How Exclusion of Women and African-Americans Undermines the Value of Treatment Research

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Poll Question #1

• What is your primary role in VA?
  – student, trainee, or fellow
  – clinician
  – researcher
  – manager or policy-maker
  – Other
Logic of the evidence-based medicine movement

• High-quality, well-controlled research can identify what works

• Everyday clinical practice in many areas (e.g., alcohol treatment) is often ineffective

• Translation of science into practice will improve health care provision and outcomes
Do parachutes provide protection from “gravitational challenge”? 

G.C. Smith and J. P. Pell, 2003  BMJ, 327: 1459-1461
“Lies, damned lies and evidence-based medicine”

--D.P. Kernick The Lancet 1998; 351:1824
Demographics of researched vs real-world alcohol patients in U.S.

Research data from review by Swearingen et al (2003), Addictive Behaviors, 28, 415-436
Could eligibility criteria in treatment outcome research be a place where we could lessen this problem?

• Impose rules unlike clinical practice

• Create unrepresentative samples by design

• Are in part under researchers’ control
Moncrieff & Drummond (1998)

- Reviewed methodological quality of 25 highly-cited trials of alcohol treatment
- Mentioned that half of studies failed to report number of patients excluded
- Of reported studies, mean = 50% with a range of 4-92%
Questions for research program on eligibility criteria and alcohol patients

• What criteria do alcohol treatment researchers use and how often?
• How do criteria affect the composition of samples?
• Do criteria affect the outcomes of treatment research studies?
Study 1: What eligibility criteria do alcohol treatment researchers use and how often?

Data Source: Finney meta-analysis

- All 683 English-language alcohol treatment outcome studies that:
  - Included a follow-up
  - Had at least 5 adult patients per condition
  - Appeared between between 1980 to 1998 (Dissertations, journals and books)
Methods

- Data are the verbatim published text
- Coded by independent raters
- Test for rater drift each 50 studies
- Range of agreement 95-100%, Kappa 0.94
Psychiatric Category

• Cannot be psychotic
• Cannot have co-occurring “psychiatric problems”
• Cannot pose a threat to self or others
• Cannot be taking psychiatric medication
Compliance/motivation category

- Must agree up front to attend all treatment
- Cannot be “difficult” or “uncooperative”
- Must agree to be available for a follow-up research interview
- Must be motivated to change
Number of eligibility criteria used in 683 alcohol treatment studies
Prevalent criteria

• Psychiatric/emotional problems (37.8%)
• Alcohol treatment (31.8%)
• Medical conditions (31.6%)
• Compliance/motivation (31.5%)
• Neuro-cognitive problems (23.0%)
• Illicit drug use (22.7%)
• Social/Residential Stability (19.6%)
National differences in average rate of eligibility criteria

- UK  2.41
- Anzus    2.48
- USA    2.84
- Scandinavia 3.22
- Canada 3.25
- Ger/Fra/Ita 3.79
Major predictors of greater exclusivity in study design

<table>
<thead>
<tr>
<th></th>
<th>b-weight</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.60</td>
<td>0.27</td>
<td>.03</td>
</tr>
<tr>
<td>Decade of Publication</td>
<td>0.77</td>
<td>0.11</td>
<td>.000</td>
</tr>
<tr>
<td>US NIAAA Funding</td>
<td>1.22</td>
<td>0.25</td>
<td>.000</td>
</tr>
<tr>
<td>Private Sector Funding</td>
<td>0.82</td>
<td>0.41</td>
<td>.047</td>
</tr>
<tr>
<td>Randomized design</td>
<td>1.39</td>
<td>0.19</td>
<td>.000</td>
</tr>
<tr>
<td>Inpatient/Residential TX</td>
<td>-.21</td>
<td>0.18</td>
<td>ns</td>
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</tbody>
</table>

Note. Positive weight means increased exclusiveness
Summary of study #1 key findings

• Eligibility criteria widely used, poorly described

• Alcohol treatment research is getting more exclusive (less representative)

• Eligibility criteria more common with particular designs and funders
Study 2: Are certain populations disproportionately excluded?

Two key populations of interest

- U.S. National Institutes of Health policy on “burden and benefits” of treatment research
- Every grant proposal rated on representation of women and racial minorities
Research approach (study 2 and 3)

• Operationalize widely used eligibility criteria using the Addiction Severity Index
• Apply them to “take all comers” health services data sets
• Observe how criteria change the composition and outcomes of the sample
**Example Operationalization:**

**Psychiatric/Emotional Problem Eligibility Criteria**

<table>
<thead>
<tr>
<th>Degree of exclusivity</th>
<th>Operationalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Any of: IP treatment, halluc, suicidality, psychotropic med</td>
</tr>
<tr>
<td>Moderate</td>
<td>Any 2 of above</td>
</tr>
<tr>
<td>Low</td>
<td>All of above</td>
</tr>
</tbody>
</table>
Example real world data sets

- National Drug Evaluation Network
- National Veterans Affairs system
- Target Cities studies
- State data systems from Michigan and Washington
- Community Epidemiology Laboratory
One illustrative sample:
State of Washington

- 502 alcohol patients admitted to one of 13 programs statewide
- No eligibility criteria for study entry
- 7.3% African-American, 38.0% female
- All assessed with Addiction Severity Index
POLL QUESTION #2

Which sort of exclusion criteria do you think would be most likely to disproportionately exclude African-Americans?

- Psychiatric
- Medical
- Drug use
- Compliance
- Social-Residential
POLL QUESTION #3

Which sort of exclusion criteria do you think would be most likely to disproportionately exclude women?

- Psychiatric
- Medical
- Drug use
- Compliance
- Social-Residential
Proportion of patients ineligible under less and more exclusive operationalization

<table>
<thead>
<tr>
<th></th>
<th>Less</th>
<th>More</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>0.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>14.9%</td>
<td>62.4%</td>
</tr>
<tr>
<td>Medical</td>
<td>27.9%</td>
<td>31.3%</td>
</tr>
<tr>
<td>Drug use</td>
<td>69.7%</td>
<td>75.5%</td>
</tr>
<tr>
<td>Compliance</td>
<td>7.4%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Social-Residential</td>
<td>10.4%</td>
<td>53.2%</td>
</tr>
<tr>
<td>Average</td>
<td>21.8%</td>
<td>40.2%</td>
</tr>
</tbody>
</table>
Relative risk of being excluded for African-Americans versus patients of other races

<table>
<thead>
<tr>
<th>Category</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>na</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>0.95</td>
</tr>
<tr>
<td>Medical</td>
<td>0.86</td>
</tr>
<tr>
<td>Drug use</td>
<td>1.08</td>
</tr>
<tr>
<td>Compliance</td>
<td>0.44</td>
</tr>
<tr>
<td>Social-Residential</td>
<td>1.13</td>
</tr>
</tbody>
</table>
Relative risk of being excluded for Women versus Male patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk</th>
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</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>1.09</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1.11</td>
</tr>
<tr>
<td>Medical</td>
<td>1.01</td>
</tr>
<tr>
<td>Drug use</td>
<td>1.15</td>
</tr>
<tr>
<td>Compliance</td>
<td>0.47</td>
</tr>
<tr>
<td>Social-Residential</td>
<td>1.14</td>
</tr>
</tbody>
</table>
Summary of findings

• Not all criteria are of concern (neurological)
• Social-residential and drug use criteria exclude high proportions of patients, especially women and African-Americans
• Other criteria (e.g., compliance) may work in the opposite direction
Other related findings

• In both public and private systems, exclusion is related to:
  • Being African-American
  • Being low income
  • Having more severe comorbidities

Less than half of drug dependent patients are eligible and willing to participate in RCTs

Note. These results are weighted for sample size across 33 RCTs. Melberg, H. O., & Humphreys, K. (2010). Drug and Alcohol Review, 29, 193-201
Depression Studies Also Have Low Enrollment Rates

- Study of 216 consecutive real-world depression patients in outpatient care
- Applied 28 eligibility criteria from an ongoing double-blind RCT
- 215 patients ineligible
- The 1 eligible patient refused to participate!

Studies of study exclusion rates for other disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>% Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers</td>
<td>~50%-70%</td>
</tr>
<tr>
<td>CVD</td>
<td>~65%-85%</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>~50%</td>
</tr>
<tr>
<td>SCZ</td>
<td>~80%</td>
</tr>
<tr>
<td>Alzheimer’s</td>
<td>~90-95%</td>
</tr>
</tbody>
</table>
Summary of study #2 findings and related work

• A high proportion of real-world alcohol patients are ineligible under most common criteria

• Those excluded tend to be from socially marginal groups which NIH mandates be included

• Not correctable by over-sampling
Study 3: Can eligibility criteria change the outcomes a study obtains?

Logic of Study 3

- Bias in outcome estimates is a function of two factors:
  - Size of excluded group
  - Difference between outcomes of excluded and included patients
- Can test bias using same method as Study 2
Washington State as example

- Patients followed up at 6 months
- ASI Alcohol Composite Index Improvement used as outcome
- Mean improvement 0.28 on a 0-1 scale
## Effects on ASI composite score of applying criteria

<table>
<thead>
<tr>
<th>psychiatric</th>
<th>8.7% worse outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>10.1% worse outcomes</td>
</tr>
<tr>
<td>Drug use</td>
<td>7.2% better outcomes</td>
</tr>
<tr>
<td>Compliance</td>
<td>5.8% better outcomes</td>
</tr>
<tr>
<td>Social-Residential</td>
<td>15.6% better outcomes</td>
</tr>
</tbody>
</table>
What this means practically

• A treatment with a true success rate of 50%
• Could look like a treatment with a 60% rate if the researcher excluded non-compliant and homeless patients
• Or like a treatment with a 40% rate if the researcher didn’t exclude patients with medical/psychiatric co-morbidities
Implications

• Research studies can be designed to generate substantially different outcomes than does everyday practice

• Integration of studies across the literature must consider eligibility criteria
Other key point

• Review of RCTs in influential medical journals by Van Spall et al
• Less than half of eligibility criteria employed were well-justified
• Current status of criteria appears to be that they “go without saying”
Implications across all studies

- Eligibility criteria should be better tailored and reported
- Need to shift to viewing them as like any other methodological decision
- Drug use criteria may not be justifiable
- High bar should be set for those criteria that exclude marginalized groups and/or dramatically changes study conclusions
Collaborators

Molly Carney       John Finney
Doyanne Horst      Helena Kraemer
Alex Sox-Harris    Tom McLellan
Bertram Stöffelmayr Hans Melberg
Ken Weingardt     Connie Weisner

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Thank you for your attention
Questions/Comments?

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