Substance Abuse in Your Patients: Beyond What is Taught in Your Residency

Clinical Implications and Applications of Advances in Addiction Research to the Evaluation and Treatment of Adolescents

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Learning Objectives

What does research tell us about:

– Developmental pathways and neurobiological underpinnings of adolescent addiction?
– Common co-occurring disorders?
– Assessment and treatment?

What are the clinical implications of addiction research?
Verbal IQ; school performance; hobby; empathic gatekeeper, second chance

Impedes development of:
- Coping skills
- Social/interpersonal skills
- Communication skills
- Identity, values consolidation
- Affect identification/regulation
- Self-Efficacy/external locus control
- Pro-social network

SUD, abuse, neglect
Failure; truancy
Deviant, drug involved
Experimentation (90%) → SUD (drug 3-9%; alcohol 5-8%)

Individual
ODD
ADHD
CD
ASP
Mood / Anxiety

Temperament and co morbidity
Gray Matter Development

Gogtay et al., 2004
Brain Mechanisms in ADHD

- Posterior Parietal Cortex
- Prefrontal Cortex
- Sensory input
- Striatum
- Cerebellum
- Locus Coeruleus
- VTA
- Substantia Nigra

NE enhances relevant signal
DA suppresses irrelevant signal

Neuropathology overlap ADHD, SUD

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Prevalence</th>
<th>risk SUD</th>
<th>Effective Tx</th>
<th>Tx with SUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>30-50%</td>
<td>Yes</td>
<td>Stimulants</td>
<td>1 RCT n=69</td>
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<tr>
<td></td>
<td>vs 10%</td>
<td></td>
<td>Lower abuse</td>
<td>Efficacy &gt; PBO</td>
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<td></td>
<td></td>
<td></td>
<td>pemoline*</td>
<td>Good safety profile</td>
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<td></td>
<td></td>
<td></td>
<td>Atomoxetine</td>
<td>No impact on SUD</td>
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<td></td>
<td></td>
<td></td>
<td>Bupropion</td>
<td>absent SUD tx</td>
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<td></td>
<td></td>
<td></td>
<td>Modafinil**</td>
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<tr>
<td>Depression</td>
<td>15-25%</td>
<td>Yes</td>
<td>SSRI*</td>
<td>1 RCT n=126</td>
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<tr>
<td></td>
<td>vs 5-7%</td>
<td></td>
<td>Psychotherapy</td>
<td>Efficacy &gt; PBO</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CBT</td>
<td>Good safety profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interpersonal</td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>10-15%</td>
<td>Yes</td>
<td>mood</td>
<td>1 RCT lithium n=22</td>
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<tr>
<td></td>
<td>vs 1%</td>
<td></td>
<td>stabilizers</td>
<td>Good safety profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treats bipolar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not SUD</td>
</tr>
<tr>
<td>Anxiety</td>
<td>15-35%</td>
<td>Yes</td>
<td>SSRI /CBT</td>
<td>No RCTs</td>
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<tr>
<td></td>
<td>vs 5-10%</td>
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</tbody>
</table>
Randomized Controlled Trial
Fluoxetine vs Placebo
+ 16 weeks CBT

Study Flow Diagram

- 328 Telephone Pre-Screen Calls
- 143 Assessed for Eligibility
- 126 Randomized

Fluoxetine N = 63
- Withdrawals:
  - 4 Went to Jail/Detention
  - 3 Went to Residential Treatment at a Facility Unable to Continue Study
  - 3 Lost to Follow-up
  + 1 Moved Out of Area
  = 11 Participants Withdrawn
- 16 week completers N=52

Placebo N= 63
- Withdrawals:
  - 1 Went to Jail/Detention
  - 4 Admitted to Residential Treatment
  - 3 Lost to Follow-up
  - 3 Moved Out of Area
  + 2 Withdrew Consent
  = 9 Participants Withdrawn
- 16 week completers N = 54

13 Not Meeting Inclusion Criteria
+ 4 Admitted to Residential Treatment
17 Excluded
## Demographics

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Placebo (n=63)</th>
<th>Fluoxetine (n=63)</th>
<th>Overall (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender n (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>20 (31.7)</td>
<td>21 (33.3)</td>
<td>41 (32.5)</td>
</tr>
<tr>
<td>Male</td>
<td>43 (68.3)</td>
<td>42 (66.7)</td>
<td>85 (67.5)</td>
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<tr>
<td><strong>Age: mean (SD)</strong></td>
<td>17.02 (1.49)</td>
<td>17.29 (1.81)</td>
<td>17.16 (1.66)</td>
</tr>
<tr>
<td><strong>Ethnicity n(%)</strong></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>28 (44.4)</td>
<td>33 (52.4)</td>
<td>61 (48.4)</td>
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<tr>
<td>African American</td>
<td>9 (14.3)</td>
<td>9 (14.3)</td>
<td>18 (14.3)</td>
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<tr>
<td>Native American</td>
<td>3 (4.8)</td>
<td>1 (1.6)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17 (27.0)</td>
<td>17 (27.0)</td>
<td>34 (27)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (7.9)</td>
<td>3 (4.8)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td><strong>SES: group IV category</strong></td>
<td>43.98 (15.49)</td>
<td>44.56 (17.60)</td>
<td>44.27 (16.5)</td>
</tr>
<tr>
<td><strong>Referral Source: n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Court-Ordered</td>
<td>12 (19.0)</td>
<td>14 (22.2)</td>
<td>26 (20.6)</td>
</tr>
<tr>
<td>Non Court-Ordered</td>
<td>51 (81.0)</td>
<td>49 (77.8)</td>
<td>100 (79.4)</td>
</tr>
</tbody>
</table>
Fluoxetine vs. Placebo
Compliance: Medication & CBT

Fluoxetine
Placebo

% Compliance:

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT Therapy</td>
<td>N=52</td>
<td>N=54</td>
</tr>
<tr>
<td>Medication visit</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = Not Significant
Fluoxetine vs. Placebo
Depression Remission

70% vs. 52%
P < .05

Final CDRS < 29

Riggs et al Archives of Pediatric and Adolescent Medicine in press
A. Children’s Depression Rating Scale-Revised T-Scores

- Placebo Non-Remitter
- Placebo Remitter
- Fluoxetine Non-Remitter
- Fluoxetine Remitter

**NON REMITTERS**

**REMITTERS**

Week 0 Week 4 Week 8 Week 12 Week 16
**Change in Drug Use**

- **Week 0**: Remitters’ pre post drug use (p<.001) (0.5 effect size) (U/A R> NR p<.02)
- **Non-Remitters**: no change in drug use (NS)
Conclusions and Clinical Implications

- Fluoxetine > Placebo for MDD in non-abstinent adolescents with active SUD; good safety profile

- Remission was better predictor of reduced drug use than medication group
  - Remitters showed significant decrease in drug use
  - Non-remitters’ drug use did not decrease from baseline levels
  - CBT probably active ingredient in treatment of MDD despite focus on SUD, not depression

- Increased access to treatment (80% not court-mandated)

- Empirical support for integrated SUD/mental health tx
  - Depression outcomes as good or better than controlled trial in depressed teens without SUD
  - Change in drug use, compliance, retention as good or better than substance treatment in adolescents without comorbidity / < severe psychopathology
Treatment
- Pharmacotherapy
- Psychotherapy (individual, behavioral, family)

Neuropathology
- Pre-existing?
- Substance induced?

Changes with treatment?
- Differences in neuroplasticity: adolescents vs adults?
- What recovers? What doesn’t?
On STROOP test:
Substance dependent adolescents exhibited activation in the rostral & caudal ACC…

…and R orbito-frontal cortex (OFC)
Non-dependent controls did not

…..but are differences pre-existing or caused by drug use?
Greater Pretreatment Brain Activation Drug > Food

- Ventral Tegmentum
- Nucleus accumbens
- Amygdala
- Thalamus
- Anterior Cingulate
- Medial frontal cortex
- Midbrain
- Posterior visual cortex
- Cerebellum

Preliminary results in 11 adolescents with cannabis and other substance use disorders suggests greater activation of reward circuit in response to drug cues than food before treatment.
Greater post-treatment activation Drug > Food in areas of cognitive control* compared to pre-treatment
(n=10 post scans; n=6 valid; p < .01)

* ACC and cortical regions --medial frontal, lateral inferior frontal, dorsolateral, prefrontal

Pretreatment

Post-treatment
Clinical Implications

Directions for future research

- Decrease barriers to treatment access
- Expand integrated /coordinated continuum of care (medical, psychiatric, substance treatment)
- Earlier interventions & improved continuing care
  - school based, indicated prevention
  - parity for mental health and SUD treatment
  - utilization of existing community based resources
- Relapse Prevention: build “internalized motivation” to maintain treatment gains by involvement in positively rewarding activities incompatible with drug use during treatment
Clinical Implications

Directions for Future Research

Medication Development

- Monotherapy better than polypharmacy
- Clinical trials using medications that target both SUD and comorbidity such as bupropion
  - controlled trials support efficacy for ADHD, MDD, nicotine dependence
  - reducing methamphetamine craving and use
Research
- Primary care
- Medical services
- Mental Health
- Substance treatment
- Translational Research CTSA
- NIDA Clinical Trials Network CCTN

Training
- NIDA AACAP K 12

Screening
- Dx Assessment
- Psychiatric Comorbidity

Incentives
- • internalized motivation
- • involve in positive activities, incompatible with drug use
- • use of existing community resources to augment treatment services

Assessment of SUD (e.g., CRAFFT)
- Assessment

Practice
- • internalized motivation
- • involve in positive activities, incompatible with drug use
- • use of existing community resources to augment treatment services