional-defiant disorder</td>
</tr>
<tr>
<td>Autism (weak effect)</td>
<td>Conduct disorder (weak effect)</td>
</tr>
</tbody>
</table>

Antipsychotic Medications

1. Old generation:
   Classical (typical) antipsychotics
   [halidol, largactil, perphenan]
Old Generation Antipsychotics: Mode of Action

• Blockade of D2 receptors

Dopaminergic pathways

- Positive symptoms
- Negative symptoms
- Extrapyramidal symptoms

Major Side Effects of Typical Antipsychotics

• Extrapyramidal symptoms
  - Dystonia
  - Parkinsonism
  - Tremor
  - Akathisia
  - Tardive dyskinesia
• Deterioration in negative symptoms and cognitive functioning
• Hyperprolactinemia

Antipsychotic Medications

1. Classic (typical) antipsychotics
   [halidol, perphenan, largactil]
1. Atypical antipsychotics
   [clozapine, risperidal, zyprexa]

Antipsychotics Mode of Action

<table>
<thead>
<tr>
<th></th>
<th>D2</th>
<th>D1, D4</th>
<th>5-HT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atypical</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Advantages of Atypical vs. Typical Antipsychotic Medications

• Less extrapyrmidal side effects
Major Side Effects of Atypical Antipsychotics

- Metabolic syndrome
  - Weight gain
  - Hyperlipidemia
  - Diabetes mellitus

- Occur in about 40% of adult schizophrenia patients treated with atypical antipsychotics

A Meta-analysis of Antipsychotic-Induced Weight Gain in Adults After 10 Weeks of Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight Gain (Kgs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>1.1</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>2.1</td>
</tr>
<tr>
<td>Clozapine</td>
<td>4.5</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>4.2</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Risk Factors for Antipsychotics-Induced Weight Gain in Adolescents

- Males
- Thin
- Low concern about gaining weight
- The rate of antipsychotics-induced weight gain in adolescents is double than that in adults

Caloric Intake and Energy Expenditure At Baseline and after 4 Weeks of Zyprexa Treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 4 weeks</th>
<th>P value weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kgs)</td>
<td>73.8±23.8</td>
<td>77.2±22.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5±5.9</td>
<td>25.9±5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total calories</td>
<td>2127±1032</td>
<td>2716±958</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>REE/kg</td>
<td>24.7±4.6</td>
<td>24.5±3.0</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Physical activity: 90% spent <10 minutes in moderate activity during the day both at baseline and after 4 weeks of treatment !!!
Antidepressant Medications

Iproniazide - The First Antidepressant Medication

Patients with TB treated with iproniazide became “inappropriately happy”

Electroconvulsive Treatment

Invented awing to the false notion that there are very few epileptics who are also schizophrenics

SSRI Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Trade names</th>
<th>Efficacy in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>prozac</td>
<td>depression</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>luvox</td>
<td>anxiety disorders</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>seroxat</td>
<td>not safe in children</td>
</tr>
<tr>
<td>Sertraline</td>
<td>zoloft</td>
<td>not yet established</td>
</tr>
<tr>
<td>Citalopram</td>
<td>cipramil</td>
<td>not yet established</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>cipralex</td>
<td>not yet established</td>
</tr>
</tbody>
</table>

Indications for Antidepressant Medications (SSRIs) in Children

- **Depressive disorders**
  - Major depressive disorder
  - Dysthmic disorder

- **Anxiety disorders**
  - Obsessive-compulsive disorder
  - Separation anxiety disorder
  - Generalized anxiety disorders
  - Panic disorder
  - Posttraumatic stress disorder
  - Social phobia

Serotonergic Synapse
Other Antidepressant Medications

1. Tetracyclines: not effective in children (elatrol, deprexan)
2. NRIs (Norepinephrine reuptake inhibitors) (pramipexol): not controlled studies in children
3. Dopamine reuptake inhibitor (wellbutrin): no controlled studies in children
4. Nonselective reuptake inhibitors (effexor, cymbalta): no controlled studies in children
5. Others (miro): no controlled studies in children

FDA Black Box Warning (October, 2004)

• "Increased rate of suicidality for all antidepressants used in individuals under the age of 18."
• Suicidality:
  – Suicidal ideation: thoughts about death not accompanied by preparatory behavior.
  – Preparatory actions toward imminent suicidal behavior.
  – Suicide attempt

Meta-Analysis of SSRIs in Children

• 24 placebo-controlled trials of antidepressants among 4400 children and adolescents.
• Medications pose a 2 fold increased risk for suicide ideations or attempts (4% on medication vs. 2% on placebo).

SSRIs Efficacy and Suicidality

<table>
<thead>
<tr>
<th></th>
<th>Respond to SSRIs</th>
<th>Respond to Placebo</th>
<th>NNT</th>
<th>Suicidality SSRIs</th>
<th>Suicidality Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>61%</td>
<td>50%</td>
<td>10</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>OCD</td>
<td>52%</td>
<td>32%</td>
<td>6</td>
<td>1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Other Anx. D.</td>
<td>69%</td>
<td>39%</td>
<td>3</td>
<td>1%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Stimulants Treatment for ADHD- History

Bradley first prescribed stimulant medication (Benzedrine) to alleviate headaches following spinal taps.
Methylphenidate (Ritalin) for ADHD

- High short-term efficacy- 80% of children improve
- Very high rate of side effects:
  - Loss of appetite
  - Growth retardation
  - Insomnia
  - Dysphoria
  - Tics
  - Rebound.

Omega-3 Fatty Acids Deficiency in Major Depression

<table>
<thead>
<tr>
<th>Disorder</th>
<th>N</th>
<th>Sex</th>
<th>Age</th>
<th>HDL</th>
<th>DHA</th>
<th>EPA</th>
<th>ALA</th>
<th>LA</th>
<th>All</th>
<th>Total</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>30</td>
<td>F</td>
<td>16-20</td>
<td>700</td>
<td>650</td>
<td>425</td>
<td>58</td>
<td>54</td>
<td>51</td>
<td>36</td>
<td>69</td>
</tr>
<tr>
<td>PDD</td>
<td>30</td>
<td>F</td>
<td>16-20</td>
<td>700</td>
<td>650</td>
<td>425</td>
<td>58</td>
<td>54</td>
<td>51</td>
<td>36</td>
<td>69</td>
</tr>
<tr>
<td>PPD</td>
<td>30</td>
<td>F</td>
<td>16-20</td>
<td>700</td>
<td>650</td>
<td>425</td>
<td>58</td>
<td>54</td>
<td>51</td>
<td>36</td>
<td>69</td>
</tr>
<tr>
<td>SA</td>
<td>30</td>
<td>F</td>
<td>16-20</td>
<td>700</td>
<td>650</td>
<td>425</td>
<td>58</td>
<td>54</td>
<td>51</td>
<td>36</td>
<td>69</td>
</tr>
</tbody>
</table>

MDD = major depressive disorder, PDD = postpartum depression, SA = suicide attempt
CE = Cholesterol esters, PP = plasma phospholipids, EP = erythrocyte phospholipids

Omega-3 Fatty Acids Deficiency in Major Depression


Omega-3 Fatty Acids Treatment for Mood Disorders

Omega-3 Treatment of Childhood Depression


Omega-3 Fatty Acids Treatment for ADHD

What can we do to find more effective treatments for psychiatric disorders?

- Personalized medicine
- Medications that target the causes or deficits of the disorders


* 400mg EPA and 200mg DHA per 1,000mg capsule
**Pharmacogenetics**

- Identifies the relationship between genetic polymorphisms relevant to the mode of action or metabolism of specific drugs and their clinical response.
- The ultimate goal is to enable clinicians to plan therapeutic regimens tailored to the individual patient genetic background.

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**The Serotonin Transporter (5-HTTLPR) Gene**

The S allele of the serotonin transporter is less active than the L allele.

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**Serotonin Transporter Genotype and Response to Citalopram in Children**

- Change in CDRS-R score, adjusted to base-line. 5-HTT(ss) genotype vs. 5-HTT(sL / L).

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**Medications That Target the Causes of Diseases**

- Insulin for Diabetes
- Tissue plasminogen activator (tPA) for ischemic heart disease

Injection of tPA
Psychiatry Lags Behind Medicine in Identifying Pathophysiologically-Based Medications

S-Adenosylmethionine (SAMe) Treatment for Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and SAMe dose</th>
<th>Comparator</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farcher et al. [52]</td>
<td>4-week double-blind 400 mg PO (n=146)</td>
<td>IR 100 mg PO (n=144)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Delle Chies et al. [51]</td>
<td>4-week double-blind 1600 mg PO (n=140)</td>
<td>IR 100 mg PO (n=138)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Joffe et al. [50]</td>
<td>6-week double-blind 1600 mg PO (n=139)</td>
<td>IR 100 mg PO (n=137)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>De Vivo et al. [49]</td>
<td>8-week double-blind 1600 mg PO (n=137)</td>
<td>IR 100 mg PO (n=136)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Strous et al. [48]</td>
<td>12-week double-blind 1600 mg PO (n=136)</td>
<td>IR 100 mg PO (n=134)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Papakostas et al [47]</td>
<td>16-week double-blind 1600 mg PO (n=134)</td>
<td>IR 100 mg PO (n=132)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Joffe et al. [46]</td>
<td>18-week double-blind 1600 mg PO (n=132)</td>
<td>IR 100 mg PO (n=130)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Della Chies et al. [45]</td>
<td>20-week double-blind 1600 mg PO (n=128)</td>
<td>IR 100 mg PO (n=126)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>De Vivo et al. [44]</td>
<td>24-week double-blind 1600 mg PO (n=126)</td>
<td>IR 100 mg PO (n=124)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Joffe et al. [43]</td>
<td>28-week double-blind 1600 mg PO (n=124)</td>
<td>IR 100 mg PO (n=122)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>De Vivo et al. [42]</td>
<td>32-week double-blind 1600 mg PO (n=122)</td>
<td>IR 100 mg PO (n=120)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Joffe et al. [41]</td>
<td>36-week double-blind 1600 mg PO (n=120)</td>
<td>IR 100 mg PO (n=118)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>De Vivo et al. [40]</td>
<td>40-week double-blind 1600 mg PO (n=118)</td>
<td>IR 100 mg PO (n=116)</td>
<td>SAMe/IR</td>
</tr>
<tr>
<td>Joffe et al. [39]</td>
<td>44-week double-blind 1600 mg PO (n=116)</td>
<td>IR 100 mg PO (n=114)</td>
<td>SAMe/IR</td>
</tr>
</tbody>
</table>

SAMe Treatment for Schizophrenia: A Double Blind Placebo Controlled Trial

- Improvement of quality of life and reduction in aggressive symptoms in schizophrenia patients

SAMe is Also an Effective Treatment For

- Osteoarthritis
- Liver diseases

SAMe Synthesis
Biological Pathways of SAMe

SAMe Possible Therapeutic Mechanisms

• SAMe-dependent methylation reactions are necessary for synthesis and inactivation of biogenic amines.

SAMe for Velo-Cardio-Facial / DiGeorge / 22q11.2 Deletion Syndrome

Velo-Cardio-Facial / DiGeorge Syndrome

Typical facial features
• Cleft anomalies
• Congenital cardiac anomalies
• Immunological deficiencies
• Hypocalcemia
• Cognitive Deficits and Average Borderline intelligence
• High rate of psychiatric morbidity

VCFS
DiGeorge Syndrome
**Prevalence of VCFS**
- 1:4,000 live births
- The most common known microdeletion syndrome

**Common Psychiatric Disorders in VCFS**
- ADHD 40%
- Anxiety disorders 50%
- Schizophrenia 30%
- Depressive disorders 20%

**The 22q11.2 Microdeletion Causing VCFS**

**Developmental Effects of COMT Deficiency on Neuropsychiatric Development in VCFS**
- Reduced verbal abilities
- Reduced prefrontal grey matter volume
- Development of schizophrenia, ADHD and other psychiatric disorders

**SAMe Possible Therapeutic Mechanisms**
- SAM-e increases COMT activity
  - by virtue of its methyl donor capability
  - by binding to the COMT enzyme and inhibiting its degradation.

**SAMe: A Pilot Study**
- 4 subjects with VCFS
- Age 15 to 25 years
- COMT Met carriers
- Schizoaffective disorder

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Gothelf et al. Nat Neuroscience, 2005;11:1500-2
Results of SAMe Pilot Study

Thank You