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Ethical Considerations for Administering Alcohol or Alcohol Cues to Treatment-Seeking Alcoholics in a Research Setting: Can the Benefits to Society Outweigh the Risks to the Individual?:

A commentary in the context of the National Advisory Council on Alcohol Abuse and Alcoholism—Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation (2005)

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There has recently been a welcome surge of interest in the development of medications to augment psychosocial behavioral therapies to treat alcoholics. Preclinical studies are identifying candidate medications that may block reinstatement of alcohol-seeking behavior, a model of relapse in humans. The development of effective therapeutic agents can be speeded up by the establishment of research paradigms such as craving reduction, by which novel drugs can be initially evaluated with higher throughput and lower cost than a full clinical trial. If medications that facilitate abstinence are to be developed they may need to be tested in the target population—treatment-seeking alcoholics—rather than in heavy drinkers or non-treatment-seeking alcoholics. Thus to test whether a new medication is able to reduce or abolish craving for alcohol it may be necessary to administer alcohol or alcohol cues to treatment seeking, abstinent alcoholics in a research setting. The alcohol exposure could take the form of inhalation of alcohol fumes (George et al., 2008), tasting alcoholic beverages, drinking alcoholic beverages, or receiving alcohol intravenously either passively (alcohol-clamp method; Ramchandani and O'Connor, 2006) or actively (CASE method; Zimmermann et al., 2008). Some of the research designed to identify treatments may also involve the administration of drugs that may mimic the actions of alcohol, for example as shown in drug discrimination studies. Administration of these alcohol-like drugs may entail some of the same risks as administration of alcohol.

The purpose of this commentary, distilled from ideas put forth at a roundtable at the 2008 RSA Annual Meeting, is to discuss whether the administration of alcohol to treatment-seeking alcoholics is ever justified. Can it ever be ethical to induce craving or give alcohol to treatment

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seeking, abstinent alcoholics? Can the benefits to society outweigh the risks to the individual? Can these risks be reduced to acceptable levels? What safeguards are currently in place and what research is currently being done in this domain? Can this whole issue be avoided by conducting research on alcoholics who choose harm reduction (reduced alcohol consumption) rather than abstinence as a treatment goal? The issue of administering alcohol to treatment-seeking alcoholics has been raised periodically (Dolinsky and Babor, 1997; Modell et al., 1993) and indeed there are national guidelines. This commentary will examine the issues described above in the context of the National Advisory Guidelines. In this commentary "alcoholics" refers to all individuals with alcohol dependence (American Psychiatric Association, 1994).

THE NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND ALCOHOLISM—RECOMMENDED COUNCIL GUIDELINES ON ETHYL ALCOHOL ADMINISTRATION IN HUMAN EXPERIMENTATION (HTTP://WWW.NIAAA.NIH.GOV/RESOURCES/RESEARCHRESOURCES/JOB22.HTM)

The Guidelines, last revised in May 2005, are currently referred to by IRBs, research grant applicants, Initial Review Groups, and others in the alcohol research field. The National Advisory Guidelines state that: "Preferably, alcohol administration experiments should be conducted in individuals who are not seeking treatment."

BENEFITS AND RISKS FOR NON-TREATMENT-SEEKING ALCOHOLICS IN ABSTINENCE-BASED STUDIES

"A special circumstance involves the risk of eliciting a withdrawal reaction in actively drinking alcohol dependent individuals who enter a research protocol requiring a period of abstinence. With strong justification, short-term abstinence prior to alcohol administration may be instituted for the purposes of the study, with appropriate safeguards." As stated in these National Advisory Guidelines, studies in non-treatment-seeking alcoholics are not without risk and should be conducted with care. Nevertheless, although there are some ethical issues with giving alcohol to known alcoholics (Tucker and Vuchinich, 2000), there are potential benefits for non-treatment-seeking alcoholics who participate in such research studies. Indeed, the one reported alcohol administration study that also provided non-treatment-seeking alcoholics with brief intervention about their harmful drinking behavior found an increase in the percentage of days abstinent and a decrease in the number of drinks consumed on drinking days, at least in the 6 weeks following the study (Pratt and Davidson, 2005).

CAN THE RESULTS OF STUDIES IN NON-TREATMENT-SEEKING ALCOHOLICS BE EXTRAPOLATED TO TREATMENT-SEEKING ALCOHOLICS?

Logically, abstinence promoting medications should be designed for the targeted population —treatment-seeking alcoholics. Can it be assumed that a medication that proves efficacious in non-treatment-seeking alcoholics will also work in treatment-seeking alcoholics, or that a medication that is not efficacious in non-treatment-seeking alcoholics will not work in treatment-seeking alcoholics? One line of evidence suggests that these assumptions may not be valid.

Alcoholism is a heterogeneous disorder with almost equal loading of environmental and genetic risk factors. It has been shown that non-treatment-seeking alcoholics have a different clinical course than treatment-seeking alcoholics (Fein and Landman, 2005). Moreover, a recent analysis of data from nearly 1500 individuals with alcohol dependence (68% men, 71% Caucasian) derived from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) identified 5 distinct subtypes of alcoholics in the general U.S. population (Moss et al., 2007). Two of these subtypes are relevant to this discussion. Alcoholics of the "chronic, severe subtype," 9.2% of the total sample, have the same characteristics as most alcoholics within treatment facilities: severe symptoms, positive family history, multiple comorbidities, and a high rate of relapse. In contrast, alcoholics classified as the "functional subtype," 19% of the total sample, have no family history or comorbidity, few seek treatment and those that do have good recovery rates. For several reasons, the functional subtype of alcoholics may be more likely to be recruited into research studies within the broad grouping of "heavy drinkers, non-treatment-seeking alcoholics" than the chronic, severe subtype. For example: as they are "functioning" members of society they may be more likely to respond to advertisements and to complete the study; they are more likely to fit the profile of "healthy" drinkers that may be an inclusion criterion and finally they are twice as abundant. In terms of pragmatic treatment options, abstinence may be more relevant for the severe subtype and harm reduction for the functional subtype. The different characteristics and clinical courses of the 2 groups of alcoholics suggest that while they are not necessarily at opposite ends of the spectrum of alcohol consumption severity they may well differ in etiology including genetic risk, which theoretically could manifest itself in differential responses to medications. One hypothetical scenario involves the gene encoding the mu-opioid receptor (*OPRM1*), in which there is a functional polymorphism (Asn40Asp). The *OPRM1* Asp40 allele has been associated with increased levels of subjective intoxication and alcohol-induced sedation that may protect against alcoholism severity (Ray and Hutchison, 2004). Therefore it could be hypothesized that this variant might be more abundant in the "functional" subtype than in the "chronic, severe subtype" of alcohol dependence. Moreover, the Asp40 allele has been associated with better treatment response to naltrexone, including lower relapse rates (Anton et al., 2008; Gelernter et al., 2007; Oslin et al., 2003). Therefore testing the efficacy of naltrexone in non-treatment-seeking "functional subtype" alcoholics may give different results from testing the efficacy in treatment-seeking alcoholics if the *OPRM1* Asp40 allele frequency difference is true. Regardless of whether *OPRM1* has specific value as a predictor of these subtypes of alcoholism, it is highly likely that other pharmacogenetic variants will be identified that may differ in frequency between treatment-seeking and non-treatment-seeking alcoholics, thereby influencing medication efficacy.

Furthermore, non-treatment-seeking alcoholics may not have the same motivation to remain abstinent. Utilizing craving reduction as a research paradigm to test abstinence-promoting medications may therefore not be as effective in non-treatment-seeking alcoholics because of the fact that physiological and cognitive responses to alcohol or alcohol cues may differ between temporarily abstinent, non-treatment-seeking alcoholics and alcoholics who intend to be permanently abstinent. Individuals in the former group know that they can return to drinking at the end of the study; the latter group is making a real effort to remain sober. Thus by studying non-treatment-seeking alcoholics an additional confounding factor may have been added to the complex mix of factors that determine outcomes in clinical trials of pharmacotherapies for alcoholism.

SHOULD ABSTINENCE-BASED ALCOHOL ADMINISTRATION STUDIES RECRUIT ALCOHOLICS SEEKING HARM REDUCTION TREATMENTS?

There is debate in the research community over whether the only acceptable treatment goal is abstinence or whether the more pragmatic goal of controlled, reduced drinking should be

pursued, the main objective being to mitigate the potential dangers and health risks associated with heavy drinking (Brown et al., 2005; Marlatt and Witkiewitz, 2002). Harm reduction may be a realistic treatment strategy for some individuals who just meet the minimum criteria for alcohol dependence, but most would agree that permanent abstinence is the only solution for individuals with severe dependence. Key concerns in a research setting would be how to identify a priori those individuals who would be unable to reduce drinking to safe levels over the long term and exclude them from participation. Moreover, although alcohol administration to alcoholics seeking harm reduction treatment may appear to have fewer ethical problems, conflicts may emerge. For example, alcohol administration may reinforce the harm reduction goal for the patient even when it would be in their best interest to aim for abstinence. Finally, just as with non-treatment-seeking alcoholics, harm reduction seeking alcoholics may have different clinical characteristics and a different disease course and may differ in motivational, cognitive, and physiological responses to research study tests compared with abstinence-seeking alcoholics.

ADMINISTERING ALCOHOL TO ABSTINENT, TREATMENT-SEEKING ALCOHOLICS: WHAT ARE THE RISKS TO THE INDIVIDUAL OF A RESEARCH INTERVENTION DURING THE RECOVERY PROCESS?

The National Advisory Guidelines state that: “subjects who have achieved a sustained period of abstinence while living in the community should not be included as subjects in research involving alcohol administration.” Although “sustained period” is not defined, it is implicit that individuals who have adjusted to a life of abstinence should never be included in alcohol administration studies. However, the Guidelines make it clear that: “in some circumstances alcohol exposure or alcohol cue exposure research may be appropriate in individuals who are seeking or receiving abstinence-oriented treatment. A strong scientific justification…and a strongly favorable risk/benefit assessment are both necessary.” Moreover, “Researchers shall refrain from doing harm and, wherever possible, they should promote the well-being of the research subjects and other individuals with a similar disease, or society as a whole.” Clearly, the research under discussion poses potentially serious risks for treatment-seeking alcoholics who have finally come to the stage where they are ready to accept help to become and remain abstinent. By participating in research studies that involve administration of alcohol or alcohol cues, the period of the subject’s desired abstinence, however brief, is ended. In a recovery environment, even the deliberate inhalation of alcohol fumes for more than a brief moment is considered by some to be an end of abstinence. The key indoctrination message (never take that first abstinence-ending drink) is eroded. It could be argued that by being asked to participate in an alcohol-administration study, the recovering alcoholic is being given an undermining message that it is alright to drink under certain circumstances. Nevertheless, the long-term effects of brief research interventions on the recovery process are not known. In an earlier documented study, Kranzler and colleagues (1990) gave ethanol to abstinent, inpatient alcoholics to judge compliance with disulfiram. The 36 alcoholics were followed for 6 months and appeared to suffer no immediate adverse effects, and persistence with disulfiram treatment, which was considered a limited proxy for treatment outcome, did not appear to be affected as a consequence of ethanol exposure. Without the availability of more data an objective risk assessment cannot be made for the effects of brief alcohol exposure early in recovery on long-term abstinence.

CAN NEWLY ABSTINENT ALCOHOLICS TRULY GIVE INFORMED CONSENT?

According to the National Advisory Guidelines: “It is important to avoid using subjects merely because of their easy availability, low social or economic status or limited capacity to understand the nature of the research. Respect for the person requires meaningful, informed

and voluntary consent." Treatment-seeking alcoholics are easily available in treatment facilities and are a vulnerable group: they may have been overwhelmed enough by their disease to get beyond denial and may feel desperate. Within the United States, many alcoholics do not have health insurance and participation in a research program may be their only means to obtain treatment. Are newly abstinent alcoholics ever able to provide objective informed consent to participate in research involving alcohol consumption? A basic principle of human dignity is respect for individual autonomy, which includes the right to choose. The addictive relationship to the substance itself, feelings of indebtedness to the medical personnel responsible for the detoxification and maintenance of abstinence and perhaps the need for free treatment may be synergistic obstacles to objective, informed, voluntary consent. It has even been suggested that one component of the informed consent process should be to ask the potential participant's loved ones (who have watched them suffer from and struggle with this disease) whether they should break their abstinence for a research study.

CAN THE BENEFITS TO SOCIETY OUTWEIGH THE RISKS TO THE INDIVIDUAL?

Studies derived from treatment centers show that 40 to 60% of treatment-seeking alcoholics remain abstinent for the first few months post-treatment and only 20 to 30% are still abstinent at the end of 1 year; moreover, a history of prior relapse and severity of dependence are associated with relapse (Dawson et al., 2007). Clearly, new, more efficacious, abstinence promoting, long-term medications are needed to complement psychosocial treatments. Current medications approved for the treatment of alcohol dependence are limited to disulfiram, naltrexone and acamprosate which are only modestly efficacious. A meta-analysis of 29 U.S. studies involving naltrexone that included nearly 6000 alcohol dependent patients found that 70% of 27 trials that measured reduction in heavy drinking demonstrated an advantage for prescribing naltrexone over placebo in contrast to only 36% of 25 clinical trials measuring abstinence (Pettinati et al., 2006). Among alcoholics who chose to be abstinent at the initiation of the study, a long-acting formulation of naltrexone maintained abstinence for 6 months in 32% of alcoholics compared with 11% who received placebo (O'Malley et al., 2007). In Europe, many centers routinely offer a trial of acamprosate to newly detoxified patients aiming for abstinence. Results from the 3 major European studies showed that the rate of complete abstinence in the acamprosate group was 3 times that of the placebo group at 3 months and 1.8 times that of placebo treatment at 1 year (Kranzler and Gage, 2008). Although these results are somewhat promising, they highlight the urgent need for the development of more effective pharmacological interventions to treat alcoholism that might be facilitated by alcohol administration studies in treatment-seeking alcoholics. It could be argued that as rates of long-term abstinence are low, the risk to the participating alcoholic may not be much higher than the background risk. The counter argument is that it is even more important not to jeopardize each individual participant's chances of long-term abstinence. Clearly there is an urgent need for studies to settle this issue by investigating the long-term effects of brief research interventions on the risk of relapse.

WHAT CAN BE DONE TO MINIMIZE THE RISKS? CLINICAL SAFEGUARDS

The National Advisory Guidelines state that: "For individuals in abstinence orientated treatment, the research staff and the treatment personnel, with the subject's permission, should consider the potential for untoward effects on the treatment process. Treatment should be continued after conclusion of research participation for a sufficient period to ensure continued recovery." Clinical safeguards can be instituted to minimize the risk that research-dictated interruption in a recovery program could reduce prospects for long-term maintenance of abstinence. These safeguards include: conducting the study in a research setting within a safe environment such as a hospital; establishing a therapeutic alliance with the participant;

separating research staff from treatment staff (although educating treatment staff about the research protocol and its value), thus limiting the possibility of coercion; providing the participant with a clear understanding of the study; performing a thorough assessment of craving and mood; having trained staff who are equipped to assist the participant with cravings and mood changes etc. that could potentially arise during the study; providing continued hospitalization and treatment after the alcohol challenge to ensure that the participant is back to his or her prechallenge state; encouraging the participant to apply study compensation toward the cost of a sober living arrangement following discharge from the hospital; providing outpatient aftercare to promote sobriety and considering re-hospitalization if the participant relapses. For further discussion of this topic see Dolinsky and Babor (1997).

SUMMARY AND CONCLUSIONS

The National Advisory Council on Alcohol Abuse and Alcoholism published guidelines in 2005 which attempted to find a delicate balance between the need to administer alcohol to research subjects and the potential to compromise important ethical principles. To date, research studies have mostly limited the use of alcohol challenges to non-treatment-seeking individuals. Although useful, this does not help to identify risk factors for relapse or suitable interventions for it. As only 20 to 30% of treatment-seeking alcoholics remain abstinent after 1 year new, effective medications are urgently needed to augment psychosocial treatments and the limited number of medications currently approved for this indication. The field is now at the crossroads of exploring the necessity to administer alcohol to treatment-seeking individuals. This need is generated by the results of recent studies indicating that treatment-seeking alcoholics have a different clinical course than non-treatment-seeking alcoholics. As discussed in this commentary, there are concerns that results obtained from non-treatment-seeking alcoholics can be falsely generalized to treatment-seeking alcoholics. On the other hand, with more accurate subtyping of the heterogeneous group of individuals with alcohol dependence (for example, Moss et al., 2007) it may be possible to select a sample of non-treatment-seeking alcoholics with characteristics that overlap with the treatment-seeking group. At the present time, we lack adequate information on this distinction to guide research and clinical practices. Few data exist on which to base a determination as to whether the individual risk of giving alcohol to newly abstinent alcoholics can be sufficiently minimized to justify the benefits to society of developing novel and effective medications that promote abstinence. As has been noted previously (Brandon and Lisman, 2000), very little empirical research is currently available to support ethical concerns, and ethical arguments have largely been based on philosophical notions and belief systems. There is an urgent need for new research studies to resolve the ethical issues associated with administering alcohol to treatment-seeking alcoholics in a research setting.

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References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. 4. American Psychiatric Association; Washington, DC: 1994.

Anton RF, Oroszi G, O’Malley S, Couper D, Swift R, Pettinati H, Goldman D. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence:

results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry 2008;65:135–144. [PubMed: 18250251]

Brandon TH, Lisman SA. Introduction to the special section on empirical underpinnings of the ethics of alcohol administration in research settings. Psychol Addict Behav 2000;14:315–318. [PubMed: 11130150]

Brown CG, Stewart SH, Larsen SE. Experiences of harm reduction among women with alcohol use problems. Can J Commun Ment Health 2005;24:95–113. [PubMed: 16568624]

Dawson DA, Goldstein RB, Grant BF. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: a 3-year follow-up. Alcohol Clin Exp Res 2007;31:2036–2045. [PubMed: 18034696]

Dolinsky ZS, Babor TF. Ethical, scientific and clinical issues in ethanol administration research involving alcoholics as human subjects. Addiction 1997;92:1087–1097. [PubMed: 9374005]

Fein G, Landman B. Treated and treatment-naive alcoholics come from different populations. Alcohol 2005;36:19–26. [PubMed: 16440475]

Gelernter G, Gueorguieva R, Kranzler HR, Zhang H, Cramer J, Rosenheck R, Krystal JH. VA Cooperative Study #425 Study Group. Opioid receptor gene (*OPRM1*, *OPRK1*, and *OPRD1*) variants and response to naltrexone treatment for alcohol dependence: results from the VA Cooperative Study. Alcohol Clin Exp Res 2007;31:555–563. [PubMed: 17374034]

George DT, Gilman J, Hersh J, Thorsell A, Herion D, Geyer C, Peng X, Kielbasa W, Rawlings R, Brandt JE, Gehlert DR, Tauscher JT, Hunt SP, Hommer D, Heilig M. Neurokinin 1 receptor antagonism as a possible therapy for alcoholism. Science 2008;319:1536–1539. [PubMed: 18276852]

Kranzler HR, Dolinsky Z, Kaplan RF. Giving ethanol to alcoholics in a research setting: its effect on compliance with disulfiram treatment. Br J Addict 1990;85:119–123. [PubMed: 2310844]

Kranzler HR, Gage A. Acamprosate efficacy in alcohol-dependent patients: summary of results from three pivotal trials. Am J Addict 2008;17:70–76. [PubMed: 18214726]

Marlatt GA, Witkiewitz K. Harm reduction approaches to alcohol use: health promotion, prevention, and treatment. Addict Behav 2002;27:867–886. [PubMed: 12369473]

Modell JG, Glaser FB, Mountz JM. The ethics and safety of alcohol administration in the experimental setting to individuals who have chronic, severe alcohol problems. Alcohol Alcohol 1993;28:189–197. [PubMed: 8517890]

Moss HB, Chen CM, Yi HY. Subtypes of alcohol dependence in a nationally representative sample. Drug Alcohol Depend 2007;91:149–158. [PubMed: 17597309]

National Advisory Council on Alcohol Abuse and Alcoholism—Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation. 2005. Available on the National Institute on Alcohol Abuse and Alcoholism website (http://www.niaaa.nih.gov/) under ‘About NIAAA—Advisory Council—Research Guidelines and Resources’: http://www.niaaa.nih.gov/Resources/ResearchResources/job22.htm

O’Malley SS, Garbutt JC, Gastfriend DR, Dong Q, Kranzler HR. Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent before treatment. J Clin Psychopharmacol 2007;27:507–512. [PubMed: 17873686]

Oslin DW, Berrettini W, Kranzler HR, Pettinati H, Gelernter J, Volpicelli JR, O’Brien CP. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology 2003;28:1546–1552. [PubMed: 12813472]

Pettinati HM, O’Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM, Dackis CA. The status of naltrexone in the treatment of alcohol dependence: specific effects on heavy drinking. J Clin Psychopharmacol 2006;26:610–625. [PubMed: 17110818]

Pratt WM, Davidson D. Does participation in an alcohol administration study increase risk for excessive drinking? Alcohol 2005;37:135–141. [PubMed: 16713501]

Ramchandani VA, O’Connor S. Studying alcohol elimination using the alcohol clamp method. Alcohol Res Health 2006;29:286–290. [PubMed: 17718408]

Ray LA, Hutchison KE. A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans. Alcohol Clin Exp Res 2004;28:1789–1795. [PubMed: 15608594]

Tucker JA, Vuchinich RE. Creating a research context for reducing risk and obtaining informed consent in human alcohol studies. Psychol Addict Behav 2000;14:319–327. [PubMed: 11155893]

Zimmermann US, Mick I, Vitvitskyi V, Plawecki MH, Mann KF, O'Connor S. Development and pilot validation of computer-assisted self-infusion of ethanol (CASE): a new method to study alcohol self-administration in humans. Alcohol Clin Exp Res 2008;32:1321–1328. [PubMed: 18540908]