ACTIVE Workgroup Meeting Minutes
November 03 - 04, 2021
Virtual Live Meeting

Participants:
Ray Anton, Medical University of South Carolina, Chair
Sarah Akerman, Alkermes
Maryam Afshar, FDA Guest
Arnie Aldridge, RTI
Sarah Arnold, FDA Guest
Henri Jean Aubin, Hôpitaux Universitaires Paris-Sud
Bartholt Bloomfield-Clagett, FDA Guest
Heather Davidson, Otsuka
William Dowd, RTI
Dan Falk, NIAAA Advisor
Alison Fisher, Dicerna
Angela Haeny, Yale University School of Medicine
John Hanrahan, Dicerna
Deborah Hasin, Columbia University
Michaela Hoffman, University of South Carolina
Keith Isenberg, Blue Cross Blue Shield
Hank Kranzler, University of Connecticut Health
Raye Litten, NIAAA Advisor
Karl Mann, University of Heidelberg
Roger Meyer, Penn State Hershey College of Medicine
Stephanie O'Malley, Yale University School of Medicine
Amy O'Sullivan, Alkermes
Bernard Silverman
Celia Winchell, FDA
Katie Witkiewitz, University of Mexico
Gary Zarkin, RTI
Laura Reynolds, Parthenon Management Group
Lindsay Snyder, Parthenon Management Group

Wednesday, November 03, 2021

1. New members and guests were welcomed to the meeting.

2. ***A Toolkit for Predicting Daily Drinking Patterns:*** K. Witkiewitz presented on the development of a "machine learning toolkit" that can help alcohol researchers, clinicians, and patients gain new insights into alcohol use patterns and predictors of drinking. The goal of the project is to identify a combination of risk and protective factors that predict individual patterns of alcohol use. The toolkit could potentially be used in clinical practice and mobile apps in the future, but currently it is being used by researchers. K. Witkiewitz will provide an update on the toolkit.

3. ***Sleep As An Important Target or Modifier in AUD Clinical Trials: Examples from Recent Gabapentin Clinical Trials:*** M. Hoffman began the presentation stating in a healthy population alcohol impacts a number of objective sleep variables, particularly earlier onset of sleep but with more disruption in the second half of the night. The severity of alcohol problems was found to be a predictor

of sleep disturbance in problem drinkers. Based on this information, she showed how medications that are useful for AUD can also have an impact on sleep, providing data on Gabapentin as an example. K. Witkiewitz will work on a paper on the sleep in the Horizant trial. She will look at the Gabapentin data from M. Hoffman's slides to help guide some initial analyses.

4. ***Introduction to the Development of a Craving Patient Rated Outcome Measure:*** S. O'Malley introduced A. Haeny. A. Haeny discussed the development of a patient-rated outcome measure of alcohol and drug craving, stating that there are numerous measures of craving, but very few have the type of psychometric support generally required by the FDA for a Patient Reported Outcome Measure. She briefly outlined the steps in developing an alcohol and drug craving patient-rated outcome measure and reported on what her team had done in each of the below steps:
    i. Literature review to identify all existing craving items
    ii. Develop an item bank and conceptually organize the items
    iii. Conduct focus groups to ensure comprehensive coverage of craving

    She also discussed the next steps that have not yet been addressed by her team.

5. ***Comparison of The WHO-RDL Categories with Binge Drinking Measurement: Relationship to Various NESARC Alcohol Consequences:*** D. Hasin provided the rationale for using epidemiologic data in investigating validity of risk drinking indicators, stating that extensive epidemiologic evidence shows that drinking levels are related to risk of mortality and many chronic disseases. Additionally, exclusive focus on clinical samples of heavy drinkers could produce biased results because those in treatment may not be representative of heavy drinkers in the general population. D. Hasin concluded by sharing that the differences between associations of the WHO risk drinking levels as well as "binge drinking" at least weekly were tested across a set of validators covering many domains. Where differences occurred, the WHO risk drinking levels had consistently stronger associations with various negative alcohol related outcomes (both psychological and medical) and that these results provide further support for the WHO risk drinking levels as being as or more useful than the binge drinking concept alone.

6. ***WHO RDLs as an Outcome Measure in a Combined Analysis of Two Topiramate Pharmacogenetic Studies:*** H. Kranzler discussed two studies he and his team conducted, with the first being the placebo-controlled rial of Topiramate to reduce heavy drinking and the second being prospective randomized pharmacogenetic study of topiramate for treating alcohol use disorder.

7. ***Rationale and Methods for The Alcohol Trial Simulation Project:*** R. Anton introduced A. Aldridge's presentation stating that this is the culmination of what an ACTIVE Subcommittee has been focusing on most recently, and this is a pilot example of the work. A. Aldridge shared the objective of his presentation stating that he plans to describe a model of AUD RX RCTs that uses decision theory, simulation modeling, and real-world information. The presentation was divided into two parts. The first part included the obejctives and rational for the completed model, as well as the description of the framework for developing the model. The latter part of the presentation was a demonstration of the simulation model. The ultimate product would be a publically accessible algorithm/program to aid crucial decision making in for AUD trial design.

8. ***Process and Progress of Identifying Key AUD Multisite Trial Variables. Medical Student Project:*** S. O'Malley began her presentation by explaining the project she is working on with A. Aldridge and two medical students as an initial stage of the Simulation Project mentioned above. The project entails 1) identifying key AUD multi-site variables to inform the simulation and 2) abstracting data on these variables from the American AUD Multi-site trial literature. S. O'Malley highlighted the goals of the

project, the study approach, inlcusions/exclusion criteria, and a draft of the variables that were to be extracted. She concluded by sharing the preliminary results.

9. ***Administrative Details of the Clinical Simulation:*** R. Anton shared with the group what data had been used, as well as plans for funding the project.
    a. **Data:** R. Anton showed the group the spreadsheet of publicly available AUD clinical trial data that is proposed a data to be used for the simulation project. Additionally, D. Falk also stated that the NIAAA has a new data archive program where all trials will be archived from 2019 going forward will be made available to conduct secondary analysis.

10. ***Future ACTIVE considerations:*** The group concluded the two-day meeting by addressing the following items:
    a. **Alcohol Consequence Reporting (PROMIS):** S. O'Malley provided an update on PROMIS stating that one more validation study is needed. Additionally, she shared that it had been incorporated into the NIAAA lab studies, as well as a larger phase 2 trials and laboratory trials.
    b. **Upcoming Meetings with RSA**: Once the FDA responds to the ACTIVE/NIAAA dossier, it was suggested to create a presentation to share during a future RSA meeting.
        a. M. Hoffman will present sleep data at the upcoming RSA Meeting.
    c. **Next Meeting:** The group discussed plans for the next meeting.
11. ***Discussion of Future Papers and Presentations:*** The group discussed future ACTIVE considerations and projects.

ACTIVE Published/In-Press/Submitted Papers*:*

- Aldridge AP, Zarkin GA, Dowd WN, Witkiewitz K, Falk DE, Hasin DS, Litten RZ, O'Malley SS, Anton RF. The Relationship between Reductions in WHO Risk Drinking Levels during Treatment and Subsequent Healthcare Costs. Journal of Addiction Medicine. (Accepted)
- Witkiewitz K. Sustainability of the WHO Risk Drinking Level Shift in Two Clinical Trials (Pharmacotherapy and Psychosocial) and Two Continents (USA and Europe): Relationship to AUD Severity. Addiction. (Accepted)
- Witkiewitz K, Kranzler H, Hallgren K, Hasin D, Aldridge A, Zarkin G, Mann K, O'Malley S, and Anton RF. Stability of Drinking Reductions and Long-term Functioning Among Patients with Alcohol Use Disorder. Journal of General Internal Medicine. 2021 Feb; 36(2):404-412. PubMed PMID: 33180306; PubMed Central PMCID: PMC7878601.
- Shmulewitz D, Aharonovich E,Witkiewitz K, Raymond RF, Kranzler HR, Scodes J, Mann KF, Wall MM, Hasin D. The World Health Organization Risk Drinking Levels Measure of Alcohol Consumption: Prevalence and Health Correlates in US Adult Nationally Representative Surveys, 2001-2002 and 2012-2013. American Journal of Psychiatry. 2021 Jan 21. PubMed PMID: 33472388.
- Knox J, Scodes J, Witkiewitz K, Kranzler H, Mann K, O'Malley S, Wall M, Anton R, Hasin D, ACTIVE Group. Reduction in World Health Organization (WHO) Risk Drinking Levels and Cardiovascular Disease. Alcohol Clinical and Experimental Research. 2020 Aug; 44(8):1625-1635. PubMed PMID: 32619058; PubMed Central PMCID: PMC7484295.
- Anton RF, Witkiewitz K, Falk D, Litten R, Hasin D, Mann K, O'Malley SS., Response to Dr. Mark Litt Commentary. Alcohol Clinical and Experimental Research. 2019 Aug 5. PubMed PMID: 31381170.
- Witkiewitz K, Falk DE, Litten RZ, Hasin DS, Kranzler HR, Mann KF, O'Malley SS, Anton RF. Maintenance of World Health Organization Risk Drinking Level Reductions and Posttreatment Functioning Following a Large Alcohol Use Disorder Clinical Trial. Alcoholism: Clinical and Experimental Research. 2019 May; 43(5): 979-987. PubMed PMID: 30951210; PubMed Central PMCID: PMC6502682.

- Knox J, Wall M, Witkiewitz K, Kranzler HR, Falk DE, Litten R, Mann K, O'Malley SS, Scodes J, Anton R, Hasin DS. Reduction in Non-abstinent World Health Organization (WHO) Drinking risk Levels and Drug Use Disorders: 3-year Follow-up Results in the US General Population. Drug Alcohol Depend. 2019 Apr 1; 197: 228-235. PubMed PMID: 30852375; PubMed Central PMCID: PMC440807.
- Falk DE, O'Malley SS, Witkiewitz K, Anton RF, Litten RZ, Slater M, Kranzler HR, Mann KF, Hasin DF, Johnson B, Meulien D, Ryan M, & Fertig J. Evaluation of Drinking Risk Levels as Outcomes in Alcohol Pharmacotherapy Trials: A Secondary Analysis of 3 Randomized Clinical Trials. JAMA Psychiatry. 2019 March 13. PubMed PMID: 30865232l; PubMed PMCID: PMC6450273.
- Knox J, Scodes J, Wall M, Witkiewitz K, Kranzler HR, Falk DE, Litten RZ, Mann KF, O'Malley SS, Anton RF, Hasin DS; Alcohol Clinical Trials (ACTIVE) Workgroup. Reduction in non-abstinent WHO drinking risk levels and depression/anxiety disorders: 3-year follow-up results in the US general population. Drug Alcohol Depend. 2019 Feb 14; 197:228-235. PubMed PMID: 30852375.
- Witkiewitz K, Kranzler HR, Hallgren KA, Hasin DE, Mann KF, Falk DE, Litten RZ, O'Malley SS, & Anton RF. Drinking Risk Level Reductions Associated with Improvements in Physical Health and Quality of Life Among Individuals with Alcohol Use Disorder. Alcoholism: Clinical and Experimental Research. 2018 Dec; 42(12):2453-2465. PubMed PMID: 30395350; PubMed Central PMCID: PMC6286196.
- Knox J, Wall M, Witkiewitz K, Kranzler HR, Falk DE, Litten RZ, Mann KF, O'Malley SS, Scodes J, Anton RF, & Hasin DS. Reduction in Non-Abstinent WHO Drinking Risk Levels and Change in Risk for Liver Disease and Positive AUDIT-C Scores: Prospective 3-Year Follow-Up Results in the US General Population. Alcoholism: Clinical and Experimental Research. 2018 Nov; 42(11)2256-2265. PubMed PMID: 30204248; PubMed Central PMCID: PMC6263142.
- Mann K, Aubin HJ, Charlet K, & Witkiewitz K. Can Reduced Drinking be a Viable Goal for Alcohol Dependent Patients? World Psychiatry. 2017 Oct; 16(3):325-326. PubMed PMID: 28941117; PubMed Central PMCID: PMC5608854.
- Mann K, Aubin HJ, & Witkiewitz K. Reduced Drinking in Alcohol Dependence Treatment, What is the Evidence? European Addiction Research. 2017 Sep 22;23(5):219-230. PubMed PMID: 28934736.
- Litten RZ, Falk DE, O'Malley SS, Witkiewitz K, Mann KF, Anton RF. Letter to Editor in Response to Johnson's Commentary (2017) on the Witkiewitz et al. (2017) Article. Alcoholism: Clinical and Experimental Research. 2017 May 4. PubMed PMID: 28471501.
- Witkiewitz K, Wilson AD, Pearson MR, Hallgren KA, Falk DE, Litten RZ, Kranzler HR, Mann KR, Hasin DS, O'Malley SS, & Anton RF. Temporal Stability of Heavy Drinking Days and Drinking Reductions Among Heavy Drinkers in the COMBINE Study. Alcoholism: Clinical and Experimental Research. 2017 May;41(5):1054-1062. PubMed PMID: 28295414; PubMed Central PMCID: PMC5404970.
- Hasin DS, Wall M, Witkiewitz K, Kranzler HR, Falk D, Litten RZ, Mann K, O'Malley SS, Scodes J, Robinson RL, Anton RF. Change in Non-Abstinent World Health Organization Risk Drinking Levels and Alcohol Dependence: A 3-Year Follow-Up Study in the United States General Population. Lancet Psychiatry. 2017 Jun; 4(6):469-476. PubMed PMID: 28456501.
- Witkiewitz K, Hallgren KA, Kranzler HR, Mann KR, Hasin DS, Falk DE, Litten RZ, O'Malley SS, & Anton RF. Clinical Validation of Reduced Alcohol Consumption after Treatment for Alcohol Dependence using the World Health Organization Risk Drinking Levels. Alcoholism: Clinical and Experimental Research. 2017 Jan;41(1):179-186. PubMed PMID: 28019652; PubMed Central PMCID: PMC5205540.
- Witkiewitz, K, Falk, DE, Kranzler HR, Litten RZ, Hallgren KA, O'Malley SS, & Anton RF. Missing Data in Alcohol Clinical Trials with Binary Outcomes. Alcoholism: Clinical and Experimental Research. 2016 Jul;40(7):1548-57. PubMed PMID: 27254113.
- Witkiewitz K, Falk DE, Kranzler HR, Litten RZ, Hallgren KA, O'Malley SS, & Anton RF. Methods to analyze treatment effects in the presence of missing data for a continuous heavy drinking outcome

measure when participants drop out from treatment in alcohol clinical trials. Alcoholism: Clinical and Experimental Research. 2014 Nov;38(11):2826-34. PubMed PMID: 25421518; PubMed Central PMCID: PMC4244651.

- Stout RL, Braciszewski JM, Subbaraman MS, Kranzler HR, O'Malley SS, Falk D and ACTIVE group. What happens when people discontinue taking medications? Lessons from COMBINE. Addiction. 2014 Dec; 109(12):2044-52. PubMed PMID: 25098969 PubMed Central PMCID: PMC4254710.
- Falk DE, Litten RZ, Anton RF, Kranzler HR, Johnson BA, Active Workgroup. Cumulative proportion of responders analysis (CPRA) as a tool to assess treatment outcome in alcohol clinical trials. J Stud Alcohol Drugs. 2014 Mar;75(2):335-46. PubMed PMID: 24650828; PubMed Central PMCID: PMC3965687.
- Greenfield TK, Ye Y, Bond J, Kerr WC, Nayak MB, Kaskutas LA, Anton RF, Litten RZ, Kranzler HR. Risks of alcohol use disorders related to drinking patterns in the US general population. J Stud Alcohol Drugs. 2014 Mar;75(2):319-27. PubMed PMID: 24650826; PubMed Central PMCID: PMC3965685.
- Anton RF, Litten RZ, Falk DE, Palumbo JM, Bartus RT, Robinson RL, Kranzler HR, Kosten TR, Meyer RE, O'Brien CP, Mann K, Meulien D. The Alcohol Clinical Trials Initiative (ACTIVE): purpose and goals for assessing important and salient issues for medications development in alcohol use disorders. Neuropsychopharmacology. 2012 Jan;37(2):402-11. PubMed PMID: 21900883; PubMed Central PMCID: PMC3242301.

ACTIVE Posters:

- Knox J. (2019, June). WHO Findings from the NESARC. Poster presented at the College on Problems of Drug Dependence 81st Annual Scientific Meeting, San Antonio, Texas.
- O'Malley SS. (2018, June). Response to Pharmacotherapy: A Comparison of Endpoints Based on Abstinence, No Heavy Drinking and Reductions in WHO Drinking Levels in Three Trials. Poster presented at the Research Society on Alcoholism Scientific Meeting, San Diego, CA.
- Hasin D. (2018, June). WHO-Defined Risk Drinking Levels and Drinking Consequences: Prospective Findings From the NESARC Waves 1 & 2 (2001-2005). Poster presented at the Research Society on Alcoholism Scientific Meeting, San Diego, CA.
- Falk DE. (2017, December). Novel Efficacy Endpoints Based on Shifts in the World Health Organization (WHO) Risk Levels of Drinking: Treatment Effects in Alcohol Pharmacotherapy Trials. Poster presented at the American College of Neuropsychopharmacology 56th Annual Meeting, Palm Springs, CA.

ACTIVE Data Presentations:

- O'Malley S. (2021, June). WHO Risk Drinking Reduction A New Endpoint for Clinical Trials. Symposium presented at the Research Society on Alcoholism Scientific Meeting, Virtual.
- Anton, R. (2021, June). WHO Risk Drinking Level: A Harm Reduction Outcome For Clinical Trials For Alcohol Use Disorder. Symposium presented at the Research Society on Alcoholism Scientific Meeting, Virtual.
- Knox J. (presenter), Scodes J., Witkiewitz K., Kranzler H., Mann K., O'Malley S., Wall M., Anton R., Hasin D. (2021, June). Reduction in WHO Risk Drinking Levels and Cardiovascular Disease: 3-year Follow-up Results in the US General Population. Symposium presented at the Research Society on Alcoholism Scientific Meeting, Virtual.
- Schacht J., Anton R. (2019, June). Prediction Of Alcohol Harm Reduction (Who RDL) Outcomes From Cue-Elicited Brain Activation In A Randomized Trial Of Naltrexone. Symposium presented at the Research Society on Alcoholism Scientific Meeting, Minneapolis, Minnesota.
- Witkiewitz K. (2019, June). Beyond Abstinence: Reductions in Drinking as an Endpoint for Alcohol Clinical Trials. Symposium presented at the College on Problems of Drug Dependence 81st Annual Scientific Meeting, San Antonio, Texas.

- Hasin D. (2019, June). Validation of a Measure of Opioid Use Disorder Among Chronic Pain Patients Treated With Opioids. Workshop presented at the College on Problems of Drug Dependence 81st Annual Scientific Meeting, San Antonio, Texas.
- Anton RF. (2018, December) Harm Reduction as a Goal in AUD Pharmacotherapy– Role For the WHO Risk Drinking Category Change. Symposium presented at the AAAP Annual Meeting and Scientific Symposium, Bonita Springs, FL.
- O'Malley SS. (2018, June) 2018 RSA Distinguished Researcher Awardee: Beyond Abstinence: An Evolving Perspective on Naltrexone and Pharmacotherapy for Alcohol Use Disorder. Plenary presented at the Research Society on Alcoholism Scientific Meeting, San Diego, CA.
- Anton RF. (2018, June) Insights From The Design and Implementation of Medications Development Trials for Alcohol Use Disorder. Panel presented at the Research Society on Alcoholism Scientific Meeting, San Diego, CA.
- O'Malley SS. (2018, May) ACTIVE Update: Reduction in World Health Organization (WHO) Drinking Risks Level as a Primary Endpoint for Alcohol Treatment Trials. Panel presented at the ASCP Annual Meeting, Miami Beach, Florida.
- Witkiewitz K. (2017, August). Reduction in World Health Organization (WHO) Drinking Risk Level as an Endpoint for Alcohol Clinical Trials. Symposium presented at the APA Annual Meeting, Washington D.C.
- O'Malley SS. (2017, May). The Development and Selected Performance of Patient Reported Outcomes (PRO) in Psychopharmacotherapy Trials – is the Juice Worth the Squeeze? A Review of Initiatives by the FDA, NIH, and the Alcohol Clinical Trials Initiative (ACTIVE). Panel presented at the ASCP Annual Meeting, Miami Beach, Florida.

ACTIVE Press Coverage:

- O'Connor, A. (2021, July 12). Alcohol Abuse Is on the Rise, but Doctors Too Often Fail to Treat It. *The New York Times*, Retrieved from https://www.nytimes.com/2021/07/12/well/live/alcohol-abuse-drinking-treatment.html?referringSource=articleShare

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