Is early substance use bad news?

Michael T. Lynskey
Is Early Substance Use Bad News?

Michael T Lynskey, Ph.D.

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  -- None

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  -- NONE

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  -- NONE
Birth cohort of 1265 Christchurch (New Zealand) born children.

All live births in the Christchurch urban region from May-August, 1977.

Data collected at birth, 3 months, one year and annual intervals to age 16, and at ages 18, 21 and 25
Data included:

- Parental report (birth-16 years)
- Self report (8-25 years)
- Teacher report (6-13 years)
- “Significant other” report (18, 21 25)
- Official records
  - Hospital/medical
  - Police

Response rates: By age 21 the study had retained 1,011 members of the original cohort, which represented 90% of those still alive and resident in New Zealand.
The origins of the correlations between tobacco, alcohol and cannabis use during adolescence
Data from the CHDS were used to examine whether the correlations between:

- Tobacco
- Alcohol
- Cannabis use

Could be explained by a common vulnerability to substance use behaviors.

Analyses based on parental and self-report of young people’s substance use collected at age 16 years.

Data analyzed using methods of structural equation modeling.
Vulnerability to Substance Use

Tobacco

Parental Report: 0.78 (0.03)
Self-report: 0.95 (0.05)

Alcohol

Parental Report: 0.56 (0.04)
Self-report: 0.84 (0.07)

Cannabis

Parental Report: 0.44 (0.05)
Self-report: 0.90 (0.09)

Vulnerability to Substance Use

Peer Affiliations

Parental Report: 0.61 (0.05)
Self-report: 0.26 (0.03)

Novelty Seeking

Parental Report: 0.10 (0.03)
Self-report: 0.06 (0.03)

Parental Illicit Drug Use

Parental Report: 0.76 (0.10)
Conclusions

- Variations in tobacco, alcohol and cannabis use partially determined by common vulnerability to substance use
- Correlations between tobacco, alcohol and cannabis were adequately explained by their correlations with this latent vulnerability
- Associations between risk factors and use of individual substances were mediated by their associations with “vulnerability”
- Peer factors emerged as a potent risk factor with influence of some other factors (e.g., conduct mediated) through their association with peer affiliations

Lynskey et al, 1998
Monitoring the Future

- Annual survey of drug use, conducted since 1975.
- Nationally representative samples of:
  - 18,000 8th graders from 150 schools
  - 17,000 10th graders from 140 schools
  - 16,000 12th graders from 133 schools
- Powerful design for studying age, period, cohort and other subgroup differences in rates of drug use
Lifetime use

8th Grade
10th Grade
12th Grade

Alcohol
Been Drunk
Cigarettes
Marijuana
Any Illicit
Daily use of marijuana (past month)
5+ drinks during past 2 weeks

Female
Male

8th
10th
12
Daily cigarette smoking (past month)
Is Early Substance Use Bad News?
Adolescent substance use

- In the US 5000 young people under the age of 21 die from alcohol-related injuries associated with under-age drinking.
  - Motor Vehicle Accidents
  - Homicide
  - Suicide
  - Unintentional Injuries
The acute effects of alcohol and other drug use has also been linked to increased risks of:

- violence
- sexual risk taking
- other adverse outcomes
The (still developing) adolescent brain is uniquely sensitive to drug exposure
Is Early Substance Use Associated with increased risks for the subsequent development of substance dependence, mental health problems and other adverse outcomes?
Early onset substance use

- Continuing concerns that early onset substance use is associated with increased risks for:
  - Transitions to dependence
  - The development of mental health problems
  - Escalating drug use
Volume smoked (in cigarettes) among Lifetime Smokers by Age of Smoking Onset

Hanna & Grant, 1999
Drug-Related Characteristics of Lifetime Smokers by Age of Smoking Onset and Lifetime Nonsmokers

Hanna & Grant, 1999
% Lifetime Sedative Abuse by Age at First Non-medical Use

(N=1556)  P <0.001  McCabe et al, 2007
Alcohol dependence According to Age Started Drinking

Hingson et al, 2006
Past year alcohol dependence According to Age Started Drinking

Hingson et al, 2006
Duration of Longest Dependence Episode According to Age Started Drinking

Longest Duration 25+ months

Among Persons Ever Alcohol Dependent - %

Hingson et al, 2006
What Mechanisms Underlie the Frequently Associations Between Early Onset Substance Use and increased risks for the subsequent development of substance dependence, mental health problems and other adverse outcomes?
Early onset substance use

- Uncertainty surrounding the causal mechanisms underlying observed associations make implications for prevention uncertain
- Early substance use can be conceptualized either as:
  - A marker for risk (both genetic and environmental)
  - A causal influence on the development of later problems
Can associations be explained by common confounding factors? 

(ie, the observed associations are non causal)
Early onset cannabis use and risks of depression

- Emerging area of public concern – particularly concerning the effects of cannabis use among youth
- Strong belief that cannabis causes depression
- Largely based on anecdotal reports
Prevalence of Affective Disorders by Cannabis Use: Adults

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cannabis use</td>
<td>6.2</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Use</td>
<td>12.1</td>
<td>2.24</td>
<td>1.73-2.91</td>
</tr>
<tr>
<td>Abuse</td>
<td>18.6</td>
<td>2.88</td>
<td>1.61-5.17</td>
</tr>
<tr>
<td>Dependence</td>
<td>13.6</td>
<td>2.85</td>
<td>1.86-4.35</td>
</tr>
</tbody>
</table>

Degenhardt et al, 2001
Prevalence of Depression by Cannabis Use: Adolescents (14-17)

- Rates of CES-D defined depression higher among those reporting cannabis use
  - No use = 9.6% depressed
  - 1-2 times = 17.6% depressed
  - 3+ times = 16.3% depressed
- After control for wide range of covariates (incl other drug use, conduct disorder, ADHD, demographics) ever use of cannabis was associated with a 1.89 (1.07-3.34) increase in the odds of depressive disorder.

Rey et al, 2002
Possible Hypotheses

- “artifactual” comorbidity
  - Sample selection/response biases
  - Assessment issues

- “real” comorbidity
  - Cannabis use causes MDD
  - MDD causes cannabis use
  - Both caused by common risk factors
Does cannabis use predict later depression/ anxiety?

<table>
<thead>
<tr>
<th>Waves 1-6</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression/ anxiety</td>
<td>5.1 (3.6-7.3)</td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>&lt;weekly</td>
<td>1.4 (0.94-2.0)</td>
</tr>
<tr>
<td>&gt;weekly</td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>0.47 (0.17-1.3)</td>
</tr>
<tr>
<td>- Female</td>
<td>1.9 (1.1-3.3)</td>
</tr>
<tr>
<td>Female sex, not &gt;weekly cannabis use</td>
<td>1.6 (1.1-2.3)</td>
</tr>
</tbody>
</table>

*Patton et al, 2002*
Frequent cannabis use during teenage years is associated with increased risks for the subsequent development of depression/anxiety.

This association is explained by common confounding factors in males but NOT in females.

- BUT: Uncontrolled sources of confounding?

Evidence for heritable influences on both cannabis use/dependence and on MDD.
Genetically Informative Research?

- Previously reported associations may be due to influence of genetic/ shared environmental factors.

- 311 same-sex twin pairs discordant for cannabis use before age 17.

- Conditional logistic regression models were fitted to test for excess risk to early onset cannabis users from discordant pairs, compared to their co-twin controls.
Does early onset cannabis use predict depression?

<table>
<thead>
<tr>
<th>Major Depressive Disorder</th>
<th>Lifetime Prevalence</th>
<th>Co-twins</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early cannabis users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZ twins</td>
<td>30.9</td>
<td>33.8</td>
<td>.86</td>
<td>.50-1.48</td>
</tr>
<tr>
<td>DZ twins</td>
<td>39.4</td>
<td>28.0</td>
<td>1.14</td>
<td>.66-1.97</td>
</tr>
</tbody>
</table>

Lynskey et al, 2004
## Does cannabis dependence predict depression/suicide?

<table>
<thead>
<tr>
<th>Major Depressive Disorder</th>
<th>Cannabis Dependence</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ twins</td>
<td>Yes</td>
<td>39.4</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>35.8</td>
<td></td>
</tr>
<tr>
<td>DZ twins</td>
<td>Yes</td>
<td>49.3</td>
<td>3.40</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>23.6</td>
<td></td>
</tr>
</tbody>
</table>

*Lynskey et al, 2004*
Bivariate model fitting

- Genetic liability to MDD correlated with:
  - Cannabis age of onset
    - Males \( r = .23 \ (0.05-.43) \)
    - Females \( r = .35 \ (0.18-.57) \)
  - Lifetime cannabis dependence
    - Males \( r = .44 \ (0.17-1.0) \)
    - Females \( r = .69 \ (0.30-1.0) \)
Conclusions

- Early onset cannabis use does not predispose to later MDD
- Significant association only in DZ twins pairs discordant for early use, suggests that common genetic factors may predispose to both behaviors
  - Conclusion supported by evidence of moderate/high genetic correlation between MDD and cannabis dependence.
Does EARLY cannabis use “cause” later stimulant use/ abuse/ dependence?
- Concern that early cannabis use increases risks for later “hard” drug use and drug related problems.

- Stage theory: “invariant sequence” of drug use - cannabis precedes use of other drugs.
  - but temporal order does not indicate causality.

- Yamaguchi & Kandel: early cannabis use predicted transition to other illicit drug use:
  “….prevention of early involvement in cannabis use would reduce involvement in other drugs.”
**Importance of familial factors and early onset use**

<table>
<thead>
<tr>
<th>Stimulants</th>
<th>Conc. Early</th>
<th>Early/Discordant</th>
<th>Non-early/Discordant</th>
<th>Conc. Non-Early</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants</td>
<td>77</td>
<td>62</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>N</td>
<td>248</td>
<td>305</td>
<td>305</td>
<td>5,834</td>
</tr>
</tbody>
</table>

*Grant et al, submitted*
Stimulant Use & abuse/dependence in Twin Pairs Discordant for Cannabis Use Before Age 17

Lynskey et al, 2003

<table>
<thead>
<tr>
<th></th>
<th>Early use</th>
<th>Co-twins</th>
<th>Cond OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use</td>
<td>52.6</td>
<td>34.6</td>
<td>3.05</td>
<td>1.75-5.33</td>
</tr>
<tr>
<td>Abuse/dependence</td>
<td>15.4</td>
<td>5.6</td>
<td>3.79</td>
<td>1.60-9.01</td>
</tr>
</tbody>
</table>
What mechanisms underlie this potential association?
Pharmacological mechanisms?

- Δ9 – THC and heroin have similar effects on dopamine transmission through a common μ 1 opioid receptor mechanism.
- Chronic treatment with Δ9 – THC induces cross-tolerance to amphetamine and opioids in rats.
- However, self-administered doses of THC inhaled by humans have been estimated to be from 5000 to 25000-fold lower than doses typically used to study cannabinoid dependence in rats or mice (Gardner, 2002).
Other mechanisms?

- Initial experiences with cannabis, which are frequently rated as pleasurable, may encourage broader experimentation with other drugs.
- Seemingly safe early experiences with cannabis may reduce perceived barriers to the use of other drugs.
  - Iatrogenic effects of some drug education programs?
Other mechanisms?

- Experience with & access to cannabis may provide ready access to other drugs
- This argument provided a strong impetus for the Netherlands to effectively decriminalize cannabis use
Drug use in early cannabis users and co-twin controls from the Netherlands

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Users</td>
<td>Co-twins</td>
</tr>
<tr>
<td>Party drugs</td>
<td>16.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Hard drugs</td>
<td>12.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Any</td>
<td>17.9</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Lynskey et al, 2006
Findings do not necessarily discount social mechanisms

- Despite the liberal legal approach to cannabis in the Netherlands, the rate of cannabis use is in fact lower there (12.3%) than in the U.S (28.8%) or Australia (39.3%) (Vega et al, 2002; AIHW, 1999)

- As early cannabis use may represent a ‘norm violating’ behavior in the Netherlands, social mechanisms (e.g., peer affiliations, approval of use) may underlie this association
Conclusions

- Early cannabis use was associated with significantly increased risks for stimulant use and abuse/dependence.
- These results & other studies suggest early cannabis use may causally influence later drug use & drug-related problems.
- Multivariate genetic tests of comorbidity between early onset cannabis use and other illicit drug use can not fully discount the possibility that early onset cannabis use causally influences escalation to the use of other drugs.
Implications

- Early substance use partially reflects familial risk
- May also be a marker for ‘social’ risk, including peer affiliations
  - Early onset cannabis use has been reported to be associated with disengagement from education – but not with other educational outcomes
  - In contrast, alcohol use is not consistently associated with educational disengagement
- Do the “effects” of cannabis use vary with the prevalence of use?
Birth Cohort Trends in Cannabis Use

Degenhardt et al, 2000
### Weekly cannabis use & school leaving

<table>
<thead>
<tr>
<th>Weekly cannabis use</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 10</td>
<td>5.6</td>
<td>2.0-15</td>
</tr>
<tr>
<td>Year 11</td>
<td>2.2</td>
<td>0.91-6.0</td>
</tr>
<tr>
<td>Year 12</td>
<td>1.1</td>
<td>0.40-2.90</td>
</tr>
</tbody>
</table>

*Lynskey et al, 2003*
Consideration of mechanisms underlying frequently observed associations between early onset substance use and increased risks for later adverse outcomes has important implications for prevention.
Association is non-causal

- Family, social and background factors associated with early onset substance use are also independently associated with risks for dependence etc.

- Important goals of prevention should be to:
  - Reduce exposure to known risk factors
  - Targeted interventions for those identified as being at greatest risk?
Mechanism is drug exposure

- e.g., Due to increased sensitivity of adolescent brain to the neurotoxic effects of drug exposure

- An important goal of prevention should be to delay/prevent adolescent substance use
  - In addition to preventing acute effects of intoxication (and associated risks, e.g., DUI), such delays should reduce risks for later onset of dependence, mental health problems etc.
Social mechanisms surrounding context of use/ availability

- Strategies focusing on risk behaviors associated with early substance use (e.g., disengagement from education, peer affiliations) rather than substance use *per se*.

- Early substance use may provide a marker for vulnerable individuals
Collaborators

- **Mid-West Alcoholism Research Center, WUSM**
  - Arpana Agrawal
  - Kathy Bucholz
  - Julie Grant
  - Andrew Heath
  - Pam Madden
  - Elliot Nelson
  - Carolyn Sartor

- **Queensland Institute of Medical Research**
  - Nick Martin
  - Dixie Statham

- **Christchurch Health and Development Study**
  - David Fergusson
  - John Horwood

- **Center for Adolescent Health**
  - Carolyn Coffey
  - George Patton


References


