Advances in Research on the Treatment of Adolescents with Co-occurring Psychiatric and Substance Use Disorders

California Society of Addiction Medicine
Annual Meeting

San Francisco
October 9, 2009

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University of Colorado, Denver
## Disclosures of Potential Conflicts

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<tr>
<th>Source</th>
<th>Consultant</th>
<th>Advisory Board</th>
<th>Stock or Equity</th>
<th>Speakers’ Bureau</th>
<th>Research Support</th>
<th>Honorarium for this talk or meeting</th>
<th>Expenses related to this talk or meeting</th>
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Educational Objectives

- Attendees will learn about risk and protective factors that contribute to development of adolescent substance abuse and psychiatric comorbidity.

- Attendees will learn the clinical and treatment implications of research advances in adolescent brain development.

- Attendees will learn about evidence-based interventions for adolescents and young adults with co-occurring psychiatric and substance use disorders.
Introduction

- 1/2 of psychiatric disorders
  - Onset before age 15
  - 3/4 by age 24
- 60-80% adolescents with SUD
  - have co-occurring psychiatric disorder
  - associated with poorer treatment outcomes
- Growing clinical and research consensus supporting integrated or concurrent treatment but progress impeded
  - by systemic barriers and research gaps
  - lack empirical research to guide development of an integrated treatment model
The Developmental Relationship Between Psychiatric Disorders and SUD

Substance Use Disorders
- 85% experiment before graduating HS;
- 10% develop problem use, abuse, dependence

Brain Development
- stimulatory (DA, Glutamate) > suppressive elements (5HT, GABA)

Genetics
- Gene - Environment Interactions (eg HPA dysfunction)

Fetal Exposure
- Nicotine, alcohol, drugs

Difficult temperament
- ODD
- 50%

Difficult temperament
- ADHD
- 50%

Conduct Disorder
- 50%

Antisocial PD

Pediatric onset psychiatric disorders
- ½ before 15; 3/4 by 24
- Most childhood psychiatric disorders increase risk for SUD; treatment decreases risk

Adolescent onset SUD
- 80% alcohol, nicotine; 60% of other drugs
- SUD increases risk psych comorbidity; poorer tx outcomes
  - ADHD (30-50%)
  - Depression (15-35%)
  - Anxiety (20-40%)

Bipolar Disorder
- Childhood onset reduces risk;
  - adolescent onset increases SUD risk

Depression
- 1/2 start before, 1/2 after SUD; Boys=girls before puberty; Girls 2x risk puberty--adulthood

Anxiety Disorders
Age of Onset of Brain Disorders

13 – 20 Years
Social Phobias
Panic Disorder
Drug Abuse

10 – 13 Years
Eating Disorders
Obsessive-compulsive disorders

5 – 10 Years
Anti-social Behavior
Conduct Disorder
Depression
Anxiety

Infancy to 5 Years
Attention Deficit Hyperactivity Disorder
Autism

Source: Gfroerer, JC et al., SMA 02-3711, OA, SAMHSA – Data from National Survey of Drug Use and Health
Developed from Time Magazine, January 20, 2003, p. 82
**Longitudinal Development**

- Pre-natal; attachment

**Building resilience**

- Family
  - Abuse, neglect, conflict, SUD
  - Family management
  - Parental monitoring

**Onset and Progression of Psychiatric Symptoms**

- ODD/CD
- ADHD
- Depression
- Mania/hypomania
- Anxiety (SP, PTSD, GAD, OCD)
- Psychosis

**School**

- Behavior problems
- Academic performance

**Peers**

- Deviancy
- Substance Use
- Gang

**Substance Use**

- Onset, experimentation
- For all substances used >5x
  - Progression to regular use
  - Peak use
  - Current use (last month)
  - Last use

**Lifetime Timeline**

- Family
  - Abuse, neglect, conflict, SUD
  - Family management
  - Parental monitoring

- School
  - LD; special education
  - Behavior problems
  - Academic performance

- Peers
  - Deviancy
  - Substance Use
  - Gang

- Substance Use
  - Onset, experimentation
  - For all substances used >5x
    - Progression to regular use
    - Peak use
    - Current use (last month)
    - Last use
## Background and Significance

### Co-occurring Problems by Dependence on Specific Substances

<table>
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<tr>
<th>Disorder</th>
<th>Abuse</th>
<th>Dependence</th>
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<tr>
<td>Conduct Disorder</td>
<td>49%</td>
<td>79%</td>
</tr>
<tr>
<td>ADHD</td>
<td>33%</td>
<td>64%</td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>14%</td>
<td>47%</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>19%</td>
<td>51%</td>
</tr>
<tr>
<td>Traumatic Stress Disorder</td>
<td>18%</td>
<td>43%</td>
</tr>
<tr>
<td>Any Co-Occurring Disorder</td>
<td>64%</td>
<td>89%</td>
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Source: CSAT’s Cannabis Youth Treatment (CYT), Adolescent Treatment Model (ATM), and Persistent Effects of Treatment Study of Adolescents (PETS-A) studies (2003)
Recent Studies Have Shown that Maturation of the Brain’s Gray Matter Moves from Back to Front.

Late to develop is the prefrontal cortex, involved in circuitry to control impulses, judgment, and decision-making.

Source: From Lenroot and Giedd, 2006
Imaging the Developing Brain

Developmental course of human brain development

Experience-dependent synapse formation and dendritic arborization
Prefrontal cortex
Parietal and temporal association cortex
Sensorimotor cortex

Synaptogenesis and synaptic pruning
Myelination

Conception

Cell proliferation and migration
Neurulation

-8 -6 -4 -2 0 2 4 6 8 10 12 2 4 6 8 10 12 14 16 18 20
Months Years

Source: Casey et al., Trends in Cog Sci, 9(3), pp. 104-110, 2005
Total Arrest Rate by Age and Sex, 1993-2001

Uniform Crime Reports, FBI, 2001
Top 3 Causes of Death among Youth and Young Adults: 2002

Source: National Center for Health Statistics, CDC, Mortality Data 2002
Addiction is a Developmental Neurobiological Disease
Age at Which Marijuana Use Is First Initiated

Source: Gfroerer, JC et al., SMA 02-3711, OA, SAMHSA – Data from National Survey of Drug Use and Health
Addiction Is a Developmental Disease
starts in childhood and adolescence

Age for tobacco dependence, as per DSM IV

National Epidemiologic Survey on Alcohol and Related Conditions, 2003
Addiction Is a Developmental Disease
starts in childhood and adolescence

Age for tobacco and alcohol dependence, as per DSM IV

National Epidemiologic Survey on Alcohol and Related Conditions, 2003
Addiction Is a Developmental Disease
starts in childhood and adolescence

Age for tobacco, alcohol and cannabis dependence, as per DSM IV

National Epidemiologic Survey on Alcohol and Related Conditions, 2003
Where Drugs of Abuse Act in the Brain

Mesocorticolimbic DA System

Brain Reward Pathway

Dopamine
Neurotransmission
Natural Rewards Elevate Dopamine Levels

Source: Di Chiara et al.

Source: Fiorino and Phillips
Effects of Drugs on Dopamine Levels

Di Chiara and Imperato, 1988
The Adolescent Brain Responds to Drugs Differently than the Adult Brain

Increases in Nicotine Self Administration

Treatment of adolescent rats (but not young adults) with nicotine leads to:

- Increases in Nicotine Self Administration
- Increases in Nicotine Receptors

Source: Adriana et al., J Neurosci, 23(11), pp. 4712-4716, 2003
Early exposure to cannabinoids renders DA cells more reactive which could trigger a psychotic episode in a vulnerable individual.

Adolescent Cannabis Use Effects
Adult Psychosis in Individuals with Variations in the COMT Gene

Source: Caspi et al., Biol. Psychiatry, 57: 1117-1127; 2005
Dopamine D2 Receptors Are Lower in Addiction

Cocaine
Alcohol
Meth
Heroin

Reward Circuits

Dopamine D2 Receptor Availability

New Drug Abuser

Drug Abuser
Among those without history of conduct problems, drug exposure led to:

- More than triple risk of substance dependency
- Almost 3x risk of herpes infection
- Increased HIV risk
- Nearly 4x risk of early pregnancy
- About 3x the number of criminal convictions

Source: Odgers et al., 2008
"Strategies such as raising prices of cigarettes, more vigilantly enforcing laws governing the sale of alcohol, expanding adolescents’ access to mental health and contraceptive services, and raising the driving age would likely be more effective in limiting adolescent smoking, substance abuse, pregnancy, and automobile fatalities than attempts to make adolescents wiser, less impulsive or less shortsighted. Some things just take time to develop, and mature judgment is probably one of them." (Steinberg, 2008)
Evidence-Based Psychiatric and Substance Treatments for Adolescents

**Substance Use Disorders**
- Family-based interventions
- Behavioral intervention
- Motivational Enhancement Therapy (MET)
- Cognitive Behavioral Therapy (CBT)
- Pharmacotherapy

**Psychiatric Disorders**
- Conduct Disorder (60-80%)
  - Family-Based Intervention
  - CBT
- Depression, Anxiety (30-40%)
  - CBT
  - Pharmacotherapy
- ADHD (30-50%)
  - Pharmacotherapy
Meta-Analysis of Evidence-Based Psychosocial Treatments for ASUD

3 Month Post-Treatment Effect Size

<table>
<thead>
<tr>
<th>Family-Based Therapy</th>
<th>MET/CBT</th>
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<tbody>
<tr>
<td>2/18</td>
<td>9/12</td>
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<tr>
<td>7/18 =</td>
<td>2/12</td>
</tr>
<tr>
<td>9/18</td>
<td>1/12</td>
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*Waldron H, Turner C. Evidence-Based Psychosocial Treatments for Adolescent Substance Abuse Journal of Clinical Child Adol Psychology 37:1, 238-261

Synthesized findings from well-designed controlled outcome studies of empirically supported adolescent drug treatment interventions since 1998
Treatment is Effective......but,

- Lack of continuing care
- High relapse rates (60-80%)
- Poor coordination of care

Co-morbidity is the rule ...but,
- Lack of integrated treatment
- Lack of research-based model
- Lack dually-trained clinicians
  - Lack of systemic, third-party payer support

Lack of early intervention (eg school-based)

Treatment access <10%

Symptoms
We Need a New Model

Mental Health

Increase & Extend Access to Care

SUD

Continuing Care

The Evolution of an Evidence-Based Integrated Treatment Model
Randomized Controlled Trial
Fluoxetine with CBT in Adolescents with
Major Depression, Behavior Problems, Substance Abuse

NIDA R01 DA 00013

Riggs PD, Mikulich-Gilbertson SK, Davies RD et al.,
Archives of Pediatric and Adolescent Medicine 161 2007
Fluoxetine vs Placebo + 16 weeks CBT

328 Telephone Pre-Screen Calls

Randomized Controlled Trial

Cannabis Youth Treatment Study:
Main findings from two randomized trials

“Of the adolescents assigned to one of the four 12- to 14-week treatment interventions, 52% had lengths of stay that reached 90 days”

Dennis et al J Subst Ab Tx 2004

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

Placebo N = 63

Withdrawals:
  1 Went to Jail/Detention
  3 Lost to Follow-up
  3 Moved Out of Area
  + 2 Withdraw Consent
  9 Participants Withdrawn

85% tx completion; medication follow up compliance weekly medication visits; >70 % compliance with CBT
Change in Depression

**Change in Depression (CDRS-R)**

- **Fluoxetine v Placebo**

  - Week 1
  - Week 5
  - Week 9
  - Week 13
  - Week 17

  - P < .05
  - P < .01

**Depression Remission (CDRS<29)**

- **Fluoxetine v Placebo**

  - Fluoxetine: 70%
  - Placebo: 52%

  - P < .05

*High remission in both fluoxetine and placebo groups support antidepressant action of CBT*
Depression Outcomes

Acute Treatment and 1 Year Follow up

CDRS T-score: Follow-up Sample by Medication Group

CDRS T-score: Follow-up Sample by Remission Status

Fluoxetine v Placebo

Remitters v Non-remitters
Drug Use Outcomes

Acute Treatment and 1 Year Follow up

Fluoxetine v Placebo

Remitters v Non-remitters

Treatment ends
Conduct Disorder Outcomes
Acute Treatment and 1 Year Follow up

Fluoxetine v Placebo

Remitters v Non-remitters

Number of CD Symptoms: Follow-up Sample by Medication Group

Number of CD Symptoms: Follow-up Sample by Remission Status
Changes in Brain Activation Patterns Before and After Treatment in Adolescents Addicted to Marijuana

Before treatment, adolescents showed greater brain reward activation to marijuana cues vs food*

Riggs et al., Drug and Alcohol Dependence, 91, 2007

After 16 weeks of CBT adolescents showed greater activation to marijuana vs food in areas of cognitive control than before treatment
Change in Biological Markers of Stress, Aggression, Depression with Treatment

**Salivary Cortisol**

**Baseline**
- “flattened diurnal range”

**Post treatment change:**
- FLX main effect trend p=.07
- Remitters
  - am cortisol (p=.017)
  - diurnal range (p=.007)

**Serotonin Receptors**

**Significant pre-post treatment**

- serotonin receptor binding affinity with fluoxetine

**No change in density of receptors**

Riggs et al. Drug Alc Dep 2007
Randomized Controlled Trial

MAIN STUDY FINDINGS

DEPRESSION

- Fluoxetine (71%) > placebo (52%)
- Higher than expected remission in both groups; ?CBT additive

DRUG USE

- Fluoxetine & placebo; no difference between groups
  - Remitters: significant drug use
  - Non-remitters: no change in drug use

CONDUCT PROBLEMS

- Fluoxetine & placebo; no difference between groups
  - Remitters > non-remitters

1 YEAR FOLLOW-UP

- Treatment gains maintained or continued to improve
National Drug Abuse Treatment Clinical Trials Network

NIDA-CTN-0028
Randomized Controlled Trial Osmotic-Release Methylphenidate (OROS-MPH)
Attention Deficit Hyperactivity Disorder in Adolescents with Substance Use Disorders

Paula Riggs MD
Principal Investigator
Randomized Controlled Trial OROS-MPH + CBT in Adolescents with ADHD and SUD

Results and Implications for Integrated Mental Health/Substance Treatment

- Comparable treatment retention, completion, compliance to single site study—generalizability
- OROS-MPH safe, well-tolerated despite non-abstinence
- Individual CBT may contribute to ADHD treatment response as it does for co-occurring depression.
- Feasible to integrate assessment and treatment of co-occurring psychiatric and substance use disorders in “real world” treatment settings
- “free” treatment for adolescents broadens access to treatment
Evolution of an Integrated Treatment Model

Research to “Real World” Practice
ENCOMPASS

Integrated Treatment for Adolescents and Young Adults
SAMSH/ National Registry of Evidence-based Programs and Practices (NREPP)

Requirements

- One or more positive mental health and/or substance use outcomes (p<.05)
- Results published in peer-reviewed publication
- Documentation of implementation feasibility and availability of training, implementation tools, fidelity/adherence

Priorities

- Behavioral + pharmacotherapy interventions to reduce mental health, substance abuse, HIV, suicide risk in adolescents, young adults
- Divert adolescents with mental health/substance problems from juvenile justice systems
Research

Incentives/CM
- paid $25 per visit; free tx*
- Could not apply additional incentives/contingencies to enhance abstinence rates

Psychiatric treatment
- Constrained by single pharmacotherapy/placebo
- Could not individually tailor treatment as clinically indicated

Relapse prevention/continuing care
- Constrained by research protocol

Practice

16 week CBT + Contingency Management/Incentives "fishbowl"
- Compliance
- Abstinence

Psychiatric treatment
- Broader range of options
- Psychotherapy
- Pharmacotherapy

Relapse prevention
- Early involvement in + community-based activity to build internalized motivation
- Augment paucity of continuing care treatment services

Target common aspects of neuropathology
Addiction-psychiatric disorders
The Role of Pharmacotherapy

Psychiatric Disorders
- ADHD
- Depression
- Anxiety

Substance Abuse
- Reduce craving
- Relapse prevention

common neurobiological targets
How Many of You Treat Adolescents With Substance Use Disorders?

Audience response question 1
Approximately what percentage of adolescents with SUD have a co-occurring psychiatric disorder?

a. Less than 10%
b. About 20%
c. Unknown due to insufficient research
d. About 35%
e. More than 50%

Audience response question 2
Approximately what percentage of adolescents with SUD have a co-occurring psychiatric disorder?

a. Less than 10%
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d. About 35%
e. More than 50%

audience response question 2
answer: e
Which of the following statements is true?

a. About ½ of all psychiatric disorders have an onset before the age of 15.

b. Most psychiatric disorders do not have an onset before the age of 24.

c. The majority of adults with addiction began using substances during college.

d. Among adolescents who experiment with drugs and alcohol, older adolescents have a greater risk of becoming addicted than younger adolescents who experiment.

e. None of the statements above are true
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b. Most psychiatric disorders do not have an onset before the age of 24.

c. The majority of adults with addiction began using substances during college.

d. Among adolescents who experiment with drugs and alcohol, older adolescents have a greater risk of becoming addicted than younger adolescents who experiment.

e. None of the statements above are true

Answer a.
Which of the following statements is false?

a. Research has shown that some individuals have a greater genetic risk of psychosis if they regularly smoke marijuana during adolescence.

b. Research shows that the risk of addiction is lower in individuals who begin using substances before the brain has reached maturity compared to individuals who begin using drugs or alcohol after age 30.

c. Research has shown that the positive effects of cognitive behavioral therapy may continue to increase after treatment.

d. Research has shown that the brain may recover from neurobiological damage caused by drugs of abuse with sustained abstinence.

e. None of the statements above are false
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b. Research shows that the risk of addiction is lower in individuals who begin using substances before the brain has reached maturity compared to individuals who begin using drugs or alcohol after age 30.

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d. Research has shown that the brain may recover from neurobiological damage caused by drugs of abuse with sustained abstinence.

e. None of the statements above are false.

f. All of the statements above are false.

Audience response question 4 : answer b
Which of the following statements is true?

a. Research shows that family-based interventions are the only effective treatment modalities for adolescents with substance use disorders.

b. Acupuncture is emerging as one of the most promising research-based treatment interventions for adolescent drug abuse.

c. None of the existing research-based interventions for adolescents or adults with addiction are associated with sustained or continued post-treatment improvement.

d. Numerous research studies have shown that psychiatric disorders cannot be validly diagnosed and therefore should not be treated in individuals who have not achieved at least 3 months of sustained abstinence from drugs and alcohol.

e. None of the statements above is true?

f. All of the statements above are true?
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