Brain Science and Addiction
NCLS Opioid Policy Fellows
Second meeting: evidence and innovations

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Conflicts of Interest: Dr. Sakai received reimbursement in 2012 for completing a policy review for the WellPoint Office of Medical Policy & Technology Assessment (OMPTA), Wellpoint, Inc., Thousand Oaks, CA. He also served as a board member of the ARTS (Addiction Research & Treatment Services) Foundation until 2015.

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Defining terms...what is addiction?
Is it the amount used?
Frequency of use?
Is it something else?

Addiction, substance use disorder:

Substance Use Disorder
- Role failures
- Hazardous use
- Interpersonal problems
- More than intended
- Cut down
- Time spent
- Activities limited
- Use despite consequences
- Tolerance
- Withdrawal
- Craving

2-3 mild; 4-5 moderate; ≥6 severe
Common in general population

<table>
<thead>
<tr>
<th></th>
<th>Alcohol abuse</th>
<th>Alcohol dependence</th>
<th>Drug abuse</th>
<th>Drug dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime</td>
<td>17.8%</td>
<td>12.5%</td>
<td>7.7%</td>
<td>2.6%</td>
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<tr>
<td>12-month</td>
<td>4.7%</td>
<td>3.8%</td>
<td>1.4%</td>
<td>0.6%</td>
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</tbody>
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COMORBIDITY (odds ratios – alcohol dependence):

- Depressive symptoms 2.7 4.1
- Manic symptoms 8.1 4.7
- Generalized anxiety symptoms 3.7 2.8
- Social anxiety symptoms 2.0 2.6
- Post-traumatic stress sx’s 2.7 3.4

Grant et al Arch Gen Psychiatry 61: 361-368 J Clin Psychiatry 66:677-685

Kessler et al Arch Gen Psychiatry 54(4): 313-321
Even more prevalent in clinical populations...

- General medical clinics
  - 1/5 non-tobacco substance abuse problem

- Inpatient medical services
  - 23% current smokers
  - 14% alcohol misuse
  - 12% drug misuse

  Common also in ED setting

Mercy, 2003
Kouimtsidis et al., 2003

With a common onset in adolescence...

Age at onset of alcohol dependence from Li et al.,
Biological Psychiatry 56:718-20
With a common onset in adolescence...

Age at onset of cannabis abuse and dependence – from Grant Psychological Medicine 36:1447-1460.

Age at onset of cocaine abuse and dependence – unpublished data.
Preventable causes of death in 1990:
- #1 Tobacco (400,000 deaths per year)
- #3 Alcohol (100,000 deaths per year)
- #9 Illicit drugs (20,000 deaths per year)

Actual causes of death in 2000:
- #1 Tobacco (435,000 deaths per year)
- #3 Alcohol (85,000 deaths per year)
- #9 Illicit drugs (17,000 deaths per year)

Mokdad et al. JAMA 2004; 291:1238-45

Dramatic rise in drug-related deaths...
Physicians generally – poor job of screening

Survey of FP’s (n=648)
90% failed dx substance abuse when presented with early symptoms of alcohol abuse in an adult patient

40% of pediatricians presented with classic description of drug abusing teen – did not include substance abuse in their differential

Another study in primary care practices – patients with alcohol dependence received assessment and referral to treatment only 10% of the time

Only about 3% of those with alcohol use disorder in past 12-months report that they had received help from a physician or other health care professional

A biological basis...

- A disorder historically relatively ignored...
- More difficult to have compassion for...self-induced vs. a victim...a behavioral component.
- Not a “moral failing” or “willful misconduct”
A biological basis...

- Twin and adoption studies ~50% of variance in the population related to genes
- Animal studies –
  - rats become addicted to the same substances that humans do
  - rats can be bred to create strains that are likely to become quickly and severely (measured in level presses/dose) addicted to substances

Cloninger, 1999; American Journal on Addictions 9: 285
Many youths try substances of abuse, why do some progress to a clinical diagnosis of a substance use disorder?
Pre-Existing Risk:

- N=1,000
- Enrolled from birth to age 32 years
- Self Control - 3, 5 yrs observational; 5, 7, 8, 11 parent, teacher and self report of impulsive aggression, hyperactivity, lack of persistence, inattention, and impulsivity.

Moffitt et al., PNAS 2011; 108:2693
Adolsecent-onset SD:

- No-go
- Go
Pre-Existing Risk:

12-14 years, very limited substance use; Scanned using Go/No-Go at baseline
Followed into adolescence and categorized based on progression to heavy substance use

Adolescent-onset SUD:

Crowley et al., J Am Acad Child Adolesc Psychiatry 2006; 45:175
Figure 1. Negative relationship between brain activation and externalizing behavior scores. Children 9-11 years old are imaged as they decide to take risks. Significant areas include the reward-related circuitry (including midbrain and bilateral caudate and nucleus accumbens) and frontal regions (including inferior frontal gyrus, superior frontal gyrus and cingulate gyrus).

Adolescent-onset SUD:

Laboratory studies using various modalities such as:
- Delay discounting
- Measures of impulsivity
- Measures of inhibition
- Measures of executive function
- Emotion regulation and anger

Show that adolescent patients with SUD perform more poorly than controls.
A biological basis...

- We are not all equally likely to develop a substance use disorder...some pre-existing risk
- What brain changes are associated with developing addiction...

DRUGS OF ABUSE TARGET THE BRAIN’S PLEASURE CENTER

These brain circuits are important for natural rewards such as food, music, and sex.

Typically, dopamine increases in response to natural rewards such as food. When cocaine is taken, dopamine increases are exaggerated, and communication is altered.
Reward-related behavior:

Galvan et al., J Neuroscience 2005; 25:8650
Adolescent-onset SD:

Koob & Volkow Neuropsychopharmacology 2010; 35:217
Crowley et al., PLoS ONE 2010; 5(9):e12835
Case:

“It’s not even fun anymore. I just feel like I have to use it to feel normal.”

Koob & Volkow, 2010
“Cortically regulated cognitive and emotional processes, which result in the overvaluing of drug reinforcers, the undervaluing of alternative reinforcers, and deficits in inhibitory control...”

Goldstein & Volkow, 2002 (review) Am J Psychiatry 159:1642
Adolescent-onset SD:

Brain differences cause drug use

Vs.

Drug use causes brain problems

Alcohol effects on brain:

Kril et al., Neuroscience 1997: 79:983
Sullivan & Pfefferbaum Alcohol Alcohol 2009: 44:155
Inhalant-related brain injury:

- Toxic Leukoencephalopathy

The adolescent brain may be particularly vulnerable to substance induced damage

Crews & Boettiger Pharmacol Biochem Behav 2009; 93:237
Adolescent-onset SUD:

Not all youths are equally likely to develop SUD. Problems of inhibition, high novelty seeking, poor delay discounting, affective regulation and rewards sensitivity etc. are related to increased risk. Early data suggest less GM volume and hypoactivation in both reward related pathways and frontal control circuits in those at risk or with early SUD. Exposure to substances then causes further brain changes in both reward, frontal control circuits and circuits important to stress, memory and learning.

The Future: