BEYOND ABSTINENCE: REDUCTIONS IN DRINKING AS AN ENDPOINT FOR ALCOHOL CLINICAL TRIALS

KATIE WITKIEWITZ PHD | UNIVERSITY OF NEW MEXICO

Co-Authors:
Daniel E. Falk, Deborah Hasin, Karl F. Mann, Raye Z. Litten, Stephanie S. O’Malley, Henry R. Kranzler, and Raymond F. Anton, on behalf of the Alcohol Clinical Trials Initiative (ACTIVE) Group

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OVERVIEW

- Food and Drug Administration Guidance for Alcohol Medications
- European Medicines Agency guidance
- World Health Organization (WHO) risk levels of drinking
- Examination of WHO risk level reductions and patient drinking consequences, mental health, physical health, and quality of life
  - WHO risk levels are associated with how a patient “feels and functions”
  - WHO risk levels are stable and associated with outcomes over time
DRINKING AS A “SURROGATE ENDPOINT” FOR HOW A PATIENT “FEELS AND FUNCTIONS”

Alcoholism: Developing Drugs for Treatment Guidance for Industry

Because drinking behavior is considered a surrogate endpoint, sponsors should document a pattern of behavior that can be reasonably predictive of clinical benefit (e.g., improvement in the way the patient feels or functions).

Two surrogate endpoints:
- abstinence
- no heavy drinking days (4+/3+ drinks men/women)
The EMA provides the option of “evaluating the proportion of subjects with a significant categorical shift in WHO risk levels of drinking” as a primary endpoint for an intermediate harm reduction goal.
<table>
<thead>
<tr>
<th>Drinks per day (in grams)</th>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
<th>Very High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinks per day (in standard drinks)</td>
<td>1 to 40 g</td>
<td>41 to 60 g</td>
<td>61 to 100 g</td>
<td>101+ g</td>
</tr>
<tr>
<td>0 - 2.9 drinks</td>
<td>3.0 - 4.3 drinks</td>
<td>4.4 - 7.1 drinks</td>
<td>7.2+ drinks</td>
<td></td>
</tr>
</tbody>
</table>

**World Health Organization Alcohol Risk Levels (for males)**

<table>
<thead>
<tr>
<th>Drinks per day (in grams)</th>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
<th>Very High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinks per day (in standard drinks)</td>
<td>1 to 20 g</td>
<td>21 to 40 g</td>
<td>41 to 60 g</td>
<td>61+ g</td>
</tr>
<tr>
<td>0 - 1.4 drinks</td>
<td>1.5 - 2.8 drinks</td>
<td>2.9 - 4.3 drinks</td>
<td>4.4+ drinks</td>
<td></td>
</tr>
</tbody>
</table>

**World Health Organization Alcohol Risk Levels (for females)**

Dear Katie

I’m surprised how many requests I get for this old work. I certainly wouldn’t be basing alcohol drinking guidelines on this material.

Dallas English
Professor
Centre for Epidemiology and Biostatistics
Level 3, 207 Bouverie St
The University of Melbourne,
Victoria 3010
Australia
CURRENT STUDY

- Are WHO risk drinking level reductions “reasonably predictive of clinical benefit (e.g., improvement in the way the patient feels and functions)”?

At least 1-level reduction

- Very high to high risk
- High to medium risk
- Medium to low risk
- Low risk to abstinent

At least 2-level reduction

- Very high to medium risk
- High to low risk
- Medium risk to abstinent
COMBINE STUDY

- **COMBINE study, medication conditions (n=1226)**
  - Individuals with alcohol dependence recruited from 11 research units
  - Randomized to 16 weeks of medications (acamprosate, naltrexone, placebo) and psychosocial intervention

- **Measures**
  - Form-90 was used to assess WHO risk levels of drinking based on grams of ethanol per day
  - Drinker Inventory of Consequences (DrInC) to assess drinking-related consequences
  - Short Form Health Survey (SF-12) to assess mental health
  - Clinic visits to assess systolic blood pressure, liver enzymes
  - World Health Organization Quality of Life – Brief version to assess quality of life
Change in WHO Risk Level from Baseline to Last Month of Treatment (Month 4)

- 88% with at least 1-level reduction
- 77% with at least 2-level reduction
MORE INDIVIDUALS ACHIEVE A 1- AND 2-LEVEL REDUCTION THAN ALTERNATIVE ENDPOINTS

% achieving outcome in last month of treatment

- Abstinence: 36%
- No Heavy Drinking Days: 54%
- 1-Level Reduction: 77%
- 2-Level Reduction: 88%
AT LEAST 1- OR 2-LEVEL REDUCTIONS ASSOCIATED WITH SIGNIFICANTLY FEWER DRINKING CONSEQUENCES AND GREATER HEALTH

- Statistically and clinically significant effects for all outcomes
  - 1-level reduction
    - Systolic blood pressure (p=.0001)
    - Liver function: %CDT, AST, and ALT (all p<.001)
    - Quality of life, drinking consequences, and mental health (all p<.001)
  - 2-level reduction
    - Systolic blood pressure (p=.001)
    - Liver function: %CDT, AST, and ALT (all p<.001)
    - Quality of life, drinking consequences, and mental health (all p<.001)

DIFFERENCE BETWEEN NO CHANGE OR INCREASE/NON-ABSTINENT AND AT LEAST 1-LEVEL REDUCTION VS ABSTINENCE ON FUNCTIONING OUTCOMES OVER TIME (all $p<.05$)

-20 -15 -10 -5 0

SBP (mm/Hg) AST (IU/L) ALT (IU/L) GGT (IU/L) DrInC

Average reduction vs no change or increase

-20 -15 -10 -5 0

-5

-10

-15

-20

-20 -15 -10 -5 0

No change or increase/Non-Abstinent

At least 1-level reduction (exclude abstainers)

Abstainers

STABILITY OF WHO RISK LEVEL REDUCTIONS UP TO ONE YEAR POST-TREATMENT

Achieved 1-level reduction at end of treatment (88%)
- 89%
- 11%
- No change or increase at 1 year
- 1-level reduction at 1 year

Achieved 2-level reduction at end of treatment (77%)
- 77%
- 23%
- 1-level reduction, no change or increase at 1 year
- 2-level reduction at 1 year

STABILITY OF WHO RISK LEVEL REDUCTIONS UP TO THREE YEARS POST-TREATMENT (PROJECT MATCH DATA)

Achieved 1-level reduction at end of treatment:
- 18% no change or increase at 3 years
- 82% 1-level reduction at 3 years

Achieved 2-level reduction at end of treatment:
- 26% 1-level reduction, no change or increase at 3 years
- 74% 2-level reduction at 3 years

Witkiewitz et al in preparation.
STABILITY OF WHO RISK LEVEL REDUCTIONS UP TO ONE YEAR POST-TREATMENT BY AUD SEVERITY (COMBINE)

MILD AUD
Achieved 2-level reduction at end of treatment (77%)
- 1-level reduction, no change or increase at 1 year
- 2-level reduction at 1 year

MILD AUD
Achieved 2-level reduction at end of treatment (79%)
- 1-level reduction, no change or increase at 1 year
- 2-level reduction at 1 year

SEVERE AUD
Achieved 2-level reduction at end of treatment (74%)
- 1-level reduction, no change or increase at 1 year
- 2-level reduction at 1 year

Witkiewitz et al in preparation.
CONCLUSION (AND SOME OTHER FINDINGS)

- WHO 1- and 2-level reductions are associated with significant improvements in:
  - drinking consequences, systolic blood pressure, liver enzyme levels, mental health, and quality of life in clinical samples (Witkiewitz et al., 2017, 2018, 2019)
  - lower risk of alcohol dependence (Hasin et al., 2017), liver disease (Knox et al 2018)
  - medication effect sizes (Falk et al., 2019)
- WHO 1- and 2-level reductions are stable over time (up to 3 years) and comparable to abstinence when examining a range of functioning and physical health outcomes
- Results are not driven by abstainers and consistent across levels of severity
- Reductions in WHO risk drinking levels are “reasonably predictive of clinical benefit (e.g., improvement in the way the patient feels and functions)”

For more information contact:
Katie Witkiewitz, PhD
Professor of Psychology
Center on Alcoholism, Substance Abuse, and Addictions
University of New Mexico

Alcohol Clinical Trials Initiative (ACTIVE) Group: FDA, NIAAA, Pharma, Academics

Dan Falk  Raye Litten  Ray Anton  Hank Kranzler  Karl Mann  Debbie Hasin  Stephanie O’Malley
**ONE- AND TWO-LEVEL REDUCTIONS ASSOCIATED WITH FUNCTIONAL OUTCOMES OVER TIME**

<table>
<thead>
<tr>
<th></th>
<th>SBP (mm/Hg)</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>GGT (IU/L)</th>
<th>DrInC</th>
<th>PHDD</th>
<th>PDD</th>
<th>DPDD</th>
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<td><strong>Linear Mixed Models (n=1226)</strong></td>
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<tr>
<td>1-level reduction</td>
<td>-6.42 (1.11)***</td>
<td>-7.87 (2.18)***</td>
<td>-6.33 (2.09)***</td>
<td>-26.92 (10.47)*</td>
<td>-19.24 (1.32)***</td>
<td>-39.89 (1.76)***</td>
<td>-32.69 (1.62)***</td>
<td>-4.86 (.36)***</td>
</tr>
<tr>
<td>2-level reduction</td>
<td>-6.00 (.84)***</td>
<td>-7.19 (1.55)***</td>
<td>-6.00 (1.53)***</td>
<td>-21.84 (7.97)***</td>
<td>-17.40 (1.08)***</td>
<td>-38.55 (1.45)***</td>
<td>-33.65 (1.39)***</td>
<td>-4.16 (.28)***</td>
</tr>
<tr>
<td><strong>Missing = Failure Models (n=1226)</strong></td>
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<tr>
<td>1-level reduction</td>
<td>-5.69 (1.09)***</td>
<td>-7.62 (2.09)***</td>
<td>-6.12 (2.01)**</td>
<td>-25.60 (10.07)*</td>
<td>-18.21 (1.27)***</td>
<td>-29.71 (1.62)***</td>
<td>-24.53 (1.49)***</td>
<td>-3.23 (.31)***</td>
</tr>
<tr>
<td>2-level reduction</td>
<td>-5.56 (.84)***</td>
<td>-7.13 (1.53)***</td>
<td>-5.86 (1.50)***</td>
<td>-21.37 (7.67)***</td>
<td>-16.84 (1.06)***</td>
<td>-32.07 (1.41)***</td>
<td>-28.37 (1.33)***</td>
<td>-3.25 (.26)***</td>
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<td><strong>Excluding Abstainers (n=1052)</strong></td>
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<tr>
<td>1-level reduction</td>
<td>-5.14 (1.13)***</td>
<td>-6.36 (2.15)***</td>
<td>-4.17 (1.99)*</td>
<td>-12.64 (6.82)</td>
<td>-14.39 (1.22)***</td>
<td>-38.27 (1.77)***</td>
<td>-28.10 (1.63)***</td>
<td>-3.54 (.41)***</td>
</tr>
<tr>
<td>2-level reduction</td>
<td>-4.26 (.89)***</td>
<td>-5.49 (1.60)***</td>
<td>-3.87 (1.56)*</td>
<td>-8.24 (5.21)</td>
<td>-13.14 (1.02)***</td>
<td>-38.19 (1.54)***</td>
<td>-29.34 (1.45)***</td>
<td>-2.96 (.33)***</td>
</tr>
</tbody>
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Witkiewitz et al., 2019
AT LEAST 1-LEVEL REDUCTION (“SUCCESS”) ASSOCIATED WITH SIGNIFICANTLY LOWER (IMPROVED) DRINKING CONSEQUENCES AND HEALTH MEASURES, AS COMPARED TO NO CHANGE OR INCREASE (“FAILURE”)

Y-axis is z-score of outcome (Mean=0, SD=1)
d = Cohen’s d (effect size)
p = p-value for differences in means
Failure = no change or increase Mean (SD)
Success = at least 1-level reduction Mean (SD)

DrInC = Drinker Inventory of Consequences
%CDT = % carbohydrate-deficient transferrin
SBP = systolic blood pressure
AST = aspartate aminotransferase
ALT = alanine aminotransferase
GGT = γ-glutamyltransferase
AT LEAST 1-LEVEL REDUCTION (“SUCCESS”) ASSOCIATED WITH SIGNIFICANTLY GREATER (IMPROVED) MENTAL HEALTH AND QUALITY OF LIFE, AS COMPARED TO NO CHANGE OR INCREASE (“FAILURE”)

Y-axis is z-score of outcome (Mean=0, SD=1)

d = Cohen's d (effect size)

p = p-value for differences in means

Failure = no change or increase Mean (SD)

Success = at least 1-level reduction Mean (SD)

SF12 = Short Form Health Survey

PhysicalQoL = Quality of Life: Physical Domain

PsycholQoL = Quality of Life: Psychological Domain

SocialQoL = Quality of Life: Social Domain

EnviroQoL = Quality of Life: Environmental Domain
AT LEAST 2-SHIFT REDUCTION ("SUCCESS") ASSOCIATED WITH SIGNIFICANTLY LOWER (IMPROVED) DRINKING CONSEQUENCES AND HEALTH MEASURES, AS COMPARED TO NO CHANGE OR INCREASE ("FAILURE")

Y-axis is z-score of outcome (Mean=0, SD=1)
d = Cohen’s d (effect size)
p = p-value for differences in means
Failure = 1-level, no change or increase Mean (SD)
Success = at least 2-level reduction Mean (SD)

DrInC = Drinker Inventory of Consequences
%CDT = % carbohydrate-deficient transferrin
SBP = systolic blood pressure
AST = aspartate aminotransferase
ALT = alanine aminotransferase
GGT = γ-glutamyltransferase
AT LEAST 2-SHIFT REDUCTION (“SUCCESS”) ASSOCIATED WITH SIGNIFICANTLY GREATER (IMPROVED) MENTAL HEALTH AND QUALITY OF LIFE, AS COMPARED TO NO CHANGE OR INCREASE (“FAILURE”)

Y-axis is z-score of outcome (Mean=0, SD=1)

- $d =$ Cohen’s d (effect size)
- $p =$ p-value for differences in means

Failure = 1-level, no change or increase Mean (SD)
Success = at least 2-level reduction Mean (SD)

SF12 = Short Form Health Survey
PhysicalQoL = Quality of Life: Physical Domain
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