Basic principles of pediatric psychopharmacology

Eesha Sharma MD, PhD
Assistant Professor of Child & Adolescent Psychiatry
Outline

- Setting the forum
- Kinetics, dynamics and development
- Overview of evidence base
- Thoughts for the future
Beginnings of pediatric psychopharmacology

- 30 children with mixed emotional and behavioural symptoms
- Open label ‘benzedrine’
- “noisy, aggressive & domineering” became “calm & manageable"

Bradley C, Am J Psychiatry, 1937

- 93 ‘juvenile delinquents’
- RCT with benzedrine
- Improvement in learning, Motor control, Short-term memory

Molitch & Eccles, Am J Psychiatry, 1937
“.... the efforts of child and adolescent psychiatrists on behalf of troubled children are shaped not only by an evolving knowledge base, but by public opinion, evolving conditions of practice, and regulation. The resulting paradigm shift revives the biopsychosocial model, enhanced through advances in developmental psychology and neuroscience, with increased understanding of the biology of attachment and developmental trauma. In this new paradigm focus on the child’s psychosocial environment is paramount and pharmacotherapy becomes adjunctive to psychosocial interventions.”

Era of easy acceptance ...2005 AD... Era of increasing scrutiny
A paradigm shift

1990’s:
Shift in approach: “least restrictive” & “lowest effective dose” to “most effective” treatment
Outline

- Setting the forum
- Development, kinetics, dynamics
- Overview of evidence base
- Thoughts for the future
The Developing Brain

A. Developmental Course of Brain Maturation

- Sensorimotor Cortex
- Amygdala
- Striatum
- Hippocampus
- Prefrontal Cortex

B. Median Age at Onset of Psychiatric Disorders Across Development

- ADHD/Conduct
- Anxiety Disorders
- Schizophrenia
- Substance Abuse
- Mood Disorders

Meyer & Lee, Am J Psychiatry, 2019
## Pharmacokinetics

<table>
<thead>
<tr>
<th>Classification</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm newborn</td>
<td>0-28 days</td>
</tr>
<tr>
<td>Newborn</td>
<td>&gt;28 days – 12 mnth</td>
</tr>
<tr>
<td>Infant</td>
<td>&gt;12 mnth – 23 mnth</td>
</tr>
<tr>
<td>Toddler</td>
<td>&gt;12 mnth – 23 mnth</td>
</tr>
<tr>
<td>Preschool child</td>
<td>2-5 yrs</td>
</tr>
<tr>
<td>School age child</td>
<td>6-11 yrs</td>
</tr>
<tr>
<td>Adolescents</td>
<td>12-18 yrs</td>
</tr>
</tbody>
</table>

### Absorption
- Gut transit time
- Fluid composition
- Wall permeability

### Distribution
- Fat/water composition
- Protein binding

### Metabolism
- Microsomal enzymes
- Hepatic blood flow
- Gut microbial flora

### Excretion
- Glomerular filtration rate
- Tubular transporters

#### Pre-schoolers and young children:
- Lower proteins + higher blood flow – net higher mg/Kg

### Mature by early infancy
- Pre-schoolers have larger volume of distribution – higher mg/Kg

#### Crabamazepine
- Valproic acid
- Levetiracetam


### Table 2  Summary of Selected Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Results/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genome Wide Association Studies – Adult Subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uher et al 2013</td>
<td>Meta-analysis of 3 GWAS (from GENDEP, MARS, and STAR*D) with total of 2256 adults with MDD</td>
<td>• No genetic predictors linked to characteristic of treatment outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Some preliminary evidence that perhaps some patient sub-populations might improve treatment response</td>
</tr>
<tr>
<td><strong>Combinatorial Gene Guidance – Adult Subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez et al 2017</td>
<td>Subject and rater blinded RCT of PGX guided vs non-guided treatment in 316 adults with MDD</td>
<td>• No difference in primary outcome of sustained treatment response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PGX guided group had greater responder rate especially if subject previously had &gt;1 drug failure</td>
</tr>
<tr>
<td>Rosenblat et al 2018</td>
<td>Meta-analysis of 2 RCTs and 2 open label studies of PGX guided vs non-guided treatment in 1534 adult subjects with MDD</td>
<td>• PGX guided treatment increased likelihood for response and remission</td>
</tr>
<tr>
<td>Greden et al 2019</td>
<td>Subject and rater blinded RCT of PGX guidance vs non-guided treatment in 1167 adults with MDD who had failed ≥ 1 medication trial</td>
<td>• No difference in primary outcome of response at 8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increased response and remission rates in PGX guided groups on secondary analysis</td>
</tr>
<tr>
<td>Bousman et al 2019</td>
<td>Meta-analysis of combinatorial gene testing from 5 RCTs among 1737 adults with MDD</td>
<td>• Subjects with PGX guided treatment were more likely to achieve remission compared to non-guided</td>
</tr>
<tr>
<td><strong>Gene-Medication Association – Pediatric Subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson et al 2007</td>
<td>Retrospective analysis of routine PGX testing in 894 pediatric subjects with ADHD on atomoxetine</td>
<td>• Poor metabolizer status in CYP2D6 was associated with more frequent adverse effects and greater reduction in mean symptom severity relative to extensive metabolizers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 30-fold differences in concentrations of active drug in extensive metabolizers vs poor metabolizers</td>
</tr>
<tr>
<td>Brown et al 2016</td>
<td>Single dose atomoxetine administered in 23 pediatric subjects with ADHD who were stratified based on CYP2D6 metabolizer status</td>
<td>• Metabolizer phenotype was not associated with responder rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Faster metabolizer status of CYP2C19 associated with faster response rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Slower CYP2C19 metabolizer status had decreased tolerability, high discontinuation rates, and longer length of stays</td>
</tr>
<tr>
<td>Aldrich et al 2019</td>
<td>Retrospective analysis of routine PGX testing in 263 pediatric subjects hospitalized with anxiety and depression treated with es/citalopram</td>
<td>• No association between RFAs and response dose or number of adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Slower CYP2C19 metabolizers prescribed lower maximum doses of sertraline</td>
</tr>
<tr>
<td>Poweleit et al 2019</td>
<td>Retrospective analysis of routing PGX testing in 369 pediatric subjects hospitalized with anxiety and depression treated with sertraline</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacogenomics??

Relevant gene polymorphisms

1. Cytochrome P450 liver enzyme systems – 2D6, 2C9, 2C19
   • Normal (extensive) metabolizers: 2 active alleles
   • Intermediate metabolizers: 1 active allele
   • Ultrarapid metabolizers: >=3 active alleles
   • Poor metabolizers: partially/ non-functioning alleles

2. Serotonin transporter
3. Serotonin receptor
4. Catecholamine-O-methyltransferase
5. P-glycoprotein

Drugs with some evidence for pharmacogenomic considerations

CYP 2D6
• Atomoxetine
• Fluvoxamine
• Paroxetine
• Nortriptyline

CYP 2C19
• Citalopram
• Escitalopram

HLA-B HLA-A
• Carbamazepine
• Oxcarbazepine
• Phenytoin

CYP 2C9
• Phenytoin

Recommendations

• Widespread testing not recommended (APA, AACAP, ISPG)
• Role in treatment non-responders
• Start low, go slow and monitor esp in vulnerable populations - children, elderly, ethnic groups
• Drug-drug interactions

Namerow et al, Current Psychiatry Reports, 2020
Outline

- Setting the forum
- Development, kinetics, dynamics
- Overview of evidence base
- Thoughts for the future
Multimodal Treatment of ADHD Study (MTA Study)

- NIMH funded, Six American sites, ADHD-Combined, RCT
- Baseline assessments (10 hours) - Systematic FU 14 mnths - Unstructured FU >15 yrs
- Outcomes: ADHD, externalizing, internalizing, academic, parent-child, social skills

**Efficacy**
- Medication/ Combination more efficacious
- Combination more effective with comorbid anxiety, academic issues, interpersonal distress, etc
- Dose of medication lower with Combination
- High individual variation

**Side effects**
- Severe enough to discontinue ~ 4%
- Loss of appetite
- Sleep problems
- Crying spells
- Repetitive movements
- Slowed growth

**Moderators**
- Anxiety
- Parental depression
- Illness severity
- Low IQ

**Mediators**
- Treatment acceptance/ attendance
- Improved parenting

Jensen PS et al, Arch Gen Psychiatry, 1999
Hinshaw SP, Wiley Interdiscip Rev Cogn Sci, 2015
Preschool ADHD Treatment Study (PATS)

- NIMH’s flagship study in Preschoolers, 6-centre, 2000s,
- DSM-IV ADHD – Combined OR Predominant Hyperactive/Impulsive
- RCT, Effectiveness/Efficacy trial
- Outcome: Parent & Teacher rated

- Significant decreases in ADHD symptoms on MPH (vs Placebo)
  - Effect sizes 0.4-0.8
  - 2.5mg, 5mg, 7.5mg TDS doses; Not with 1.25mg TDS
  - Mean optimal daily dose for group – 14.2+/−8.1 mg
  - Remission 21% on best-dose MPH and 13% on placebo

- Side effects
  - 30% moderate-severe, spontaneously reported
  - Emotional outbursts, Difficulty falling asleep, Repetitive behaviors and thoughts, Appetite disturbances

- In follow-up (> 6 years)
  - 80% children retained diagnosis, esp those with comorbid DBDs
  - Moderate-severe symptom scores
  - Severity dropped till 3 years, not thereafter
  - Greater severity with – lower IQ, those who continued medication
  - Similar trajectories for IA and HI symptoms
  - Parent rating higher than teachers

Collins, JAACAP, 2006
March, JAACAP, 2011
Riddle, JAACAP, 2013
Vitiello, JAACAP, 2015
# Treatment of ADHD

<table>
<thead>
<tr>
<th></th>
<th>Methylphenidate</th>
<th>Atomoxetine</th>
<th>Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>DA/ NE transmission in PFC/ BG</td>
<td>NE reuptake inhibitor</td>
<td>Alpha-2 adrenergic agonist</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>0.3-0.8 mg/Kg</td>
<td>0.8-1.2 mg/Kg</td>
<td>0.05mg/d... up to 0.2-0.3 mg/d</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>2-3 divided doses</td>
<td>Single dose</td>
<td>Up to 4 divided doses</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Within hours</td>
<td>4-6 weeks</td>
<td>Immediate and delayed</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>1. Sleep disturbance</td>
<td>1. Sleep disturbance</td>
<td>1. Sedation</td>
</tr>
<tr>
<td></td>
<td>5. Headaches</td>
<td>5. Headaches</td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>6. Rebound withdrawal effects</td>
<td>6. Dyspepsia</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>7. Over-focussing on details</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. Tics/ mannerisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Choice</strong></td>
<td>First choice</td>
<td>With depressive disorders</td>
<td>With tics</td>
</tr>
</tbody>
</table>

**BLACK BOX warnings**

- Hepatitis, Aggression, Suicidality

- Sedation
- Hypotension, dizziness
- Dry mouth
- Rebound withdrawal effects
- Irritability
- Hypertension

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• Major considerations in choice of treatment:
  - Follow-up feasibility
  - Side effects monitoring
  - Co-morbidity
  - Abuse potential
  - Objective feedback (rating scales)

Lewis’ Child & Adolescent Psychiatry, Fourth edition
Monitor appetite, weight, height and body mass index (BMI) every 6 months.

Differentiate between pre-treatment eating problems and medication-induced eating problems.

Medication after meals, rather than before

High-calorific snacks and late evening meals.

Dose reduction or switching to an alternative class or formulation

Drug holidays for ‘catch up’ growth

Referral to paediatric endocrinologist/growth specialist if values below critical thresholds.


Waxmonsky, J Am Acad Child Adolesc Psychiatry, 2019

Significant reductions in weight & height within 11 months of therapy
**Selective serotonin reuptake inhibitors in children**

Most extensively used antidepressants in children; Maximum empirical support

**FDA approval**
- Fluvoxamine & Sertraline for OCD
- Fluoxetine for depression

Comparable with CBT for depression/OCD

**Duration of treatment:**
- Clinical judgment
- Relapse rates high
- Persistence of disorders like OCD into adulthood

**Adverse effects:**
- GI - nausea, reduced appetite, diarrhoea, heartburn
- Fatigue, headaches
- Behavioural activation
  - Early treatment/Dose increase/ Drug interaction
  - Restlessness, insomnia, impulsivity, disinhibition/ garrulosity
- Hypomania/ Mania - especially in prepubertal children
- Suicidality (??)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Increments</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>2.5 - 10 mg</td>
<td>1-2 weeks</td>
<td>5 - 40 mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>12.5 - 25 mg</td>
<td>Weekly</td>
<td>50 - 150 mg</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>12.5 - 25 mg</td>
<td>Weekly</td>
<td>50 - 200 mg</td>
</tr>
<tr>
<td>Citalopram</td>
<td>5 mg</td>
<td>1 - 2 weeks</td>
<td>5 - 40 mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Not recommended in children/adolescents</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lewis’ Child & Adolescent Psychiatry, Fourth edition ; Rey JM, 2006

# Other antidepressants

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Use</th>
<th>S/e</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (3-6mg/Kg/d)</td>
<td>Depression, ADHD</td>
<td>Seizures (&gt; 150mg at a time OR &gt; 300mg/day)</td>
</tr>
<tr>
<td>Venlafaxine (1-3mg/kg/d)</td>
<td>Depression</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Trazodone (25-200mg/d)</td>
<td>Insomnia</td>
<td>Hypotension, Sedation, Priapism</td>
</tr>
<tr>
<td>Mirtazapine (7.5-30mg/d)</td>
<td>Depression</td>
<td>Drowsiness, Increased appetite, weight gain</td>
</tr>
<tr>
<td>Imipramine (2.5-5mg/Kg/d)</td>
<td>Enuresis</td>
<td>Cardiac events, Sedation, Anticholinergic Seizures</td>
</tr>
<tr>
<td>Desipramine (2.5-5mg/Kg/d)</td>
<td>ADHD</td>
<td></td>
</tr>
<tr>
<td>Clomipramine (2-3mg/Kg/d)</td>
<td>OCD</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Studied in</td>
<td>Doses</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------------------------------------</td>
</tr>
</tbody>
</table>
| Risperidone         | 1. Psychosis  
2. Behaviour problems in autism/ ID  
3. Disruptive behaviour  
4. Tics & Tourette’s syndrome  
5. Augmentation       | 0.25 - 4 mg/d; OD/ BDS             |
| Clozapine           | Treatment resistant psychosis                                               | 50 - 400 mg/d; BDS/TDS             |
| Olanzapine          | 1. Schizophrenia  
2. Bipolar disorder  
3. Aggression/hyperactivity in autism                                      | 2.5 - 10 mg/d; OD/BDS              |
| Quetiapine          | 1. Bipolar disorder  
2. Psychosis                                                              | 100 - 600 mg/d; BDS/TDS            |
| Ziprasidone         | 1. Tics/ Tourette’s syndrome  
2. Behavior problems in autism                                                | 40 - 160 mg/d; BDS                 |
| Aripiprazole        | 1. Bipolar disorder  
2. Schizophrenia  
3. Tics & Tourette’s syndrome  
4. Behaviour problems in autism/ ID  
5. Augmentation       | 2-20 mg/d; OD/BDS                  |
| Haloperidol         | 1. Psychosis  
2. Aggressive behavior  
3. Tics  
4. Behavioral problems with autism                                          | 0.75 - 10 mg/day                   |
| Chlorpromazine      | Severe behavioural dyscontrol                                               | 25 - 400 mg/d; OD/BDS/TDS          |
Antipsychotic side effects in children

- Weight gain, metabolic disturbances
- Cognitive blunting
- Dysphoria
- Elevated prolactin
  - Gynecomastia in boys and galactorrhea/amenorrhoea in girls
- Extrapyramidal side effects (Dyskinesias less common in children)

Anticholinergic agents (Trihexphenidyl)
- If possible, avoid OR time-limited use
- Long-term use (esp in younger children) - Sjogren syndrome
Initial monotherapy preferable when treating an acute mixed or manic state
Atypical antipsychotics show higher response rates when compared with lithium or anticonvulsants
Limited data on long-term safety and effectiveness

<table>
<thead>
<tr>
<th>Medication</th>
<th>Phase of Bipolar Disorder</th>
<th>Age, y</th>
<th>Daily Dose Range, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Mixed/manic</td>
<td>12–17</td>
<td>300–2400 <strong>Upto 1.4 meq/L</strong></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Mixed/manic</td>
<td>10–17</td>
<td>0.25–2.5</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Mixed/manic</td>
<td>13–17</td>
<td>2.5–20</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Mixed/manic</td>
<td>10–17</td>
<td>2–30</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Mixed/manic</td>
<td>10–17</td>
<td>50–600</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine</td>
<td>Depressive episode</td>
<td>10–17</td>
<td>3/25–12/50</td>
</tr>
</tbody>
</table>
Pharmacological options for ASD

- Allow children and adolescents to maximize their benefits from behavioral and psychoeducational interventions
- Interindividual variability present in ASD also spans clinical response to psychoactive drugs and side effect sensitivity.
- No drug directly ameliorates core autism symptoms
- Target symptoms
  - Hyperactivity, impulsivity
  - Agitation, temper outbursts
  - Aggression towards self or others
  - Repetitive behaviors (anxiety and obsessive-compulsive symptoms)
  - Sleep problems

Persico et al, Prog Neuropsychol Biol Psychiatry, 2021
Thom et al, Curr Psychiatry Rep. 2021
Pharmacotherapy for aggression

- A common clinical concern
- Almost all medications tested in RCTs
  - Stimulants
  - Atomoxetine
  - Antipsychotics - typical & atypical
  - Alpha-2 agonists
  - Beta blockers
  - Mood stabilisers
  - Antidepressants
- Effect sizes range between 0.3 - 0.7
- Choice of drug:
  - ABC analysis
  - Functional behavioural analysis
  - “Impulsive (hot)” v/s “Predatory (cold)” aggression
Outline

- Setting the forum
- Kinetics, dynamics and development
- Overview of evidence base
- Thoughts for the future
Effects on developing brain

- Intervention, overall, appears to have a ‘normalizing’ effect
- Lithium normalizes amygdala and hippocampal volumes
- Neuro-cognitive functions are ‘corrected’ by stimulants, antidepressants, mood stabilisers
- Several gaps in knowledge:
  - Is there a critical window period for beneficial effects?
  - What actually mediates the brain changes and clinical benefits?
  - How do trajectories differ in children on long-term treatment?

- Neuronal/neurochemical imprinting:
  - Long-term effects of drug exposure are delayed and come to expression once the vulnerable system reaches maturation (during adulthood)
  - Occurs when the effects of the drug outlast the drug itself

Singh MK, 2012; Bottelier MA, 2014
ePOD study: effects of Psychotropic drugs on developing brain

Objectives
1. Short-term age-dependency (pharmacological MRI)
   a) MPH on developing DA system
   b) Fluoxetine on developing 5HT system
2. Long-term effects of these drugs

Outcome measures:
1. Neuroimaging: fMRI, DTI
2. Neuropsychology
3. Cortisol measurements
4. Sleep study

Participants:
• 50 stimulant treatment–naive boys (10–12 years old)
• 49 stimulant treatment–naive men (23–40 years old)
Methylphenidate effects on cortical thickness in children & adults with ADHD

Right medial cortex

Time × medication × age interaction

MPH treatment ... less cortical thinning in children, not in adults or placebo

Walhovd et al 2020, Am J Neuroradiol
Age-dependent effects of MPH on dopaminergic system in patients with ADHD

4 months of MPH –
- Significant increases in CBF - striatum & thalamus 1-week post-trial
- Increased DA neurotransmission due to neurochemical imprinting by methylphenidate??
- Short term… alterations do not induce major benefits or harm in clinical improvement
- Long-term consequences remain to be established

Schrantee et al 2017, Front Psychiatry
Effects of MPH on actigraph-assessed sleep measures in children with ADHD

Benefits:
? Rebound
? Long-term
A summary of considerations...

Difficult diagnosis - Treating diagnosis or symptoms??
Developmental process
Empirical support minimal in disorders like autism
Conducting trials and generating evidence is challenging
Limited number of studies (especially from LAMIC)
Medication overuse for lack of trained professionals
Pharmacodynamic & pharmacokinetic considerations
Duration of treatment
Long-term efficacy

Primacy of and greater advocacy for non-pharmacological methods
Combination treatment ‘gold standard’
Important to set clear ‘therapeutic targets’

Table 1  Randomised clinical trials in paediatric psychopharmacology for common medication groups and therapeutic indications*

<table>
<thead>
<tr>
<th>Medication group</th>
<th>Indication</th>
<th>Through 1998</th>
<th>1999–June 2018†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>RCTs (N)</strong></td>
<td>Patients randomised (N)</td>
<td>RCTs (N)</td>
</tr>
<tr>
<td></td>
<td>Total††</td>
<td>To medication</td>
<td>To placebo</td>
</tr>
<tr>
<td>Stimulants</td>
<td>ADHD</td>
<td>665</td>
<td>2306</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>MDD</td>
<td>10</td>
<td>462</td>
</tr>
<tr>
<td>OCD</td>
<td>6**</td>
<td>357</td>
<td>208</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td></td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Other††</td>
<td></td>
<td>7††</td>
<td>260</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Schizophrenia spectrum</td>
<td>6</td>
<td>211</td>
</tr>
<tr>
<td>Bipolar</td>
<td>Aggression and other conduct disturbances</td>
<td>7</td>
<td>242</td>
</tr>
<tr>
<td>Tic disorders</td>
<td>3††††</td>
<td>118</td>
<td>118</td>
</tr>
<tr>
<td>Lithium</td>
<td>Bipolar disorder</td>
<td>3***</td>
<td>118</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Aggression and other conduct disturbances</td>
<td>0</td>
<td>115</td>
</tr>
</tbody>
</table>

Accomplishments
1. Comparative effectiveness (not just v/s placebo)
2. Safety assessments:
   Cardiac events with stimulants, Risk of abuse with stimulants, Cardiometabolic side effects with antipsychotics, Suicidality with antidepressants

Unmet needs
1. Clinical trials in practice settings
   a. Real world outcomes
   b. v/s psychosocial interventions
2. Disease-modifying interventions (not just symptom control)
3. Targeting dimensions of psychopathology
4. Neuroscience-informed psychopharmacology
Principles of prescribing in CAP (Maudsley 14th)

Target symptoms, not diagnoses
Begin with less, go slow, monitor efficacy and adverse reactions
Multiple medications often required for the severely ill
Allow time for an adequate trial of treatment
Where possible, change one drug at a time
Monitor outcome in more than one setting
Patient and family medication education is essential
“Psychopharmacology requires a sense of humor. Sometimes, the best use of EBM is to remember how little evidence we have.”

TA Kramer, MD (Chicago Illinois)
<table>
<thead>
<tr>
<th>Study</th>
<th>Main research question</th>
<th>Sample</th>
<th>Setting</th>
<th>Randomisation to</th>
<th>Main findings</th>
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</thead>
<tbody>
<tr>
<td>Multimodal Treatment Study of Children with ADHD&lt;sup&gt;24&lt;/sup&gt;</td>
<td>How do different treatment strategies (pharmacological, behavioural and combined) compare with usual care for improving ADHD symptoms and improving functioning?</td>
<td>n=579&lt;br&gt;Age 7–8 years, with ADHD combined type</td>
<td>Outpatient university clinics</td>
<td>Medication (stimulant) management, behaviour therapy, their combination or usual care, for 14 months, followed by a 10-year naturalistic follow-up.</td>
<td>Greater improvement with medication management, either alone or in combination, with no difference between those two. Dissipation of treatment differences during naturalistic treatment.</td>
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<tr>
<td>Pediatric OCD Treatment Study&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Is SSRI combined with CBT more effective than either monootherapy in childhood OCD?</td>
<td>n=112&lt;br&gt;Age 7–17 years, with OCD</td>
<td>Outpatient university clinics</td>
<td>Sertraline, CBT, their combination or placebo, for 12 weeks.</td>
<td>Combined treatment was more effective than monotherapy, which was better than placebo.</td>
</tr>
<tr>
<td>Treatment for Adolescents with Depression Study&lt;sup&gt;27,28&lt;/sup&gt;</td>
<td>Is SSRI combined with CBT more effective than either monotherapy adolescent MDD?</td>
<td>n=439&lt;br&gt;Age 12–17 years, with MDD</td>
<td>Outpatient university and community clinics</td>
<td>Fluoxetine, CBT, their combination or placebo for 12 months, followed by unblinded maintenance treatment for 6 months.</td>
<td>Fluoxetine, either alone or combined with CBT, was better than CBT, or placebo, in improving mood. Fluoxetine as monotherapy, but not when combined with CBT, increased the risk of suicidal events. No distal differences in outcome 6 months after randomisation.</td>
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<tr>
<td>Adolescent Depression Antidepressant and Psychotherapy Trial&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Is combined CBT and SSRI treatment more effective than SSRI monotherapy for adolescent depression?</td>
<td>n=208&lt;br&gt;Age 11–17 years, with MDD</td>
<td>Outpatient practice settings</td>
<td>SSRI + routine care or CBT + SSRI + routine care, for 12 weeks.</td>
<td>No difference between combined treatment and monotherapy.</td>
</tr>
<tr>
<td>Treatment of Resistant Depression in Adolescents&lt;sup&gt;30&lt;/sup&gt;</td>
<td>After an unsuccessful treatment with SSRI, is switching to another antidepressant plus adding CBT more effective than switching to another antidepressant monotherapy?</td>
<td>n=326&lt;br&gt;Age 12–18 years</td>
<td>Outpatient university clinics</td>
<td>SSRI or venlafaxine with or without CBT for 12 weeks.</td>
<td>Combined treatment was more effective than monotherapy.</td>
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<tr>
<td>Treatment of Early Onset Schizophrenia Spectrum Disorders&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Are second-generation antipsychotics superior to first-generation antipsychotic in the treatment of early onset schizophrenia?</td>
<td>n=119&lt;br&gt;Age 8–19 years, with schizophrenia or schizoaffective disorder</td>
<td>Outpatient university clinics</td>
<td>Risperidone, olanzapine or molindone for 8 weeks (acute treatment) followed by 10-month maintenance treatment.</td>
<td>No difference among medications in efficacy, but with important differences in safety outcomes. Most patients discontinued the randomly assigned treatment after a few months.</td>
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<tr>
<td>Child-Adolescent Anxiety Multimodal Study&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Is SSRI combined with CBT more effective than monotherapy in childhood anxiety disorders?</td>
<td>n=488&lt;br&gt;Age 7–17 years, with separation anxiety disorder, generalised anxiety disorder or social phobia</td>
<td>Outpatient university clinics</td>
<td>Sertraline, CBT, their combination or placebo, for 12 weeks.</td>
<td>Combined treatment was the most effective intervention. Monotherapy with sertraline or CBT was better than placebo.</td>
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<tr>
<td>Treatment of Early Mania&lt;sup&gt;39&lt;/sup&gt;</td>
<td>How effective are antiepileptogenic vs antiepileptic interventions vs lithium or valproate for acute mania stabilisation in children?</td>
<td>n=290&lt;br&gt;Age 6–15 years</td>
<td>Outpatient university clinics</td>
<td>Valproate, lithium or risperidone for 8 weeks.</td>
<td>Risperidone was the most effective intervention, with no significant difference between lithium and valproate.</td>
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<tr>
<td>Treatment of Serious Behaviour Problems in PDD&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Does the addition of parent training to pharmacotherapy result in better outcomes in PDD?</td>
<td>n=124&lt;br&gt;Age 4–13 years, with PDD</td>
<td>Outpatient university clinics</td>
<td>Risperidone, as monotherapy or combined with behaviour therapy, for 24 weeks.</td>
<td>Medication plus parent training was more effective than medication alone at decreasing maladaptive behaviours.</td>
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<tr>
<td>Generic (Registered®) Drug Names</td>
<td>CYP 2C9</td>
<td>CYP 2C19</td>
<td>CYP 2D6</td>
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<tr>
<td><strong>ANTIDEPRESSANTS</strong></td>
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<td><strong>Bupropion</strong> (Wellbutrin®)</td>
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<tr>
<td><strong>Citalopram</strong> (Celexa®)</td>
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<tr>
<td><strong>Desvenlafaxine</strong> (Pristiq®)</td>
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<tr>
<td><strong>Duloxetine</strong> (Cymbalta®)</td>
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<tr>
<td><strong>Escitalopram</strong> (Lexapro®)</td>
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<tr>
<td><strong>Fluoxetine</strong> (Prozac®)</td>
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<td><strong>Fluvoxamine</strong> (Luvox®)</td>
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<td><strong>Levomilnacipran</strong> (Fetzima®)</td>
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<td><strong>Paroxetine</strong> (Paxil®)</td>
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<td><strong>Reboxetine</strong> (Edronax®)</td>
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<td><strong>Sertraline</strong> (Zoloft®)</td>
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<td><strong>Venlafaxine</strong> (Effexor®)</td>
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<td><strong>Vilazodone</strong> (Viibryd®)</td>
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<td><strong>Vortioxetine</strong> (Brintellix®)</td>
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<td><strong>STIMULANTS, ADHD</strong></td>
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<td><strong>Amphetamine</strong> (Adderal®)</td>
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<tr>
<td><strong>Atomoxetine</strong> (Strattera®)</td>
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<td><strong>Clonidine</strong> (Kapvay®, Catapres®)</td>
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<tr>
<td><strong>Dexmethylphenidate</strong> (Focalin®)</td>
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<tr>
<td><strong>Dextroamphetamine</strong> (Dexedrine®)</td>
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<td><strong>Guanfacine</strong> (Intuniv®, Tenex®)</td>
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<td><strong>Lisdexamfetamine</strong> (Vyvanse®)</td>
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<tr>
<td><strong>Methamphetamine</strong> (Desoxyn®)</td>
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<tr>
<td><strong>Methylphenidate</strong> (Concerta®, Ritalin®)</td>
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</tbody>
</table>

- Major, □ Minor, Drug substrate for metabolism by CYP2C9, CYP2C19, CYP2D6 isoenzyme(s)
- Drug not metabolized by CYP2C9, CYP2C19, CYP2D6 isoenzymes
- Drug with pharmacologically active metabolites
- Prodrug of [d-amphetamine]

DRUG INTERACTIONS: Drug metabolism inhibitor of CYP2C9, CYP2C19 and/or CYP2D6