

Alcoholism: The Science Made Easy

This publication includes a compilation of alcohol-related *Addiction Science Made Easy* articles from the ATTC National Office. Original source documents from *Alcoholism: Clinical and Experimental Research*, the official journal of the Research Society on Alcoholism.



The Addiction Technology Transfer Center Network
Funded by Substance Abuse and Mental Health Services Administration

ATTC National Office • Kansas City, Missouri

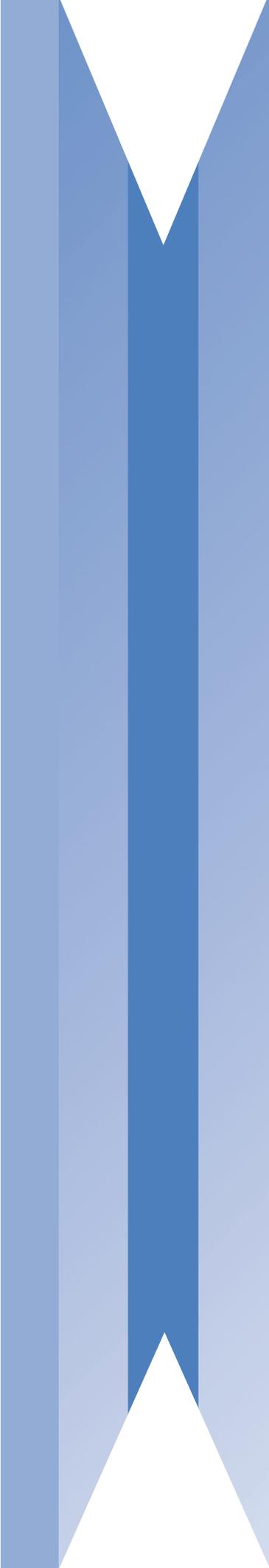
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At the time of printing, Charles G. Curie, MA, ACSW, served as the SAMHSA Administrator. H. Westley Clark, MD, JD, MPH, served as the CSAT Director, and Karl D. White, EdD, served as the CSAT Project Officer.

The opinions expressed herein are the views of the ATTC Network and do not reflect the official position of the Department of Health and Human Services (DHHS), SAMHSA or CSAT. No official support or endorsement of DHHS, SAMHSA or CSAT for the opinions described in this document is intended or should be inferred.





*I*ntroduction

HOW TO USE THIS PUBLICATION

This publication was created so the ongoing series of research based articles called *Addiction Science Made Easy (ASME)*, could be easily distributed and used for educational purposes. Although these articles are available on the Internet, our vision was to create another way for educators and practitioners to access them. Whether educating students in a formal setting, delivering continuing education courses, or discussing findings with colleagues, it is our hope that you will use this book to inform others.

There are approximately 100 articles included in this document, and we have broken them into 10 major categories. Many articles could “fall” under several different category headings. For example, the article entitled *Promising New Treatment Options for People With Co-Existing Alcohol Use and Psychiatric Disorders* could have been placed in the Prevention, Intervention and Treatment category or in the Mental Health category. For this reason, we have included a number of ways for you to locate articles. The table of contents located on the next page includes page numbers for each of the primary categories. Then you’ll find a listing of all the article titles with their corresponding page numbers and category headers. At the back is a key word index to help you locate specific topics of interest.

Please use these articles as you wish. Each page is perforated and three-hole punched for easy copying and storage. Please use these articles as the basis for presentations and handouts in trainings and classrooms. Tear out the pages, make copies, post them in your break room, pass them out to students, etc. We do ask that you site the original source whenever possible.

ARTICLES ONLINE AT
WWW.NATTC.ORG/ASME

- **More than 200 ASME articles**
- **Searchable by key word**
- **Research based, easy-to-understand**

TABLE OF CONTENTS

Listing of All Articles	6
Preface	10
Acknowledgments	12
Adolescents	17
Biology – Neurobiology	35
Gender, Ethnicity & Culture	63
Genetics & Other Risk Factors	79
Mental Health	109
Pharmacology	127
Physical Health	143
Pregnancy, Prenatal Exposure & Parenting	165
Prevention, Intervention & Treatment	189
Violence & Injury	211
Key Word Index	227

LISTING OF ALL ARTICLES

Articles in the *Adolescents* Category

1. Binge Drinking Among Jewish and Non-Jewish College Students 19
2. Binge Drinking: A Dangerous Rite of Passage 21
3. College Students May Be Drinking More Alcohol Than Even They Realize 23
4. Adolescents With Alcohol Problems: Redefining the Basics 25
5. Impulsiveness, Aggression, Alcohol and Adolescents 27
6. Alcohol, Automobiles and Youth 29
7. Teenagers, Drinking and Driving: A Quick Trip to the Grave 31
8. Tracking the Long-Term Functioning of Adolescents with Alcohol Problems 33

Articles in the *Biology – Neurobiology* Category

1. Alcohol-Damaged Brains “Recruit” New Brain Regions to Perform Simple Tasks 37
2. How Alcohol Gives and Then Takes Away 39
3. How Sensitive Is Your Brain to Alcohol-Induced Damage? 41
4. The Brain Risks of Binge Drinking 43
5. Abstinence May Make the Brain Grow Stronger 45
6. Cognitive Neuroscience Takes on Alcohol 47
7. Just a Spoonful of Thiamin? 49
8. Alcohol and Thiamin Deficiency Together: A Dangerous Combination? 51
9. Chronic Drinking Increases Cortisol During Intoxication and Withdrawal 53
10. Repeated Alcohol Detoxifications Can Impair Cognitive Function 55
11. Blocking Selected Neurotransmitter Activity May Decrease Alcohol Consumption 57
12. Probing the Role of the Delta Opioid Receptor in Alcohol Consumption 59
13. Behavioral Sensitization: A New Perspective on Alcoholism 61

Articles in the *Gender, Ethnicity & Culture* Category

1. Women Who Drink May Be at Greater Risk of Cardiovascular Complications Than Men 65
2. Specifying Alcohol-Related Brain Damage in Young Women 67
3. African American Alcoholics: At Greater Risk for Immune Disorders? 69
4. Liver Cirrhosis Is No Longer a “Black” Disease 71
5. Ethnic Difference in DUI Arrests and Use of Health Care Services in California 73
6. Re-Examining Alcohol Problems Among American Indian Communities 75
7. The Genetic Complexities of Sensation Seeking Behavior in Alcoholic Men 77

Articles in the *Genetics & Other Risk Factors* Category

1.	A Neurogenetic Approach to Alcoholism	81
2.	Untangling the Matrix of Risk Factors for Alcoholism	83
3.	Using Brain Activity to Identify Risk for Disorders	85
4.	Searching for Biochemical Markers in Children of Alcoholics	87
5.	The Eyes Have It: Seeking Expressions of the Genetic Risk for Developing Alcoholism	89
6.	On the Cutting Edge of Brain Gene Analysis	91
7.	Genetic Contributions to Alcohol Sensitivity	93
8.	Investigating a “Protective Gene” Against Alcoholism	95
9.	Bridging the Gap Between Genetics and Motivations to Drink Alcohol	97
10.	When Alcohol and Nicotine Interact	99
11.	Exploring the Genetic Commonality of Alcohol and Tobacco Abuse	101
12.	Abnormalities in Stress Hormone Response Among Alcoholics	103
13.	Taste Testing May Help Identify Alcoholism Risk	105
14.	A Sweet Tooth May Be a “Marker” for the Genetic Risk for Developing Alcoholism	107

Articles in the *Mental Health* Category

1.	Alcoholics Have Blunted Responses to Psychological Stressors Such as Public Speaking	111
2.	Alcoholics With Antisocial Personality Disorder Have Blunted Emotional Reactivity	113
3.	Childhood Abuse May Predict Social Phobia, Agoraphobia and Post Traumatic Stress Disorder Among Adult Alcoholics	115
4.	Searching for Anxiety Relief in Alcohol Can Be Dangerous	117
5.	Suicidal Behavior Among Alcoholics	119
6.	Adult Alcoholism and Attention Deficit Hyperactivity Disorder Are Connected	121
7.	Alcohol Impairs Executive Cognitive Functioning Much Longer Than Expected	123
8.	Alcohol Damages Day-to-Day Memory Function	125

Articles in the *Pharmacology Category*

1. Searching for New Detoxification Strategies	129
2. Fine-Tuning Naltrexone Treatment for Alcoholics	131
3. Searching for New Medications to Treat Alcoholism	133
4. Using Naltrexone to Treat Alcoholics With a “Mediterranean Drinking Pattern”	135
5. Behavioral Therapies Plus Pharmacotherapies Can Add Up to Success	137
6. An Anti-Nicotine Drug Reduces the Rewarding Effects of Alcohol	139
7. Promising New Treatment Options for People with Co-Existing Alcohol Use and Psychiatric Disorders	141

Articles in the *Physical Health Category*

1. Alcohol Abuse May Increase Susceptibility to HIV Infection	145
2. Alcohol and Cancer	147
3. Can Heavy Alcohol Use Lead to Some Kinds of Cancer?	149
4. Alcohol May Hasten the Progression of Cancer	151
5. Is There a Link Between Alcohol and Allergies?	153
6. How to Build Strong Bones: Get Milk, Lose the Booze	155
7. Alcohol, Sodium Sensitivity and Blood Pressure	157
8. Alcohol’s Effects on Testosterone	159
9. Moderate Alcohol Consumption After Meals Can Decrease Levels of Insulin	161
10. Chronic Alcohol Abuse Damages Regulating Hormones	163

Articles in the *Pregnancy, Prenatal Exposure & Parenting Category*

1. Alcohol Consumption During Pregnancy Alters Thyroid Function	167
2. Alcohol, Women and Pregnancy	169
3. Pregnancy, Drugs and Alcohol, Emotional Instability: What Nightmares Are Made Of	171
4. Exploring the Complexities of Prenatal Alcohol Exposure	173
5. Drinking During Pregnancy: Information May Not Be Enough	175
6. Drinking During Pregnancy: American Indians and African Americans	177
7. Genetic Protection Against Fetal Alcohol Syndrome?	179
8. Light to Moderate Drinking During Pregnancy Can Effect Adolescent Growth	181
9. Light to Moderate Drinking During Pregnancy May Lead to Learning and Memory Deficits in Adolescents	183
10. The Power of the Mother-Child Bond	185
11. Parenting, Stress and Your Child’s Risk for Alcoholism	187

Articles in the *Prevention, Intervention & Treatment* Category

1. Alcohol and Drug Treatment Among HMO Patients 191
2. Examining the Effects of Managed Care on Alcohol and Other Drug Treatment... 193
3. Doctor, Counselor, Cost-Cutter 195
4. Finding Sobriety and Saving Money Through Spirituality 197
5. Comparing Screening Instruments for Alcohol Dependence and Abuse 199
6. Brief Mail- and Computer-Generated Interventions Work Best for Problem
Drinking Among Young People 201
7. Educational Attainment May Predict Drinking Outcomes Following
Alcohol Treatment 203
8. Alcohol and Smoking: Why They Go Together 205
9. Nicotine Patch Treatment Works for Smokers with Long-Term Sobriety 207
10. Alcohol, Friends and Courtship 209

Articles in the *Violence & Injury* Category

1. Alcohol, Drugs and Violence Between Intimate Partners 213
2. Alcohol, Interpersonal Violence and Mexican American Women 215
3. Alcohol Consumption and Intimate Partner Violence 217
4. Marriage, Alcohol and Violence 219
5. Alcohol's Double Threat: A Greater Chance of Crashing and More
Severe Injuries 221
6. Alcoholics May Be More Injury Prone Than Illicit Drug Users 223
7. Drinking and Drugging Can Be Painful 225

***K* KEY WORD INDEX BEGINS
ON PAGE 227.**

PREFACE

Many professionals in direct treatment settings do not have the resources or time to read research journals; nor do their agencies have the money to subscribe to these publications. In addition, research is typically written in a technical manner which is difficult to use in every day prevention and treatment practice. In an effort to bring current research findings to direct service providers, individuals at three organizations came together in an unprecedented manner. In 1999, staff from the Addiction Technology Transfer Center (ATTC) National Office, the Research Society on Alcoholism (RSA) and the journal, *Alcoholism: Clinical and Experimental Research (ACER)*, decided to partner in an effort to translate and disseminate current research on alcoholism. Their goal was to provide frontline staff, educators and the public easy-to-read, concise research findings.

Through the synergy of these three organizations, the *Addiction Science Made Easy (ASME)* project was born. Since that time, more than 215 alcoholism research articles have been disseminated throughout the world. Each month a science writer reads and summarizes the main findings from *ACER* and “translates” them into easy-to-understand articles.

EurekaAlert!

The *ASME* articles are first distributed to journalists online through EurekaAlert! (www.eurekaalert.org), an online press service created by the American Association for the Advancement of Science. The primary goal of EurekaAlert! is to provide a forum where research institutions, universities, government agencies and corporations can distribute science-related news to the media. Once released, these articles are made available to the public.

More than half a million public visitors, and almost 20,000 registered journalists have viewed *ASME* articles via the EurekaAlert! Web site. Several articles can be directly linked to international news coverage by a variety of media groups including the New York Times, BBC, Reuters, CBC, International Herald Tribune, Yahoo News, CNN International, MSNBC and WebMD.

Distribution by the ATTC

ASME articles are available online at the ATTC Network Web site (www.nattc.org). From the home page, users can click on the *Addiction Science Made Easy* link. Once there, they can search a database of all *ASME* articles by keyword, or simply view the most current articles.

The ATTC also distributes *ASME* articles through its free electronic magazine *Eye on the Field*. This e-zine is published by the ATTC National Office each month, and is sent to more than 9,500 subscribers. Each issue features information relating to substance use disorders and includes four *ASME* articles, useful tools for practitioners, information about educational events, pertinent Web sites and timely news. Those interested can subscribe to *Eye on the Field* at www.nattc.org.

Similarly, the ATTC National Office highlights *ASME* articles in its bi-annual newsletter, *The ATTC Networker*. This free publication is mailed to approximately 5,000 subscribers. Each issue highlights an important theme relating to addiction treatment (such as co-occurring disorders), and then profiles trends, statistics, trainings, treatment methods and other publications relating to that theme. To subscribe, contact the ATTC National Office at 816-482-1200 or visit www.nattc.org.

Finally, the ATTC Network highlights *ASME* articles at trainings delivered across the country. The concise, easy-to-understand style of these articles is perfect for practitioners, educators and the public to receive at conferences and educational events.

ARTICLES ONLINE AT WWW.NATTC.ORG/ASME

- More than 200 *ASME* articles
- Searchable by key word
- Research based, easy-to-understand

ACKNOWLEDGMENTS

Since its inception, there have been many important contributors to the *ASME* project. It continues to be a truly collaborative undertaking. First and foremost, we want to thank the researchers for their tireless efforts – the steadfast scientists who spend their lives studying the effects of alcohol on the human body, mind and spirit. Their work is ground-breaking and ultimately contributes to saving lives.

Many individuals were instrumental in developing the innovative partnership that made the *ASME* project possible five years ago. Specifically, we are greatly indebted to Carlton Erickson, PhD, director of the Addiction Science Research and Education Center at the University of Texas and associate editor of *Alcoholism: Clinical and Experimental Research (ACER)*. Dr. Erickson, along with Ting-Kai Li, MD, director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the immediate past editor of *ACER*, approached ATTC National Office staff with their resourceful idea which resulted in the *ASME* project. Their ardor for making research accessible to frontline workers is evident, and their expertise and communication styles continue to build bridges between the research and treatment communities.

We also want to thank Victor Hesselbrock, PhD, president of RSA, the RSA board of directors, and countless others from RSA, who have been supportive of the *ASME* project since the beginning. RSA's monetary contribution continues to make these articles possible. Similarly, we greatly appreciate the new editor of *ACER*, Ivan Diamond, MD, PhD, who supports this partnership and continues to allow us to “translate” research from the journal. Additionally, without copyright permission from the journal's publisher Lippincott, Williams and Wilkins, none of this would be possible.

Next we commend our science writer, Sherry Wasilow-Mueller. Each month she reads, interprets and summarizes each *ASME* article for dissemination to the field. We applaud her ability to capture the essence of new research and to clearly translate technical content. Her enthusiasm for this work is evident in the excellence of her article summaries. We believe her concise writing style will help change the way practitioners view research.

It was the insightful vision of Mary Beth Johnson, MSW, director of the ATTC National Office, to create this book for educators and practitioners.

A thank you also goes to Jennifer Tate Giles, MSW, and to Angie Olson, MS, associates of the ATTC National Office, who organized, edited and designed this publication. In addition, Carla Ingram, CSACII, LCSW, associate director of the ATTC National Office, helped review and categorize the articles.

Finally, we are grateful to Iris Wilkinson, EdD, associate professor in the Human Services Department at Washburn University, and Amy Leary, LPC, counselor team leader at ReDiscover Mental Health Services, who both took the time to read and score each article for inclusion in this publication. Their insights helped us organize a final product that will be maximally useful to users.

Sherry Wasilow-Mueller – ASME Science Writer

As stated previously, we appreciate the invaluable work of the *ASME* science writer, Sherry Wasilow-Mueller. Each month, she takes four current *ACER* research articles selected by an *ACER* associate editor and creates feature stories. To develop the *ASME* features, she uses input from the corresponding authors and other scientists who comment on the value of the research being presented. Her articles highlight scientific findings from the *ACER* journal in an easy-to-read, concise manner. More than simple press releases, each feature provides a broad perspective beyond simple reporting.

In June 2001, Wasilow-Mueller was presented with the second annual RSA Journalism Award. Carlton Erickson, PhD, *ACER* Associate Editor and a national researcher on alcoholism, believes Wasilow-Mueller's work is impressive. "Sherry has done a superb job of bringing newsworthy research to the public's attention," he said. "Her work is characterized by its accuracy, understandability and a talent for condensing large amounts of information into scientifically accurate, interesting articles."

Wasilow-Mueller is married with three small boys, and hopes to eventually earn a doctorate.

THE *ASME* PARTNERS

This project was made possible through the vision and synergy of three organizations: the Addiction Technology Transfer Center (ATTC) National Office, the Research Society on Alcoholism (RSA) and its journal, *Alcoholism: Clinical and Experimental Research (ACER)*. Each organization contributes time and resources to make this project possible.

Addiction Technology Transfer Center (ATTC) National Office

University of Missouri – Kansas City
5100 Rockhill Road • Kansas City, Missouri 64110
816-482-1200 • www.nattc.org

The Addiction Technology Transfer Center (ATTC) Network is dedicated to identifying and advancing opportunities for improving addiction treatment. The Network's vision is to unify science, education and services to transform the lives of individuals and families affected by alcohol and other drug addiction. The Network is funded by the Substance Abuse and Mental Health Services Administration (SAMHSA) to upgrade the skills of existing treatment practitioners and other health professionals, and to disseminate the latest scientific findings to the treatment community.

Serving the 50 U.S. States, the District of Columbia, Puerto Rico, the U.S. Virgin Islands and the Pacific Islands, the ATTC Network operates as 14 individual Regional Centers and a National Office.

The ATTC National Office (National Office) supports the *ASME* partnership in a number of ways. The largest contribution is by contracting with a science writer to summarize the findings of four *ACER* journal articles each month. In addition, the National Office disseminates *ASME* articles in key ATTC publications, maintains an *ASME* area on the ATTC Network Web site, and developed, published and disseminated this *ASME* publication.

Research Society on Alcoholism (RSA)

7801 North Lamar Boulevard, Suite D-89
Austin, Texas 78752-1038
512-454-0022 • www.rsoa.org

The Research Society on Alcoholism (RSA) was established in 1975 to encourage scientists to use research to investigate solutions for alcohol-related problems. It is a fertile meeting ground for scientists and promotes research and the acquisition/dissemination of scientific knowledge.

RSA's current membership of more than 1,600 people is drawn from countries all over the world. Membership consists of regular scientific members, associate members and student members.

RSA provides support for the *ASME* partnership by contracting with the EurekaAlert! Web site which allows *ASME* articles to be accessed by journalists throughout the world. In addition, RSA contributed funds to publish this *ASME* book.

Alcoholism: Clinical and Experimental Research (ACER)

www.alcoholism-cer.com

Alcoholism: Clinical and Experimental Research (ACER) was founded by the National Council on Alcoholism and Drug Dependence (NCADD). In the 1980s, RSA assumed publication of the journal, and it became the Society's official journal. Each month, this publication brings health care professionals the latest clinical studies and research findings on alcoholism, alcohol-induced syndromes and organ damage.

Each month, *ACER* Associate Editor, Carlton Erickson, PhD, reviews embargoed articles from the journal and chooses four to be rewritten by the *ASME* science writer. Erickson oversees the work of the science writer, and then submits the four feature articles to the EurekaAlert! Web site for posting.

The following is an alphabetical list of everyone who has been instrumental to this ASME project:

Ivan Diamond, MD, PhD

Founding Director, Ernest Gallo Clinic and Research Center
School of Medicine, University of California, San Francisco
Editor in Chief, *Alcoholism: Clinical and Experimental Research (ACER)*

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College of Pharmacy, University of Texas at Austin
Associate Editor, *Alcoholism: Clinical and Experimental Research (ACER)*

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Contractor, Addiction Technology Transfer Center (ATTC) National Office
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Lippincott, Williams and Wilkins

Publisher
Baltimore, Maryland

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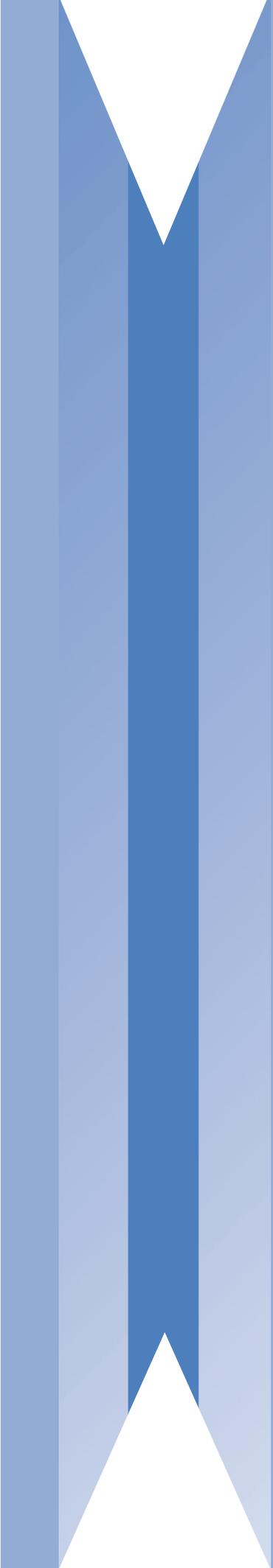
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*A*dolescents



ADOLESCENTS

Articles in the *Adolescents* Category

1. [Binge Drinking Among Jewish and Non-Jewish College Students](#)
2. [Binge Drinking: A Dangerous Rite of Passage](#)
3. [College Students May Be Drinking More Alcohol Than Even They Realize](#)
4. [Adolescents With Alcohol Problems: Redefining the Basics](#)
5. [Impulsiveness, Aggression, Alcohol and Adolescents](#)
6. [Alcohol, Automobiles and Youth](#)
7. [Teenagers, Drinking and Driving: A Quick Trip to the Grave](#)
8. [Tracking the Long-Term Functioning of Adolescents with Alcohol Problems](#)

BINGE DRINKING AMONG JEWISH AND NON-JEWISH COLLEGE STUDENTS

- *Americans who frequently attend religious services have lower rates of alcohol use and misuse.*
- *The same relationship has not been found among Jewish Americans.*
- *Heavy drinking and alcoholism are less common among Jews than Christians.*

In the United States, religious commitment, as measured by service attendance, has an inverse relationship with alcohol consumption and alcohol problems. In other words, individuals who frequently attend religious services tend to have lower rates of alcohol use and misuse. The same association has not, however, been consistently found among Jewish Americans. A study in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the relationship between religious variables and binge drinking among Jewish and non-Jewish college students. It also examines the association between binge drinking and genetic, cultural and religious variables in the Jewish sample alone.

“Binge drinking is a growing focus in the alcohol research literature, especially among college students,” said Susan E. Luczak, assistant project scientist in the department of psychiatry at the University of California, San Diego and first author of the study. “It has been related to many negative social, academic, and physical problems. Other measures of problems, such as abuse and dependence symptoms, are also important, but less prevalent in college samples.”

Luczak added that even though researchers have traditionally found a strong association between “religious service attendance” and fewer alcohol problems among Christians, heavy drinking and alcoholism are less common among Jews. “There is something about being Jewish that seems to protect people from heavy drinking and drinking problems,” she said. Perhaps this ‘protection’ is rooted in cultural differences, she noted, or perhaps ‘religious service attendance’ may have different meanings across religious groups.

Researchers examined two groups: 132 (68 female, 64 male) Jewish and 147 (72 female, 75 male) non-Jewish White college students. Participants reported their alcohol consumption for the previous 90 days and provided information about their religious affiliation and the number of religious services attended in the previous year. Study subjects also had blood drawn for genotyping at the alcohol dehydrogenase (ADH2) locus, one of several genes that encode the major enzymes involved in alcohol metabolism, and which has been associated with protection from alcoholism. Jewish study participants completed the Jewish Identity Scale, developed and published by researcher Itai Zak in *Psychological Reports* in 1973. The scale measures the degree to which being Jewish plays a part in one’s life, the importance of belonging to the Jewish community, and the closeness one feels to Jews in the world.

“This study has three key findings,” said Luczak. “First, religious service attendance is associated with lower rates of binge drinking in non-Jewish college students, but not in Jewish college students. This is consistent with previous research. Second, being religiously

continued ~

BINGE DRINKING AMONG JEWISH AND NON-JEWISH COLLEGE STUDENTS

Jewish, as compared with secularly Jewish, relates to lower rates of binge drinking, but Jewish cultural identification does not. Third, in the combined sample of Jewish and non-Jewish students, those who possessed the ADH2*2 genetic variation were approximately half as likely to binge drink as those who did not possess the variation.”

Luczak said, that for the Jewish sample alone, these findings suggest that religious, and not just cultural, Jewish affiliation is related to lower levels of alcohol consumption. Although this may seem to contradict earlier findings of a weak relationship between religious commitment and lower rates of alcohol use and misuse among Jews, Stephen Maisto, professor and director of clinical training in the department of psychology at Syracuse University, believes that the answer may lie in the design of a fundamental measure – defining religious commitment by service attendance.

“Perhaps it would have been more useful to define types of services attended and their meaning to the participants, rather than just a count of the number of services attended,” he said. The ‘religious affiliation’ variable, which summarizes a complex set of practices and beliefs regarding the Jewish religion, he noted, may have tapped into religious practices that affect overall life-styles, including alcohol consumption. “Future research definitely needs to conduct more studies that can address the mechanisms underlying drinking pattern differences according to religious affiliation,” he said. “The correlation between the two is established. The task now is to achieve a better empirical understanding of the association.”

Luczak said the study’s genetic findings are related to previous reports that found a relationship between ADH2*2 and less frequent drinking among Jews, and lower rates of alcohol dependence in Asians and non-Jewish whites. She said, “The current study examined binge drinking, which is more related to drinking problems, and is a different measure than alcohol dependence. Although these findings may not add to the literature on alcohol dependence, they do provide evidence that ADH2*2 also relates to a measure of heavy alcohol use in a combined sample of Jewish and non-Jewish whites.”

Luczak and her colleagues will continue to examine drinking behavior in Jewish and non-Jewish college students. “We are also examining the role of culture, religion and genetic variations in these and other ethnic groups including Koreans and Chinese,” she said.



Article is based on the following published research:

Luczak, S.E., Shea, S.H.,
Carr, L.G.,
T.-K. Li, Wall, T.L.
(December 2002).
Binge drinking in
Jewish and non-Jewish
White college students.
*Alcoholism: Clinical
and Experimental
Research*,
26(12), 1773-1778.



BINGE DRINKING: A DANGEROUS RITE OF PASSAGE

- *Adolescence is a time when many begin experimenting with alcohol.*
- *Some adolescents binge drink, that is, drink heavily during a short period of time.*
- *Adolescent brains may be particularly vulnerable to the neurotoxic effects of alcohol.*
- *Binge drinking during adolescence may have long-term disruptive consequences for memory.*

Adolescence is often a time of fashion consciousness, learning how to drive a car and exploring the limits of parental patience and endurance. Adolescence is also a time when most people begin drinking, often drink the most, and for some, experiment with binge drinking. A study in the August issue of *Alcoholism: Clinical and Experimental Research (ACER)* explores the long-term neurobehavioral consequences of binge drinking during adolescence.

Binge drinking can be loosely defined as an intense bout of drinking during a single session, such as a single evening. For males, that can mean five or more drinks in one sitting; for females, it can be four or more drinks. Several studies have found that a significant percentage of teenagers report regular bouts of drinking in which high blood alcohol levels are attained. Furthermore, when the above definitions are used, recent data from the Harvard School of Public Health College Alcohol Study indicates that roughly 45 percent of all college students binge drink. According to Aaron M. White, research associate in the department of psychiatry at Duke University Medical Center and first author of the *ACER* study, roughly 23 percent of all college students are frequent binge drinkers, meaning that they binge three or more times in a two-week period.

White and his co-authors used rodents to test for the effects of binge-pattern drinking. “We were particularly interested in knowing whether these treatments produced different effects in younger rats than in older rats,” he said.

After a regimen essentially comparable to multiple instances of binge drinking in humans, both adolescents and adults were tested for anxiety and learning. Following the initial alcohol exposure phase, no effects were found. However, when a later, moderate dose of alcohol was given to all of the rats, those that had previously received the adolescent alcohol exposure showed the greatest disruption of working memory. These results suggest that binge-pattern exposure to alcohol during adolescence does something to the adolescent brain that leads it to respond differently – more sensitively – to alcohol in the future.

“We believe that the adolescent brain is more vulnerable to the neurotoxic effects of alcohol than the adult brain,” White explained, “and this could account for the findings of our study. Alcohol impairs activity at a receptor called the NMDA receptor. These receptors are highly concentrated in the hippocampus, a brain region critically involved in learning and memory. During withdrawal from alcohol, NMDA receptors can become overly active, which can make the brain more vulnerable to cell death. We are currently investigating whether adolescent

continued ~

BINGE DRINKING: A DANGEROUS RITE OF PASSAGE

brains exhibit greater withdrawal-induced hyperactivity at NMDA receptors than adults, and if such hyperactivity leads to greater cell death in adolescent than adult subjects.”

“The implications of this study,” said David L. McKinzie, senior biologist at Lilly Research Laboratories and adjunct assistant professor at the Indiana University School of Medicine, “are that teenagers who drink heavily may be especially susceptible to the neurobehavioral effects of alcohol than adults with similar drinking experiences. Of special concern is the possibility that the effects of early chronic alcohol drinking may have long-lasting consequences, both as a general insult to the brain as well as changing the individual’s later reactivity to alcohol.”

Although White cautioned against generalizing from a small sample of rats to the entire human population, he noted that the findings are consistent with previous research on alcohol abuse during adolescence. McKinzie concurred.

“The few animal studies to date have consistently suggested that developing brains are especially sensitive to the toxic effects of alcohol,” said McKinzie. “This type of study is particularly important because a large percentage of adolescents consume alcohol. Unfortunately, relatively little is known about the long-term consequences of chronic alcohol drinking in adolescent individuals. If this age group is indeed found to be especially vulnerable to alcohol and its long-term effects, as this study suggests, we may need to concentrate our efforts on preventive strategies.”



**Article is based
on the following
published research:**

White, A.M., Ghia, A.J.,
Levin, E.D.,
& Swartzwelder, H.S.
(August 2000).

Binge pattern ethanol
exposure in adolescent
and adult rats:
Differential impact
on subsequent
responsiveness
to ethanol.

*Alcoholism: Clinical
and Experimental
Research,*
24(8), 1251-1256.



COLLEGE STUDENTS MAY BE DRINKING MORE ALCOHOL THAN EVEN THEY REALIZE

- *Most of what is known about alcohol consumption by college students comes from self-reports.*
- *New research shows that college students overestimate what is meant by “standard” drink sizes.*
- *These findings suggest that students drink significantly more than they report.*

Most of what is known about alcohol consumption by college students comes from survey data. Yet much of what is known about college drinking may be underestimated, according to findings published in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)*. An examination of college students’ ability to define “standard drinks” suggests that college students drink significantly more than they think they do.

“For some reason, we’ve all just sort of assumed that we can take students’ responses on surveys at face value,” said Aaron M. White, assistant research professor in the department of psychiatry at Duke University Medical Center and first author of the study. “[We’ve believed] that if they say they had three drinks, then they really had three drinks. This study suggests that it’s just not that simple. Students tend to have pretty liberal views about what constitutes a single drink. In fact, if a student tells us they had three drinks, there’s a good chance it was more like five or six. This is a big difference, particularly if we’re trying to figure out how many students qualify as ‘binge drinkers’ based on their self-reported drinking habits.”

White and his colleagues asked 106 undergraduate students (54 males, 52 females) to complete a 12-item survey. The survey was designed to gather basic information about students’ current drinking habits and three tasks relating to drink size. The tasks involved free-pouring according to each subject’s estimation of a standard drink size: 1) beer, 2) a shot of hard liquor and 3) alcohol for a mixed drink into cups of different sizes. The student-poured volumes were then compared to volumes of standard drinks used in the Harvard School of Public Health College Alcohol Study survey(s).

For every cup size in each of the three tasks, students overestimated how much fluid they would need for a standard drink size. “Regardless of which type of drink we asked students to pour,” said White, “they almost always poured too much. When asked to pour a standard size beer into a 32-ounce cup, some students filled the cup to the top! For these students, each of their drinks actually equaled 2.5 standard drinks.”

Furthermore, in all three pouring tasks, the magnitude of the discrepancy increased with cup size. “These findings suggest that students drink more than they think,” said White, “which means that survey data probably underestimate actual drinking levels on college campuses. This is obviously not good news, neither for those of us who use surveys in our research, nor for those of us trying to deal with alcohol misuse on college campuses. The scale of the problem could be bigger than we thought.”

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COLLEGE STUDENTS MAY BE DRINKING MORE ALCOHOL THAN EVEN THEY REALIZE

“The fact that many students probably consume more alcohol than their survey responses suggest could help explain some of our previous findings about the consequences of drinking,” added Courtney Kraus, second author for the study. “We’ve observed that a surprisingly high percentage of college students experience alcohol-induced memory blackouts, more than might be expected based on their self-reported consumption. The high incidence of blackouts makes more sense if students are actually drinking more than they think.”

“We need to repeat this study with a larger random sample of students,” said Ralph Hingson, professor of social and behavioral sciences and associate dean for research at the Boston University School of Public Health. “When they’re collecting information about drinks in these surveys, they ought to provide more information about what a ‘standard’ drink really is. In addition, we ought to study if alcohol-related problems are associated with miscalculation of the amount of alcohol that it takes to make a standard drink. For example, are the people who underestimate the amount of alcohol in a standard drink the ones who are more likely to be dependent, who drive after drinking, ride with drinking drivers, or engage in other alcohol-related behaviors that pose risks to themselves and others?”

“We somehow need to teach students, health educators, administrators, and anyone else involved in dealing with college-drinking issues how to accurately define a drink,” added White. “Until then, we have to be cautious about the conclusions that we draw from survey data, and about the levels of consumption that we promote to college students as ‘safe’ or ‘normal.’ Telling a student that his or her peers typically drink three or four drinks when they go out could do some damage if that kid defines a drink as a 10-ounce cup of booze with a splash of Coke.”

White also suggested a new kind of beverage labeling. “When someone picks up a box of cookies or a bag of potato chips,” he said, “one of the first things they often do is look for information about serving sizes, calories, etc. Doesn’t it make sense that these labels, or at least a rudimentary form of them, should be placed on drinks that contain alcohol? Otherwise, how is a person to know how many standard servings of alcohol are present?”

White spoke of an Australian government initiative requiring information about serving sizes on all alcoholic beverages. “By doing this, the government can now have meaningful dialogue with the populace about healthy and unhealthy drinking levels, and can measure alcohol consumption more accurately. Why the beverage industry does not voluntarily place this information on their products [in the U.S.] is beyond me. My guess is that the public would really appreciate it.”

Article is based on the following published research:

White, A.M., Kraus, C.L., McCracken, L.A., Swartzwelder, H.S. (November 2003). Do college students drink more than they think? Use of a free-pour paradigm to determine how college students define standard drinks. *Alcoholism: Clinical and Experimental Research*, 27(11), 1750-1757.



A DOLESCENTS WITH ALCOHOL PROBLEMS: REDEFINING THE BASICS

- *The Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) is widely used to define alcohol abuse and dependence.*
- *Yet little is known about the validity of DSM-IV criteria for alcohol use disorder (AUD) diagnoses when applied to adolescents.*
- *Researchers applied a statistical method called latent class analysis (LCA) to DSM-IV AUD criteria. They found that “milder” and “more severe” categories derived from LCA provided better coverage of symptomatic adolescents than DSM-IV alcohol abuse and dependence categories.*

For some nosologists – people interested in the classification of diseases – the *Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV)* lies somewhere between serving as a valuable diagnostic tool and one in need of revision. Of special concern is the validity of *DSM-IV* alcohol use disorder (AUD) diagnoses when applied to adolescents. A study in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* uses an advanced quantitative technique called latent class analysis (LCA) to examine the utility of new ways of classifying adolescent alcohol problems.

“There is controversy regarding the use of *DSM-IV* criteria with adolescents,” said Tammy Chung, assistant professor of psychiatry at the University of Pittsburgh Medical Center and lead author of the study. “For example, existing criteria include symptoms that are not commonly experienced by adolescent problem drinkers, which limits their utility when applied to this age group. Symptoms such as alcohol withdrawal and alcohol-related legal problems typically occur only after years of heavy drinking. Conversely, other *DSM-IV*-defined symptoms, such as alcohol tolerance, generally tend to have a high prevalence in adolescent drinkers, and do not clearly distinguish between adolescents with and without drinking problems. In certain cases, individuals may have alcohol-related symptoms, but fail to meet *DSM-IV* AUD criteria for a diagnosis. We need to remember that these criteria were developed for use with adults, and little is known about their validity when applied to adolescents. Although a few papers have addressed this topic cross-sectionally, this study is among the first to address this issue in adolescents using longitudinal data.”

“There are all kinds of problems with *DSM-IV* when applied to adolescents,” agreed James Langenbucher, associate professor at the Center of Alcohol Studies at Rutgers University. “One of these is that the way in which we diagnose alcohol and drug problems, and even gambling problems and eating disorders, is based on the prototype of a middle-aged White man, probably a patient in a Veterans Affairs hospital during the 1960s to 1970s. This prototype gave us all the ideas that have filtered down and been codified. No one had in mind a 17-year old Latino kid in Philadelphia when deciding what were the essential characteristics of alcohol and drug abuse disorders.”

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A DOLESCENTS WITH ALCOHOL PROBLEMS: REDEFINING THE BASICS

The first *DSM* was published by the American Psychiatric Association in 1952. Diagnostic criteria for alcohol and other drug problems were added in 1980 (*DSM-III*). In general, there are three *DSM-IV* categories of substance-use disorders: no diagnosis, abuse, and dependence. Alcohol abuse and dependence are defined by mutually exclusive criterion sets. Alcohol abuse is diagnosed by meeting at least one of four symptoms representing recurrent hazardous use and negative psychosocial consequences resulting from drinking. Alcohol dependence requires meeting three of seven symptoms within a 12-month period, precludes a diagnosis of abuse, and includes symptoms related to physical dependence, impaired control over drinking behavior, and increased salience of alcohol consumption.

For the Chung study, researchers used LCA to identify subgroups of adolescents who share a common pattern, profile of symptoms or other characteristics. They then used the subgroups' symptom profiles to refine the *DSM-IV* criteria used to diagnose AUDs. "We were able to develop severity-based categories of adolescents with milder and more severe alcohol-related problems," said Chung. "The milder and more severe categories derived in this study provided better coverage of symptomatic individuals than *DSM-IV* alcohol abuse and dependence categories, suggesting that some reorganization of *DSM-IV* AUD criteria may improve the identification of individuals who may benefit from treatment. In addition, longitudinal data indicated an overall decrease in the severity of adolescents' alcohol-related problems one year after substance abuse treatment."

"Another important finding," said Langenbucher, "is that case severity in this data seems to be carried by the number, not the type, of symptom. It's the overall number of symptoms that best accounts for the severity of the case. This argues for a dimensional system that relates abuse to dependence, perhaps not different categories, but different ranges on the severity continuum."

Chung said, "These results suggest that a proportion of symptomatic adolescents who may benefit from intervention, may not meet criteria for a *DSM-IV* AUD diagnosis, and thus may not be eligible for third-party reimbursement for substance abuse treatment. As our own findings confirmed, treated adolescents tended to show reductions in alcohol-related problems one year after substance abuse treatment, a finding that does not support the notion of an inevitable progression to more severe problems."

"What we want to eventually do," said Langenbucher, "is develop *DSM-V*. That version should be out toward the close of this decade. We want improved diagnostic rules for all kinds of psychiatric diagnoses including major depression, schizophrenia and also substance-use disorders."

Article is based on the following published research:

Chung, T., & Martin, C.S. (December 2001). Classification and course of alcohol problems among adolescents in addiction treatment. *Alcoholism: Clinical and Experimental Research*, 25(12), 1734-1742.





IMPULSIVENESS, AGGRESSION, ALCOHOL AND ADOLESCENTS

- *Adolescents with alcohol problems often manifest impulsive, aggressive and antisocial behaviors.*
- *One type of adult alcoholism (Type II) is likewise characterized by antisocial behavior, and may be linked to a decrease in function of the neurotransmitter serotonin.*
- *A recent study has found that adolescents with both alcohol and antisocial problems show an increase in serotonin function.*
- *Serotonin dysregulation, rather than high or low levels, may be key to high-risk behaviors.*

Alcohol use disorders are nearly as common among older adolescents as among adults. Adolescents who abuse alcohol or are dependent on alcohol often manifest impulsive, aggressive, and antisocial behaviors. A study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the possibility that variations in brain chemistry can set the stage for risk-taking behaviors. More specifically, it studies the role that dysregulation of central serotonergic function may play in impulsiveness, aggression and conduct disorders in older adolescents (between 16 and 21 years of age) with alcohol problems.

“Impulsive and aggressive personality traits, as well as impulsive-aggressive behavior,” explained Paul Soloff, professor of psychiatry at the University of Pittsburgh School of Medicine and lead author of the study, “are temperamental traits that lead to socially disinhibited behavior, also called ‘behavior undercontrol.’ Kids with behavior undercontrol are more likely to develop alcohol use disorders than non-impulsive-aggressive kids.”

One type of adult alcoholism, referred to as Type II, is defined by antisocial behavior, including many expressions of behavior undercontrol, as well as early onset (before age 25), and male predominance. (This is in contrast to Type I alcoholism, which is found in both males and females, occurs later in life and is not associated with antisocial traits.) Research suggests that there is a biologic (and possibly hereditary) basis for the temperament of impulsivity that is related to dysregulation of the neurotransmitter serotonin in the parts of the brain that inhibit impulses. Studies of adults with alcohol use disorders have found evidence of decreased serotonin function, especially those with Type II alcoholism (identified by antisocial behavior). Similarly, studies of impulsive-aggressive individuals, independent of alcohol use disorders, have found diminished serotonin function.

“We looked at adolescents who already had developed alcohol use disorders to see if they had higher levels of impulsivity and aggressivity than healthy control subjects, and to also see if they had lower central serotonergic function,” said Soloff. “We measured central serotonin function by giving them a single dose of a medicine called fenfluramine, which releases serotonin in the brain, and then looked for effects of that release in the blood.”

Serotonin itself cannot be measured in the blood. However, serotonin release in the brain causes a rise in the hormones prolactin and cortisol in the blood. “The changes in prolactin and cortisol provided an index of serotonin responsiveness,” he continued.

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I MPULSIVENESS, AGGRESSION, ALCOHOL AND ADOLESCENTS

“In adults with alcohol use disorders,” said Duncan Clark, director of the Pittsburgh Adolescent Alcohol Research Center, “the serotonin system is relatively insensitive or unresponsive to stimulation. In this study, the serotonin responsivity results were somewhat different than would be expected from studies of adults.”

Neither Soloff nor Clark were surprised that older adolescents with alcohol use disorders had more impulsivity and aggressivity than control subjects. The boys tended to be more aggressive in general than the girls, but both had equally high levels of impulsivity. Furthermore, overall the two groups (alcohol users and control subjects) did not significantly differ on their prolactin or cortisol responses. This suggests that not all youth with significant alcohol use disorders early in life have a dysregulation of serotonin metabolism. However, the most extreme subjects – nine boys with both alcohol use disorders and the most antisocial traits (which were diagnosed as conduct disorder) – had a significant elevation in cortisol response, which correlated with measures of aggressivity.

“These findings may be interpreted to show that the serotonin system was more responsive in these subjects,” said Clark. “[This may reflect] an earlier stage of neurobiological development. Increased responsiveness of the serotonin system in adolescence may be followed by decreased responsiveness in adulthood. However, the level of responsiveness may not be as important as the ability of the brain to regulate the response to stimulation. While not in the same direction as with adults, these results are still consistent with the idea that individuals with these high-risk behaviors have serotonin dysregulation.”

Soloff plans to further study the serotonin system using positron emission tomography (PET) neuroimaging, where metabolic changes can be “visualized.” He believes this research will ultimately reveal more about where in the brain impulsivity is controlled, how serotonin is regulated in these individuals, and whether this dysregulation can be remedied.

Clark noted, “We need to know more about the development of the serotonin system from childhood through adolescence and into adulthood. New brain imaging techniques may allow us to study brain chemistry directly rather than relying on measurement of effects of brain chemistry on blood chemistry. Through an understanding of the brain and behavior, better approaches to identifying children at risk, better prevention programs and more effective treatment interventions may be developed.”



Article is based on the following published research:

Soloff, P.H., Lynch, K.G.,
& Moss, H.B.

(November 2000).

Serotonin, impulsivity,
and alcohol use
disorders in the older
adolescent:

A psychological study.
*Alcoholism: Clinical
and Experimental
Research,*

24(10), 1609-1619.

A LCOHOL, AUTOMOBILES AND YOUTH

- *Underage drinking and driving continue to cause significant numbers of injury and death.*
- *Riding with drinking drivers may be even more dangerous for adolescents than drinking and driving.*
- *New findings indicate that drinking and driving, and riding with drinking drivers, may be particularly problematic among Latino youth.*

Although the message of “don’t drink and drive” has been a common refrain for the past two decades, much less attention has been given to the risks of riding with a drinking driver. A study in the August issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines ethnic differences among adolescents who engage in driving after drinking (DD) and riding with drinking drivers (RWDD). Findings indicate there is a distinct need to direct prevention efforts toward Latino youth.

“Adolescent alcohol use, driving after drinking, and riding with drinking drivers are significant public health problems,” said Samantha Walker, associate research scientist at the Prevention Research Center and corresponding author for the study. “Consequences can include automobile crashes, physical injury and possible death.”

In 2000, according to the National Highway Traffic Safety Administration (NHTSA), 21 percent of young drivers who were killed in crashes were intoxicated with blood alcohol concentrations of 0.10 g/dl or greater. Among those drivers who had been drinking, three percent were involved in property damage-only crashes, five percent were involved in crashes resulting in injury, and 22 percent were involved in crashes resulting in fatality. RWDD is a less-recognized practice than DD, yet may be even more dangerous for adolescents.

“The percentage of adolescents riding with drinking drivers is frighteningly high, with approximately half of all youth reporting such experiences in the past 12 months,” said Brenda A. Miller, a senior scientist at the Prevention Research Center. “This study clarifies that a greater proportion of our adolescents are at risk for injury or death due to riding with drinking drivers as compared to driving under the influence.”

Researchers used random-digit dialing procedures to recruit 1,534 15- to 20-year-olds (839 females, 695 males) living in California to participate in a telephone survey. Latinos, African Americans and Asian Americans were oversampled to allow cross-group comparisons.

“Our findings indicate that DD and RWDD may be particular problems for Latinos,” said Walker. “That is, Latino youth appear more at risk for these behaviors than are other youth at similar levels of alcohol consumption.” The study found low prevalence rates of DD and RWDD among Asian American youth, which may indicate the presence of protective factors – whether social or environmental – at work within the Asian American community.

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A LCOHOL, AUTOMOBILES AND YOUTH

“These results suggest that some ground work needs to be done to better understand why Latino youth are more vulnerable to these risks and whether our prevention message needs to be presented in a different manner that would be better heard by Latino youth,” said Miller. “We need to be cautious, however, about concluding that all Latino youth are more susceptible because the findings do not support this conclusion. Only when we account for drinking behaviors and driving practices do we see an increased risk for Latino youth.”

Miller added that although many parents likely already know that children who drink frequently are at higher risk for either DD or RWDD, they may not know that risky driving and the number of days driven are also related to an increased risk for DD or RWDD.

“Risky driving is probably part of a constellation of high-risk behaviors,” said Miller. “The total number of days driven may be related to control or ownership of a car that provides the means to engage in drinking and driving more readily. We know that parents who monitor their children are less likely to have children who engage in alcohol or drug use. However, monitoring teenagers’ behavior is increasingly more complex, especially when the access and availability of vehicles adds to freedom and independence from parental controls.”

Walker said that future research will explore some of these complexities, specifically, “clarifying the relationships among drinking patterns, driving practices, social and environmental influences such as drinking locations, and DD and RWDD, particularly among Latino youth.”

Miller suggested that future studies also explore strategies to help adolescents avoid those situations in which drinking and driving occur, especially scenarios in which they are passengers riding with a drinking driver.

“For many adolescents, the automatic loss of their license or a zero-tolerance policy of any alcohol use while driving provide a powerful external control over DD behavior,” said Miller. “However, the issue of RWDD is not so easily addressed. Our prevention strategies should make it easier for adolescents to negotiate difficult social situations that may emerge in their lives, such as what to do when a friend that drove you to a party has too much to drink. Particularly important is the need to provide constructive strategies rather than messages that simply admonish against such behavior. And ultimately, providing adolescents with an ability to handle these difficult social problems will provide them, hopefully, with the strengths they need to negotiate other social problems in their lives.”



Article is based on the following published research:

Walker, S., Treno, A.J., Grube, J.W., Light, J.M. (August 2003).

Ethnic differences in driving after drinking and riding with drinking drivers among adolescents.

Alcoholism: Clinical and Experimental Research, 27(8), 1299-1305.

TEENAGERS, DRINKING AND DRIVING: A QUICK TRIP TO THE GRAVE

- *Motor vehicle crashes are the leading cause of death for 15- to 20-year-old youth in the U.S.*
- *More than one quarter of the drivers killed in crashes had been drinking.*
- *One alcohol-prevention curriculum was found to significantly reduce first-year serious traffic offenses.*
- *The curriculum seemed to be particularly effective for kids who drank very little.*

Motor vehicle crashes are the leading cause of death for 15- to 20-year-old youth in the United States, according to mortality data from the National Center for Health Statistics. More than one quarter of the drivers killed in crashes had been drinking. While all school-based alcohol prevention programs strive to minimize alcohol use and/or misuse, little is known about the actual effects of these programs, particularly on students' driving. A study in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the effects of a high school-based alcohol misuse prevention program on participants' subsequent driving behaviors.

"A law setting a minimum drinking age of 21 years exists in all the states," explained Jean T. Shope, senior research scientist with the Transportation Research Institute at the University of Michigan and lead author of the study. "Although it has reduced underage drinking and driving fatalities, we still have a problem."

In 1999, according to the National Highway Traffic Safety Administration, 3,561 drivers 15 to 20 years old were killed – and an additional 362,000 injured – in traffic crashes. Of those young drivers fatally injured, 29 percent had been drinking. Although driving after drinking is potentially deadly under any circumstances, it is particularly dangerous when teenagers do it.

"It's important to look at the context of this behavior," said James Hedlund, a consultant in traffic safety for Highway Safety North. "Not only is their drinking illegal, because the minimum drinking age in the United States is 21 years of age, but so too is their driving after drinking. Every state has a zero-tolerance law." Under these laws, teenage drivers detected with a blood alcohol concentration of 0.02 grams per deciliter or above will lose their driver's licenses. "So driving after drinking is doubly illegal," he said.

"There are two overall methods to change someone's behavior: enforcement and education," added Hedlund. "Legal interventions have been evaluated best, because they go into place at one given time, all over a state. But a high school prevention program doesn't work that way. It's usually put into place in one high school, often for a short period of time, and it's very difficult to measure its effects. One of the really good things about Shope's study is that she finds effects in long-term traffic offense data."

Shope's research is a follow-up to the Alcohol Misuse Prevention Study, in which five hour's worth of alcohol-education sessions were given to 10th grade Michigan students during each of the 1988-1989 and 1989-1990 school years. For this study, Shope and her colleagues examined

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T EENAGERS, DRINKING AND DRIVING: A QUICK TRIP TO THE GRAVE

students' driving histories for roughly seven years following licensure, which typically occurs during or shortly after 10th grade. The study had three main findings.

"They found that the curriculum reduced serious traffic offenses, both alcohol-related and other offenses as well, by about 20 percent in the first year these kids were licensed to drive," said Hedlund. "Second, the effect disappeared after the first year of driving. Third, the effect in the first year was strongest in two particular groups of students: those who didn't drink very much, and those who had parents who didn't seem to disapprove much of teen drinking."

"I think it's important that the prevention program seemed to work best among the group that had not yet started to drink," Shope said. "This is a typical finding in prevention. To get to them at the right time makes all the difference. It's just like trying to prevent smoking; you need to stop them before the age of 13. We already know that drinking increases very much during high school. If you're going to do prevention, you have to get in there before the behavior starts, otherwise you're doing treatment or harm reduction, not prevention."

"This is one of the few studies I know that looks at an educational program and actually finds some bottom-line results of observable behavior," said Hedlund. "It gives some scientific data that say you really can teach high school kids something. I'm saying that only somewhat facetiously. This is a very difficult group to try to educate, especially in ways that are socially responsible, when a lot of these kids are looking for ways to be socially irresponsible. So it's good news that this study gives us some indication that education about socially acceptable behaviors may indeed make a bottom-line difference. The results aren't conclusive, but they are very promising."

"There really needs to be more follow-up or long-term evaluation of prevention programs," Shope said. "We also need longer-term intervention or teaching. Why would a five-hour program in 10th grade, with no revisiting of the topic ... why would that have much of an effect? Sometimes these school programs are just a drop in the bucket when there's a lot of other stuff going on in a young person's life. You can't really expect a whole lot of change from a tiny little effort. One more thing, while schools may be very convenient places to reach groups of young people, many of these programs would work much better if the same message were also being delivered from the home, family, community, youth organizations and the media. Prevention can be somewhat 'swimming up stream' when it's not really being reinforced anywhere else."



Article is based on the following published research:

Shope, J.T., Elliott, M.R.,
Raghunathan, T.E.,
& Waller, P.F.
(March 2001).

Long-term follow-up
of a high school alcohol
misuse prevention
program's effect on
students' subsequent
driving.

*Alcoholism: Clinical
and Experimental
Research,*
25(3), 403-410.



T RACKING THE LONG-TERM FUNCTIONING OF ADOLESCENTS WITH ALCOHOL PROBLEMS

- *Standard treatment may not be enough for some adolescents with alcohol problems.*
- *A significant proportion of adolescents continue to drink and/or use other drugs, have poor relations with family and friends, and experience academic problems following treatment.*

Standard treatment may not be enough for some adolescents with alcohol problems, say researchers. While many adolescents reduce their alcohol use and have fewer related problems following treatment, a significant proportion continue to drink and/or use other drugs, have poor relations with family and friends and experience academic problems. Scientists say that long-term studies of treated adolescents are essential for determining what impact treatment can have and what factors may change the severity of alcohol problems over time.

These findings, gathered from four studies of adolescents who were followed for one to eight years after treatment, were presented at a symposium during the joint 2002 Research Society on Alcoholism/International Society for Biomedical Research on Alcoholism meeting. Symposium proceedings can be found in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)*.

“We know very little about the impact that adolescent problem drinking has on academic achievement, relations with family and friends and employment through young adulthood,” said Tammy Chung, assistant professor of psychiatry at the University of Pittsburgh Medical Center and co-organizer of the symposium. “Longer-term studies can help us to understand how certain developmental milestones, such as full-time employment and independent living, affect the course of alcohol problems that begin in adolescence. Longer-term studies can also tell us which adolescents are most likely to continue or return to problem drinking and how treatment can be improved to more effectively meet their specific needs.”

Findings presented at the symposium included:

- Treatment works for many teens. At least half of the adolescents studied showed reductions in alcohol use and problems following treatment, with concurrent improvements in psychosocial functioning.
- Treatment needs can change. The severity and frequency of alcohol problems among treated youth can fluctuate over the long term.

“Researchers have identified multiple pathways of change in alcohol use and problems,” said Chung. “About half of the treated adolescents maintained low levels of alcohol use and problems through young adulthood, while some treated adolescents experienced continuing alcohol problems.”

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T RACKING THE LONG-TERM FUNCTIONING OF ADOLESCENTS WITH ALCOHOL PROBLEMS

- Use of other drugs following treatment is associated with greater alcohol use and related problems.

“Adolescents who drank and used other drugs such as marijuana after treatment,” said Chung, “generally had poorer outcomes in the areas of family relations and academic achievement. These poorer outcomes appeared to last through young adulthood.”

- Researchers and clinicians need to consider the impact of developmental milestones on the course of adolescent-onset substance use disorders.

“We need to know more about the impact of certain developmental milestones – full-time employment, obtaining a driver’s license, independent living – on the course of alcohol problems in treated youth,” said Chung. “This will allow us to improve the timing, such as the addition of booster sessions and content of interventions for youth.”

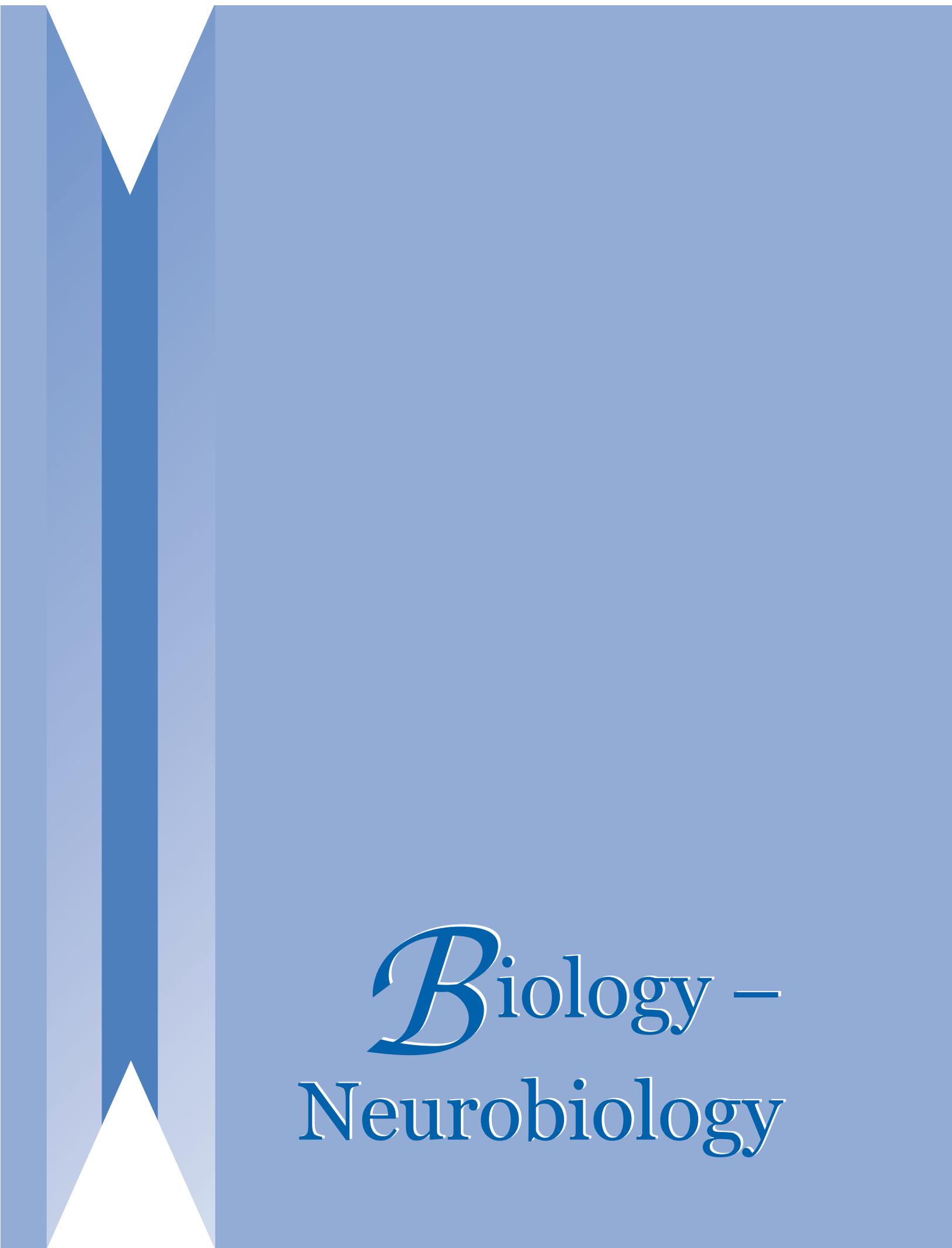
- The value of pretreatment characteristics, such as a family history of alcoholism, may become more evident as young people transition into adult roles.

“The bottom line,” said Chung, “is that alcohol problems that begin in youth do not necessarily have a chronic course. If we can identify the risk factors associated with alcohol problems that continue into young adulthood among treated youth, we can improve the effectiveness of their treatment.”



**Article is based
on the following
published research:**

Chung, T., Martin, C.S.,
Grella, C.E.,
Winters, K.C.,
Abrantes, A.M.,
Brown, S.A.
(February 2003).
Course of alcohol
problems in treated
adolescents.
*Alcoholism: Clinical
and Experimental
Research*,
27(2), 253-261.



*B*iology –
Neurobiology



BIOLOGY – NEUROBIOLOGY

Articles in the *Biology – Neurobiology* Category

1. Alcohol-Damaged Brains “Recruit” New Brain Regions to Perform Simple Tasks
2. How Alcohol Gives and Then Takes Away
3. How Sensitive Is Your Brain to Alcohol-Induced Damage?
4. The Brain Risks of Binge Drinking
5. Abstinence May Make the Brain Grow Stronger
6. Cognitive Neuroscience Takes on Alcohol
7. Just a Spoonful of Thiamin?
8. Alcohol and Thiamin Deficiency Together: A Dangerous Combination?
9. Chronic Drinking Increases Cortisol During Intoxication and Withdrawal
10. Repeated Alcohol Detoxifications Can Impair Cognitive Function
11. Blocking Selected Neurotransmitter Activity May Decrease Alcohol Consumption
12. Probing the Role of the Delta Opioid Receptor in Alcohol Consumption
13. Behavioral Sensitization: A New Perspective on Alcoholism



ALCOHOL-DAMAGED BRAINS “RECRUIT” NEW BRAIN REGIONS TO PERFORM SIMPLE TASKS

- *Chronic alcoholism is known to damage the brain’s cerebellum and frontal lobes.*
- *Researchers used brain imaging technology to watch abstinent alcoholics perform a simple motor task.*
- *Alcoholics performed the task, finger tapping, slower than non-alcoholics.*
- *Alcoholic brains also recruited other-than-normally activated regions of the brain to perform the task.*

Researchers know that many alcoholics continue to experience cognitive deficits even after long-term abstinence from alcohol. Results from a study in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* confirm that motor deficits also continue to plague abstinent alcoholics. By using functional magnetic resonance imaging (fMRI) to “watch” brain regions involved in a simple motor task – finger tapping – the study has found that the brain appears to compensate for alcohol-induced damage by “recruiting” other, unexpected brain regions.

“We know from neuropathological studies that the two parts of the brain that are most often damaged in chronic alcoholics are the cerebellum and the frontal lobes,” said Peter R. Martin, professor of psychiatry and pharmacology, director of the Vanderbilt Addiction Center at the Vanderbilt University School of Medicine and corresponding author for the study. “Rapid self-paced motor activity such as finger tapping is a function of the motor cortex, the posterior part of the frontal lobe, which initiates a stimulus to the muscles of the hand, that is then coordinated by interplay between the cerebellum and the frontal lobes. In other words, I reasoned that there would probably be abnormalities in activation of these regions in alcoholics during finger tapping.”

While undergoing MRI, two groups of participants performed repetitive, self-paced index finger-tapping exercises: eight (seven males, one female) alcohol-dependent patients after approximately two weeks of abstinence; and nine (seven females, two males) healthy volunteers or “controls.” Participants alternated between using their dominant hands (DH) and non-dominant hands (NDH) to perform the index finger-tapping exercises. Researchers used fMRI analysis to compare DH and NDH performance in each subject group in order to examine whether the groups differed in the patterns of activation they exhibited in the cerebral cortex and cerebellum.

The detoxified alcohol-dependent patients performed the finger-tapping tasks significantly slower than the control group. However, contrary to expectations, the slower tapping was not accompanied by proportionately decreased fMRI brain activation in the cerebral cortex and cerebellum. Rather, the alcoholics had a significant increase of activation in the cortical brain region ipsilateral to (on the same side as) the active hand during DH tapping. In other words, the alcoholics had to use more of their brains to do less.

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LCOHOL-DAMAGED BRAINS “RECRUIT” NEW BRAIN REGIONS TO PERFORM SIMPLE TASKS

“First, we found that alcoholics, generally speaking, tapped more inefficiently,” said Martin. “Second, in order to generate a single tap, an alcoholic would activate a larger part of their brain than a normal person. So, the results seem to indicate that even though alcoholics, as they recover from drinking, can probably demonstrate relatively normal tapping, they have to use more of their brain to generate the taps.”

“This study underlines the importance of considering the operation of brain circuitry involved even in an ostensibly simple task,” said Edith Sullivan, associate professor of psychiatry at Stanford University School of Medicine. “Further, evidence for recruitment of brain regions that are not normally involved in a given task puts a person at risk for performance inefficiency for that particular task, other tasks that need to be done simultaneously, and more complex divided-attention tasks, such as driving.”

Increased activity in the ipsilateral cortical region of the brain was highly unexpected, said Martin. “Normally, when I tap with my right hand,” he said, “it’s mostly my left motor cortex (part of the frontal lobes) that’s firing, in conjunction with my right cerebellum. ‘Ipsi’ means same side, ‘contra’ means opposite side. So, we’re talking about my contralateral cortex and my ipsilateral cerebellum. The significantly higher activity we found in the alcoholics was on the ipsilateral cortex, the side that we don’t normally expect to be activated. This finding is compatible with the idea that different regions of the brain are being called into activity that would not normally be activated in order to meet the behavioral demands. Furthermore, this suggests that even though alcoholics at some level may seem to be performing normally, if you raised the level of complexity at which they are being asked to perform, they may exhaust their capacities ... there may be no more brain to bring in, to recruit, to compensate.”

These findings lead to new questions, said Martin. “If we study patients as they progress with their abstinence, do these abnormalities get better? It may be that the brain gets better at compensating, but it doesn’t normalize, it just learns how to bring in even more parts of the brain. You could say it learns to rewire itself. Another possibility could be that as the brain heals, less activation is required, and that’s a real form of recovery. The answers rest with understanding not the tapping itself, but the mechanisms behind the tapping.”



Article is based on the following published research:

Parks, M.H.,
Morgan, V.L.,
Pickens, D.R., Price, R.R.,
Dietrich, M.S.,
Nickel, M.K.,
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(April 2003).

Brain fMRI activation
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alcohol-dependent
patients.

*Alcoholism: Clinical
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27(4), 704-712.

How Alcohol Gives and Then Takes Away

- *Alcohol may be particularly damaging to key components of the “brain reward system.”*
- *Alcohol sensitizes dopamine and serotonin neurons to toxic excessive excitation or “excitotoxicity.”*
- *A brain growth hormone called BDNF can protect neurons against excitotoxicity.*
- *BDNF may have important implications for treating alcoholics going through withdrawal.*

Mental diseases, including addiction and alcohol dependence, may indeed be “all in your head.” But not in the way you might think. Researchers have learned that alcohol may be particularly damaging to the brain’s reward pathways, specifically dopamine and serotonin neurons. This damage – a sensitization of the neurons to a process called excessive excitation or “excitotoxicity” of the *N*-methyl-D-aspartate (NMDA) glutamate receptor – could be an important component in transitioning from experimentation to addiction. However, researchers may have also discovered that a brain growth hormone called Brain Derived Neurotrophic Factor (BDNF) may be able to protect neurons against this excitotoxicity.

“If dopamine and serotonin neurons are damaged,” said Fulton T. Crews, director of the Center for Alcohol Studies at the University of North Carolina, “this would disrupt reward processes in ways that could contribute to addiction.” Crews, lead author of a study recently published in the November edition of *Alcoholism: Clinical and Experimental Research (ACER)*, explained that his findings are related to what is called a “reward deficiency hypothesis” of addiction.

The “reward deficiency syndrome” links addictive, compulsive or impulsive disorders – such as alcoholism, substance abuse, smoking, compulsive overeating and obesity, Attention deficit disorder, Tourette’s syndrome and pathological gambling – with a “chemical imbalance” in the brain. Researchers knew that pleasure, to various degrees, is a distinct neurological function that is linked to a complex reward and reinforcement system. In particular, dopamine appears to be a primary neurotransmitter of reward in the nucleus accumbens and hippocampus areas of the brain. Serotonin is believed to have an additive or synergistic effect on dopamine. Alcohol is known to initially lead to an increase in dopamine release, which supposedly enhances reward/pleasure. However, chronic and/or high levels of alcohol will eventually lead to a decrease in dopamine release. This disruption of intercellular interactions or “chemical imbalance” can result in negative feelings such as anxiety, anger or in a craving for a substance, such as alcohol, that can alleviate the negative feelings. Yet because chronic drinking releases a continuously reduced amount of dopamine, more and more alcohol is needed to feel “normal.”

“Science has come to the realization that what alcohol may be doing,” said Boris Tabakoff, chairman of the Department of Pharmacology at the University of Colorado School of Medicine, “is what I call ‘downregulating’ dopamine systems. This study shows that downregulation may actually be a result of neuronal damage. Alcohol leads to a sensitization to glutamate, the glutamate produces the damage, and the damage results in a lower function of the dopamine system.”

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HOW ALCOHOL GIVES AND THEN TAKES AWAY

“This is important,” added Tabakoff, “because it provides an explanation for why individuals may not be able to control their drinking because of biological factors. If the neurons are damaged, they can keep trying to use alcohol to attain some level of pleasure, but they’ll never be able to do it.”

Although there is no such thing as a specific gene for alcoholism, there does seem to be a “genetic predisposition” to the development of alcoholism. Tabakoff spoke of one study in which 20 to 28 percent of individuals with at least one alcoholic parent went on to develop alcoholism themselves. Normally, among those who have no familial history of alcoholism, around eight to 10 percent develop alcoholism. In short, those with a family history of alcoholism seem to have a two to three time’s greater chance of developing the disease. Although the exact role of biology in alcoholism has not yet been determined, research findings support both discovery as well as optimism.

“This is one of the first studies to show a relationship between excitotoxicity, which likely occurs during ethanol withdrawal, and NMDA receptors,” said Richard A. Morrisett, associate professor of Pharmacology at the University of Texas at Austin. “But it is the first to show that BDNF can actually protect against this. The rescue or prevention of cell death is probably one of the most important aspects of this study.”

“Clearly the future direction of this area of study is medication development and an understanding of protective factors,” said Tabakoff. “If you have an individual who is drinking a lot but decides to stop, you need to treat that person with something more than moral support. The very process of withdrawal could damage the person’s neurons.” Tabakoff spoke of developing drugs that will protect the neurons, returning the individual’s pleasure systems to normal while avoiding irrevocable damage.

Morrisett indicated there is a need for future studies that look at the effects of lower levels of alcohol on excitotoxicity. “The levels used in this study, 100 mM, are five times the legal levels of intoxication,” he said. “I would like to see what occurs at 20mM, because that’s more related to when we start to drink, when we may start to become dependent.” When a person starts to drink and is experiencing the reinforcing aspects, he said, that’s when “we’re having a little engine misfire.” At the point of full-blown alcoholism, he said, “we’re addicted, we’re dependent, we’re drinking fifths of whiskey a day, the car is wrecked.”



Article is based on the following published research:

Crews, F.T., Waage, H.G.,
Wilkie, M.B.,
& Lauder, J.M.
(November 1999).
Ethanol pretreatment
enhances NMDA
excitotoxicity in biogenic
amino neurons:
Protection by brain
derived neurotrophic
factor.
*Alcoholism: Clinical
and Experimental
Research*,
23(11), 1834.

How SENSITIVE IS YOUR BRAIN TO ALCOHOL-INDUCED DAMAGE?

- *Alcohol's neurotoxic effects can cause brain injury.*
- *Alcohol-related brain injury may, in turn, place someone at greater risk of developing alcoholism.*
- *Exercising the brain's frontal cortex during treatment may help the recovery process.*
- *Thiamin supplements may also improve recovery of the brain and response to treatment.*

Symposium findings from the June 2000 Research Society on Alcoholism meeting in Denver suggest that alcohol-induced brain injury may be the medium for the progression of alcoholism. The summary, published in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)*, may change the way researchers think about the influence of alcohol-related brain injury on how people develop addictions, respond to treatment and ultimately recover.

“What these researchers are saying is that injury to the brain resulting from alcohol consumption is sum and parcel of the progression of the illness,” said Peter R. Martin, professor of psychiatry and pharmacology and director of the Vanderbilt Addiction Center at the Vanderbilt University School of Medicine.

“It’s a different perspective on how alcoholism may progress. In the past 20 years, the emphasis of research has been on what makes some people respond to alcohol, regardless of whether their brain is damaged. What they’re saying here is that by drinking, you modify the brain, and the brain can be modified differentially in people. The neurotoxicity of alcohol ‘feeds back’ and determines, modulates or modifies the course of the alcoholism.”

Symposium proceedings included four studies that addressed both preclinical (before the onset of the disease) and clinical (related to the symptoms and course of a disease) findings. According to Fulton T. Crews, director of the Center for Alcohol Studies at the University of North Carolina and one of the presenters, the symposium’s common ground was the relation of alcohol-induced deficits in central nervous function to addiction and recovery.

“Data indicates that risk factors for alcoholism include heavy binge drinking, genetics and adolescent drinking,” said Crews. “These may also be risk factors for increased brain damage.” That’s the bad news; that simply drinking alcohol can injure someone’s brain, its neurotoxic effects depending on the individual’s genetic makeup, age, metabolism and even gender. The good news is that because of the close ‘working relationship’ between alcohol and the brain, recovery seems possible with the right kind of treatment.

“Preclinical studies have suggested that brain damage is a component of the progression from casual drinking to addiction,” said Crews. “We know that alcoholics have decreased brain size. Clinical studies have suggested that ‘exercising the brain’ likely improves brain regrowth as well as recovery from the addiction. Regrowth of the frontal cortex in particular could be

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How SENSITIVE IS YOUR BRAIN TO ALCOHOL-INDUCED DAMAGE?

essential for a successful recovery. Including certain activities in therapy – activities that require the use of the frontal cortex, the site of executive function, impulse inhibition and goal setting – have been shown to improve recovery and increase retention in the treatment program. Also, thiamin therapy seems to increase treatment effects, likely by restoring aspects of central nervous system function.”

In short, therapies that exercise certain areas of the brain can improve its function. This can, in turn, help improve an individual’s chances of recovery from alcoholism. The decrease in brain size that seems to accompany alcoholism appears to reverse during the recovery process. In addition, thiamin supplementation may help recovering alcoholics regain their capacity to remember.

“The main point to be made here for the reader is that drinking alcohol can cause brain injury,” said Martin. “Maybe what determines why some people become alcoholics is not so much how they respond to the pharmacological actions of alcohol, but how sensitive their brain is to being damaged by alcohol, which modifies their brain, thereby modifying the pharmacological actions of alcohol.”

Martin added that future research should be directed at recovery. “We need to remember that even when an alcoholic stops drinking, there have been changes in the brain. We need to spend more time trying to understand how the brain recovers after people stop drinking, because that’s going to determine how well they ultimately do.”



**Article is based
on the following
published research:**

Bowden, S.C.,
Crews, F.T., Bates, M.E.,
Fals-Stewart, W.,
& Ambrose, M.L.
(February 2001).
Neurotoxicity and
neurocognitive
impairments with
alcohol and drug use
disorders: Potential
roles in addiction and
recovery.
*Alcoholism: Clinical
and Experimental
Research*,
25(2), 317-321.

THE BRAIN RISKS OF BINGE DRINKING

- *Neurodegeneration has been commonly thought to occur during alcohol withdrawal.*
- *A new study has confirmed that neuronal damage can occur during a binge pattern of drinking.*
- *Damage to the olfactory bulb, responsible for smell, occurred after just two days of binge drinking.*
- *Damage to other regions of the brain occurred after just four days of binge drinking.*

Scientists agree that alcohol is toxic and that chronic alcohol abuse can damage all organs – including the brain – to various degrees. There is less agreement, however, on whether or how much neurodegeneration is triggered by alcohol’s toxicity during alcohol consumption or by the hyperexcitability caused by withdrawal from alcohol. A study in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* uses rodents to examine what effects just a few days of the equivalent of binge drinking can have on neuronal function.

“Most studies of alcohol-induced brain damage have looked at humans who have been alcoholic for decades or rats treated with alcohol for six to 18 months,” said Fulton T. Crews, director of the Center for Alcohol Studies at the University of North Carolina and corresponding author for the study. “Our study shows significant damage in several regions of the brain after only four days, that it occurs during intoxication, and that the process is similar to a dark-cell degeneration that is primarily necrotic.” Necrosis refers to the pathologic death of cells or a portion of tissue or organ due to irreversible damage.

Male Sprague-Dawley rats (n=120) were surgically implanted with intragastric catheters. Experimental rats (n= 80) were given alcohol at a rate equivalent to binge drinking, every eight hours for four consecutive days. Doses were based on their estimated blood alcohol levels. Control rats (n=40) were given an alcohol-free yet calorie-equivalent diet at the same rate. Several histological methods – such as amino cupric silver staining, fluoro-Jade B staining, hematoxylin and eosin staining, and transmission electron microscopy – were used to track the course, time points, and specific changes that occurred in conjunction with the alcohol intake. Some rats were sacrificed at two days, some at four days, and some after four days of alcohol and three days of withdrawal.

“This study shows significant damage in the olfactory bulb after just 2 days of heavy drinking,” said Crews, “which is a short period of time relative to the decades of drinking that alcoholics do, and may be an important early process in the progression from experimentation with alcohol to addiction. In addition, the major current hypothesis regarding alcohol-induced brain damage suggests that damage occurs during withdrawal. All of these studies, however, were done in vitro (in an artificial environment). Our findings, which are in vivo (in the living body), indicate that alcohol-induced brain damage occurs during intoxication.”

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THE BRAIN RISKS OF BINGE DRINKING

“In the rat,” explained Michael A. Collins, professor of biochemistry at Loyola University Chicago, “which on one level is a ‘walking nose,’ the overall damage to the olfactory pathway is quite significant. The olfactory neurons in the bulb are some of the few neurons that are always turning over, dying and regenerating. One guess is that the repetitively elevated alcohol levels are pushing more of these neurons ‘over the edge,’ but apparently in a necrotic fashion.”

Collins said that drinking patterns may specify the nature of neuropathology that occurs and the brain regions and neurons where it occurs. “The short-term binge pattern in these studies,” he said, “which affords periodically high blood and brain alcohol levels, seems to damage the olfactory cortical regions quite selectively. In other models in which lower alcohol levels are sustained for several months – more akin to the primary type of alcohol abuse in countries like France and Spain – rodents show significant loss of brain neurons in regions evidently not affected in the brief binge-drinking model used here, for example, the cerebellum and the frontal cortex.”

Collins added that even though chronic alcohol abuse damages all organs to greater or lesser degrees, most attention has been paid to liver damage, largely because it is easier for doctors to detect and measure, and can eventually lead to liver-failure death. However, he added, “a study of relatively young alcoholics published some time ago in the British journal *Lancet* showed that indicators of relatively permanent cognitive damage, measured by neuropsychological tests, actually showed up earlier than clinical signs of liver damage. Sadly, when the brain – the limbic cortex and dentate gyrus of the hippocampus, in this case – loses its excitable cells, for all practical purposes they are gone for good. In the day-to-day life of an alcoholic, this means a decreased ability to learn, to recall, to make decisions, and perhaps to sense and appreciate life in its fullest.”

According to some estimates, said Collins, alcohol abuse in the United States is perhaps the third or fourth most common cause of brain damage, and may be even higher in other countries. “Given this,” he said, “it is surprising that the mechanisms of brain neuronal degeneration due to a widely abused neurotoxicant are so understudied and therefore still somewhat obscure. Certainly this has implications for a college student contemplating a weekend of binge drinking. Seriously, though, it is possible that neuronal degeneration after a couple of days of heavy intoxication in the rat might translate to the human drinker who is not even a chronic alcohol abuser. There is no firm proof of this at present, and we would need brain imaging to determine whether acute short-term binge drinking in people could be permanently deleterious to olfactory or other neurons.”



Article is based on the following published research:

Obernier, J.A.,
Bouldin, T.W.,
& Crews, F.T.
(April 2002).
Binge ethanol
exposure in adult
rats causes necrotic
cell death.
*Alcoholism: Clinical
and Experimental
Research*,
26(4).



ABSTINENCE MAY MAKE THE BRAIN GROW STRONGER

- *Chronic alcohol abuse leads to structural brain damage.*
- *The damage includes loss of gray matter in the cortex and loss of white matter throughout the brain.*
- *The greatest tissue loss occurs in the frontal lobe and cerebellum.*
- *Prolonged abstinence from alcohol appears to allow some reversal of structural brain damage.*

Substantial research has demonstrated that chronic alcohol abuse leads to structural brain damage, especially to white matter, and primarily in the frontal lobes and cerebellum. Researchers have wanted to know for quite some time to what extent these effects may be reversible with abstinence from alcohol. A study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* uses quantitative neuroimaging to reveal that prolonged abstinence may lead to partial reversal of structural brain damage, which suggests that brain function can improve with abstinence.

“We wanted to know if abstinence from alcohol reverses the kind of structural and metabolic abnormalities that have been demonstrated by previous studies,” said Dieter J. Meyerhoff, associate professor of radiology at the University of California - San Francisco School of Medicine and lead author of the study. “We also wanted to know in what specific brain regions and tissue types (gray or white matter) damage would be reversed with prolonged abstinence.”

Meyerhoff and his colleagues compared two groups. One group comprised alcoholics (with an average age of 46 years) who had already undergone treatment for their alcoholism and had been abstinent for an average of two years at the time of study. The second group comprised individuals who were heavy drinkers at the time of study and had never been treated for their drinking. The current drinkers were matched in drinking severity (average monthly alcohol use over lifetime and duration of alcohol use) to the prior drinking patterns of the abstinent alcoholics. A healthy control group was not included because the study’s intent was to measure the effects of abstinence from chronic drinking on alcohol-induced injury. All participants underwent magnetic resonance imaging (MRI) and proton magnetic resonance (MR) spectroscopic imaging of the brain.

“These are non-invasive methods,” explained Meyerhoff, “which allow taking a ‘snapshot’ of the structural and metabolic integrity of all parts of the brain. As opposed to computed tomography scans, MRI can distinguish between gray and white matter tissue, which is important when we want to talk about the functional significance of brain damage in alcoholism. In addition, we used a localization approach that allowed us to investigate structural and metabolic brain changes in relatively small, yet anatomically well-defined brain regions.”

They found that the abstinent alcoholics had a greater volume of white matter in their frontal lobes than currently heavy drinkers did, but not in other parts of the brain. White matter

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BSTINENCE MAY MAKE THE BRAIN GROW STRONGER

volume was greatest in those alcoholics who had been abstinent for the longest time. In addition, the amount of white matter lesions in the abstinent alcoholics was smaller than in the current drinkers in most of the brain regions investigated. Finally, the volume of gray matter in the abstinent alcoholics was greater in some but not all regions of the frontal lobes.

“These results suggest reversal of structural abnormalities in some brain regions of abstinent alcoholics,” said Meyerhoff, “and persistent structural damage in other brain regions. We still need to learn, however, what this means for the individual’s brain function.”

“We know that alcohol abuse can cause extensive damage to the brain,” said Edith Sullivan, associate professor of psychiatry at Stanford University School of Medicine. “This can include volume deficits in cortical gray matter, which are neural cell bodies, as well as in white matter, which are the fibers that are extensions of the cell bodies and that connect cells. The regions most clearly affected are the frontal lobes. Additional brain structures affected are the corpus callosum (the large band of white matter fibers that connect the two cerebral hemispheres), the anterior aspect of the hippocampus and the mammillary bodies (brain structures that engage in consolidation of new memories) and the cerebellum (the ‘little brain’ that is critical to postural stability, motor timing and motor learning as well as certain components of cognitive functioning). The UCSF study suggests that the recovering alcoholic group, despite their older age, can experience a significant reversal of white matter abnormality with prolonged abstinence.”

Sullivan said that future research needs to focus on longitudinal studies, using different modalities of brain imaging that follow alcoholics from early detoxification through periods of sobriety and relapse. She added that these studies need to take into account nutritional factors, withdrawal symptoms and functional outcomes in alcoholic men and women of all ages.

This is in fact what Meyerhoff and his colleagues have in the works: longitudinal studies of alcoholics who undergo treatment for their drinking problem. “These studies are ongoing and include structural and metabolic MR studies integrated with careful assessment of neuropsychological functioning. Both abstainers and relapsers are examined to assess postulated improvement with abstinence and postulated status quo or further deterioration with relapse.” Although more data have yet to be collected and analyzed, said Meyerhoff, “it appears that even after many years of heavy drinking, the brain has the capacity to repair at least some of the structural damage that has occurred.”

Article is based on the following published research:

O’Neill, J.,
Cardenas, V.A.,
& Meyerhoff, D.J.
(November 2001).
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imaging in chronic
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*Alcoholism: Clinical
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25(11), 1673-1682.





C **OGNITIVE NEUROSCIENCE TAKES ON ALCOHOL**

- *Alcohol is known to impair an individual's ability to control his/her behavior.*
- *Impaired behavioral control is known to be a factor in accidents, antisocial acts and binge drinking.*
- *Psychologists are jointly investigating the effects of alcohol on brain activity that is associated with behavioral control.*
- *Findings show that specific cognitive processes, certain individual characteristics, and some environmental conditions can all influence alcohol's effects on behavioral control.*

A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines how alcohol – through its effects on underlying cognitive processes – may effect someone's self-control in different ways.

“Drinkers can sometimes display foolish, inappropriate or harmful behavior that they would not exhibit when sober,” said Muriel Vogel-Sprott, professor of psychology at the University of Waterloo and first author of the paper. “This is commonly attributed to the effects of alcohol, for example, explaining away the behavior by saying ‘I couldn't stop myself’ or ‘I didn't mean it.’” Vogel-Sprott's paper was based on research presented at a symposium during the June 2000 Research Society on Alcoholism meeting in Denver. Researchers tested the effects of a moderate dose of alcohol (approximately two or three beers) on social drinkers' performance of a task. The objective was to assess specific cognitive processes that govern behavior.

“Some of the presentations showed that alcohol could diminish cognitive control of response inhibition,” said Vogel-Sprott, “and that vulnerability to this disinhibition varied among individuals. In addition, there are some personal attributes – such as impulsivity, symptoms of attention deficit disorder, and the capacity to keep in mind the relevant information needed to guide behavior – that are related to poorer inhibition under alcohol. Yet other research used event-related functional magnetic resonance imaging (MRIs or brain scans) to identify those brain areas and networks that are activated when cognitive inhibitory tasks are performed. This work showed that both successful and unsuccessful inhibition of behavior is distinguishable by different brain activity and, furthermore, these effects are altered by alcohol.”

Vogel-Sprott's own research examined intentional control of behavior, assessing the degree to which conscious (intentional) and unconscious (automatic) cognitive processes influence performance. She found that a moderate dose of alcohol selectively diminished intentional control when social drinkers' behavior had no environmental consequence. However, when performance under alcohol had some ‘payoff’ (for example, money or verbal approval), intentional control was well retained.

“Was the behavior due to alcohol,” mused Vogel-Sprott, “or was it intentional? This question is controversial, particularly in the courts, where the intentionality of an alcohol-related offence can affect the sentence. The research presented in this symposium indicates that the answer is

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OGNITIVE NEUROSCIENCE TAKES ON ALCOHOL

complex. On one hand, it appears that alcohol can impair cognitive processes controlling inhibition and intentional behavior. But, on the other hand, the intensity of impairment may also depend upon the characteristics of the drinker and the consequences of behavior in the drinking situation.”

Mark Fillmore, assistant professor of psychology at the University of Kentucky, was another of the presenters during the symposium. His research examined how a drug such as alcohol can disturb a person’s ability to control behavior. His findings showed that alcohol-induced impairment of inhibitory control appears to have some commonalities with Attention Deficit Hyperactivity Disorder (ADHD).

“It seems that alcohol reduces the ability to stop some actions,” he said. “This is important because we all have to sometimes stop what we are doing to reflect and plan more appropriate actions. Impulsiveness can lead to a host of problems in school, work and with peer relations. My work discovered that low to moderate doses of alcohol impair the ability to stop actions much in the same way that individuals with ADHD have difficulty stopping inappropriate actions, such as throwing a punch. The effects of alcohol are short-lived, lasting only about an hour or so. But these observations suggest that alcohol can produce a temporary mental state in some individuals that resembles impulsiveness, and perhaps, ADHD-like symptoms.”

Fillmore’s work also found that stimulant drugs can block the impairing effects of alcohol so that the ability to stop actions while under the influence of alcohol is improved. This is similar to findings that stimulant drugs (such as Ritalin) can increase the ability to stop behaviors in individuals with ADHD.

“The fact that both ADHD and acute doses of alcohol can impair the ability to withhold inappropriate behavior,” he said, “raises the possibility that people with ADHD might suffer greater impairment from alcohol. The major challenge for alcohol researchers has been to figure out why some people develop problems, while others do not. The ability to identify a pre-existing trait (such as ADHD) among some individuals that contributes to alcohol problems is a very important development.”

The varied yet interconnected research presented at the symposium demonstrates how scientists using research tools from cognitive science and neuropsychology are working together to study how alcohol impairs behavioral control. “We didn’t find an easy answer,” said Vogel-Sprott, “but we have a better ‘big picture’ understanding of how alcohol impairs behavior.”

Article is based on the following published research:

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*Alcoholism: Clinical
and Experimental
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25(1), 83-88.



JUST A SPOONFUL OF THIAMIN?

- *Two neurological disorders are linked through thiamin deficiency.*
- *One disorder can be treated with thiamin supplements; the other may be incurable.*
- *Heavy drinkers, anorexics and senior citizens are considered at risk.*
- *Up to 10 percent of alcoholics in the U.S. may be affected.*
- *Australian cases decreasing, but thiamin may yet be added to beer.*

Something as simple as thiamin (vitamin B1) may help, or hinder, your brain's capacity to function and perhaps even survive. Alcoholics, anorexics and senior citizens may be especially vulnerable, according to recent studies of two neurological disorders called Wernicke's Encephalopathy (WE) and Korsakoff's Syndrome (KS). The two studies, published in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)*, jointly found that mammillary bodies in the brain may shrink as cognition and memory decrease.

"These findings are significant because they point toward the importance of nutritional factors in the condition of the brain," said Edith Sullivan, associate professor of psychiatry at Stanford University School of Medicine and lead author of one of the studies. Sullivan based her study on *in vivo*, or living patients.

WE is a potentially fatal disorder caused by thiamin deficiency. WE usually occurs in people who have been drinking heavily and not eating, but can also occur after persistent vomiting or during hunger strikes. Recent studies have shown that young women suffering from anorexia nervosa may also develop WE due to severe nutritional deficiencies. Of increasing concern is the potentially large number of senior citizens who may be apathetic about the quality of their diet, may not be eating enough, or may forget to eat altogether. Heavy drinkers are those known to be most affected by WE.

"Brain damage as a result of alcohol consumption is probably the second most common cause of dementia in the United States, behind Alzheimer's Disease," said Dr. Peter Martin of the Vanderbilt University School of Medicine. Heavy drinkers often eat improperly. Furthermore, alcohol impedes the digestive tract's normal absorption of those few nutrients that may be consumed. Nerve, muscle and brain tissue are extremely sensitive to low levels of vitamins, nutrients and minerals, and can begin to deteriorate when deprived. Body stores of thiamin can be depleted within about three weeks.

WE is characterized by double vision, mental confusion, muscle weakness and unsteady gait. Unlike other disease states caused by alcohol, WE may reverse through rapid treatment with thiamin. If left untreated, however, the person can go into a coma and die. In some cases, even if treated, they can develop permanent memory damage in the form of KS.

KS is often associated with a previous episode of WE, but is distinguished by amnesia. KS is often recognized when the confusion associated with WE clears following thiamin treatment.

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JUST A SPOONFUL OF THIAMIN?

Although KS may sometimes respond to thiamin treatment, it is often permanent. Researchers agree that the nutritional deficiencies caused by heavy drinking can lead to WE, and if not treated, eventually KS.

Exact numbers of those afflicted are difficult to find but Martin speculated that at least 10 percent of alcoholics have some degree of the two syndromes. Even though most alcoholics do not have the characteristics of an “extreme stage of brain damage” such as Wernicke’s or Korsakoff’s, “70 percent of alcoholics have some sort of brain damage,” he said. “At one point I calculated that there were about 10 million people in the U.S. who may have some sign of brain damage related to alcohol,” he said.

In Australia, the two disorders are often referred to jointly as Wernicke-Korsakoff Syndrome (WKS), according to Clive Harper, professor of neuropathology at the University of Sydney and Royal Prince Alfred Hospital and lead author of the second study. During the 1980s, Australia had the ignoble distinction of having the highest recorded rates of WE in the world, mostly among the alcoholic population, as well as large numbers of people needing long-term care because of KS. Harper estimated the former at 500 cases per year, the latter at 2,000 per year.

The problem was considered so acute that in 1991, the Australian government mandated that bread flour be enriched with thiamin. This same requirement has been mandatory for a number of years in the United Kingdom, Canada and Denmark. In the U.S., most bread flour is enriched, but enrichment is not mandatory. Since the 1991 enrichment of bread flour in Australia, WKS rates have significantly decreased but remain higher than those in most other Western countries – enough to prompt discussion of thiamin supplementation of alcoholic beverages, primarily beer (the preferred beverage of many WE patients).

Harper said that “WE diagnosis is probably missed about 80 percent of the time worldwide. About one in every hundred people who have a coroner’s autopsy are found to have WE, even though it is very easy to treat, because the diagnosis can easily be missed.” People suffering from WE or KS or WKS, whatever name you prefer, he said, clearly make up “a big hidden group throughout the world that needs further study.”



Article is based on the following published research:

Sheedy, D., Lara, A., Garrick, T., & Harper, C. (October 1999).

Size of mamillary bodies in health and disease: Useful measurements in neuroradiological diagnosis of Wernicke’s encephalopathy.

Alcoholism: Clinical and Experimental Research, 23(12), 1624.

Sullivan, E.V., Lane, B., Deshmukh, A., Rosenbloom, M.J., Desmond, J.E., Lim, K.O., & Pfefferbaum, A. (October 1999).

In vivo mammillary body volume deficits in amnesic and nonamnesic alcoholics.

Alcoholism: Clinical and Experimental Research, 23(12), 1629.

A LCOHOL AND THIAMIN DEFICIENCY TOGETHER: A DANGEROUS COMBINATION?

- *Heavy alcohol use is associated with thiamin (Vitamin B1) deficiency.*
- *Alcohol and thiamin deficiency together may have a more damaging impact on the brain.*
- *Learning and reference memory appear to be the most sensitive to their synergistic effects.*
- *The role of thiamin supplementation is examined.*

Researchers and clinicians know that chronic abuse of alcohol may lead to a deficiency in thiamin (also known as Vitamin B1). This deficiency can wreak havoc on the brain, causing a wide spectrum of deficits in cognition, behavior and motor coordination. What researchers now suspect, as noted in a recent study in *Alcoholism: Clinical and Experimental Research (ACER)*, is that chronic alcohol consumption and thiamin deficiency combined may have a synergistic and even more devastating effect on the brain and mental capacities.

“We were looking for an interaction between ethanol and thiamin deficiency,” explained Philip Langlais, professor of psychology at San Diego State University, professor of neurosciences at the University of California - San Diego, and lead author of the study. “We wanted to see if you took thiamin deficiency and combined it with chronic alcohol intake, would you then create a situation that would produce a more severe impairment of cognition and memory than you would with either thiamin deficiency alone, or exposure to chronic alcohol ingestion alone.”

Using rat subjects, they did indeed find a synergistic effect, sometimes. Learning (for example, figuring out the rules of chess) and reference memory (remembering and consistently applying the rules) appeared the most sensitive to the damaging, synergistic effects of alcohol and thiamin deficiency. Short-term working memory (incorporating the rules of chess into game strategies), on the other hand, was most affected by alcohol alone. Neurological symptoms were most associated with thiamin deficiency.

Alcohol impedes the digestive tract from absorbing needed nutrients. Nerve, muscle and brain tissue are exquisitely sensitive to low levels of vitamins, nutrients and minerals such as thiamin, magnesium, potassium and phosphorus. When nutrients disappear, tissues slowly deteriorate.

Thiamin deficiency contributes to two clinical conditions along the alcoholic’s path toward dementia. The first ‘phase’ is called Wernicke’s Encephalopathy (WE), in which people become extremely confused, develop abnormal eye movements, experience muscle weakness, and demonstrate gait disturbances. The second phase is called Wernicke-Korsakoff Syndrome (WKS). It is associated with a more severe amnesia and significant cognitive and reasoning impairments. The first two conditions may respond to, and possibly be reversed by, thiamin treatment. The final and – for all practical purposes, untreatable – phase is dementia.

“This study significantly adds to the database in at least one respect,” said David V. Gauvin, psychopharmacologist and drug science specialist at the Drug Enforcement Administration.

continued ~

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LCOHOL AND THIAMIN DEFICIENCY TOGETHER: A DANGEROUS COMBINATION?

“It shows that there are unique interactions between alcohol and thiamin deficiency. We don’t see that one plus one equals two; rather, one plus one equals three.” Gauvin said that he would add a third component to the damaging equation: thiamin supplementation.

“This unique synergism is not just about alcohol and thiamin deficiency,” he said, “it’s also about thiamin supplementation, and the whole issue of mega-dosing.” Gauvin mentioned a study in which he participated where researchers found that thiamin injections made the recipients even more sensitive to the effects of alcohol. He is concerned that the standard practice of giving alcoholics thiamin injections, in order to counteract the progression to symptoms of WE and WKS, may be more detrimental than helpful.

“When you have a surplus of thiamin,” he explained, “you have the capacity to induce magnesium deficiencies, which have been linked to a number of alcohol’s negative effects.” He conjectured that thiamin-induced magnesium deficiency could be the root cause of a new sensitization to alcohol’s effects.

Another way of counteracting thiamin deficiency – most often linked to poor nutrition among alcoholics, anorexics and senior citizens – is food supplementation. Both Langlais and Gauvin noted the Australia example (see *Just a Spoonful of Thiamin?* article).

“When we gave our animals regular food that contained thiamin, they did not develop sensitization to alcohol,” said Gauvin. “The body can naturally absorb and process low-graded doses of thiamin in the gut and the liver. It’s the whopping injections that are problematic. Gauvin is less comfortable with the proposition of supplementing alcohol with thiamin. “If you supplement alcohol with mega-doses of Vitamin B, what you may actually be doing is inducing magnesium deficiencies.”

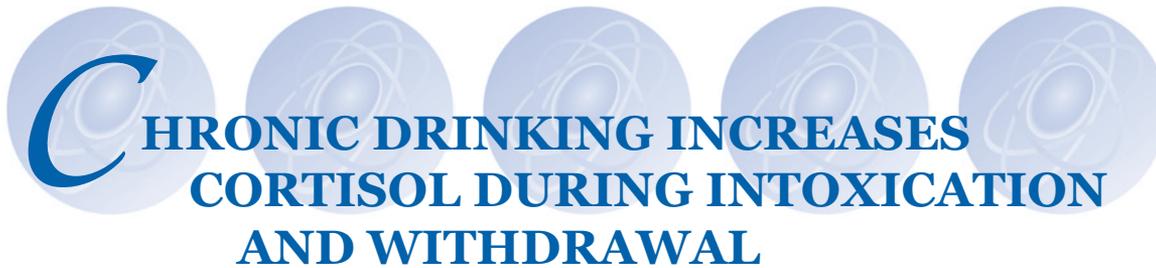
Conversely, Langlais believes that we nonetheless need to “re-examine the issue of fortifying alcoholic beverages and perhaps other foods. We also need to seriously think about educating alcoholics with respect to their diet and nutrition.”

Gauvin had one final caution. “What does this say about vitamin supplementation? We have such a benign feeling about vitamins, that we can mega-dose all we want to. Yet there is a physiological result from the overuse or abuse of vitamins. The bowel and the whole digestive system have been developed in such a way to allow for a very unique interaction between food and our needs. Yet bigger is not better, more is not better.”

Article is based on the following published research:

Ciccia, R.M.,
& Langlais, P.J.
(May 2000).
An examination
of the synergistic
interaction of ethanol
and thiamin
deficiency in the
development of
neurological signs
and long-term
cognitive and memory
impairments.
*Alcoholism: Clinical
and Experimental
Research*,
24(5), 622-634.





CHRONIC DRINKING INCREASES CORTISOL DURING INTOXICATION AND WITHDRAWAL

- *Cortisol, a “stress hormone,” plays an important role in the regulation of emotion, cognition, reward, immune functioning and energy utilization.*
- *New research has found that long-term chronic drinking produces an increase in cortisol both during intoxication and withdrawal.*
- *Cortisol appears to increase significantly during the progression from chronic intoxication to withdrawal.*
- *Health implications may include sleep disruption, cognitive deficits, diabetes and mood disturbances.*

Cortisol, known as a “stress hormone,” plays an important role in the regulation of emotion, cognition, reward, immune functioning and energy utilization. A study published in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that long-term chronic drinking produces an increase in cortisol both during intoxication and withdrawal.

“It has not been known whether the body adapts to the stress of drinking following daily heavy drinking in the non-laboratory setting, or whether cortisol levels continue to be elevated even after several weeks or months of drinking,” said Bryon Adinoff, distinguished professor in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas, medical director of the Substance Abuse Team at the Veterans Affairs North Texas Health Care System in Dallas, and first author of the study. “In this study, we show that even persons drinking for several months continue to show elevated levels of cortisol. In addition, levels of cortisol increase even further when the drinking stops. This increase occurs even before alcohol is gone from the body. The daily, heavy drinker may therefore have levels of cortisol two to three times the normal amount throughout the day and night.”

Cortisol is the primary glucocorticoid in humans. Glucocorticoids are produced by the adrenal glands, two thumb-size organs that lie behind both kidneys. When a body’s stress-response system is activated by stressors, usually unpredictable or fear- and/or anxiety-causing in nature, cortisol is increased. Stress-induced cortisol can focus alertness and attention, increase blood pressure, and suppress ‘less necessary’ bodily functions such as wound repair, bone growth, digestion and reproduction.

“Alcohol can increase cortisol through a variety of mechanisms,” said Adinoff. “Alcohol directly affects many brain chemicals that signal the adrenal glands to produce and secrete cortisol. High levels of intoxication may be interpreted as general ‘stress,’ which could stimulate cortisol release. Finally, after drinking a lot of alcohol for a long time, the sudden stopping of drinking can produce a stressful ‘withdrawal’ state, which can also increase cortisol production.”

CHRONIC DRINKING INCREASES CORTISOL DURING INTOXICATION AND WITHDRAWAL

For this study, researchers examined salivary cortisol levels and breath alcohol concentrations in two groups of males: 73 alcohol-dependent patients presenting themselves for treatment in an intoxicated, withdrawal, or post-withdrawal state; and 22 abstinent alcohol-dependent patients already enrolled in a residential treatment program.

“The usual method of obtaining cortisol levels is by obtaining a blood sample,” said Adinoff. “However, it is much easier for both the patient and researcher to obtain a sample of saliva rather than a blood sample ... and less painful for the patient.”

Salivary cortisol is also a better measure of active cortisol. When cortisol is in the blood, it is in two forms, “bound” and “unbound.” Bound cortisol is not active because it is attached to a protein. Only the unbound, or free, cortisol is physiologically active. Most of the cortisol in blood is bound. Conversely, all of the cortisol in saliva is unbound, free or active. Therefore, saliva measures of cortisol give a better picture of how much active cortisol is in the body.

Study authors found that cortisol concentrations in alcohol-dependent individuals increase during both intoxication and withdrawal, compared to abstinence. Of the 73 alcohol-dependent patients presenting themselves for treatment, 38 were intoxicated. These 38 individuals, as well as 30 non-intoxicated individuals going through acute alcohol withdrawal, had significantly increased salivary cortisol concentrations when compared to abstinent individuals. Furthermore, cortisol concentrations increased during the progression from intoxication to withdrawal.

“Up until now, it has not been known whether cortisol remains elevated in chronic drinkers not in a laboratory setting,” said Adinoff. “The confirmation that cortisol does, indeed, remain elevated throughout the drinking cycle suggests that it may be important to decrease cortisol levels during both chronic drinking and withdrawal. This suggestion is tentative, however, as it has not yet been shown that it is cortisol itself that is responsible for the medical and psychiatric problems associated with heavy drinking. Future studies should explore the relationship between elevated levels of cortisol during intoxication and withdrawal and the medical and psychiatric consequences of drinking, which may include sleep disruption, cognitive deficits, diabetes and mood disturbances.”



Article is based on the following published research:

Adinoff, B.,
Ruether, K., Krebaum, S.,
Iranmanesh, A.,
Williams, M.J.
(September 2003).
Increased salivary
cortisol concentrations
during chronic alcohol
intoxication in a
naturalistic clinical
sample of men.
*Alcoholism: Clinical
and Experimental
Research*,
27(9), 1420-1428.



REPEATED ALCOHOL DETOXIFICATIONS CAN IMPAIR COGNITIVE FUNCTION

- *Patients undergoing alcohol detoxification are more likely to have seizures if they have had previous episodes of detoxification.*
- *New research confirms that repeated detoxifications can also impair cognitive function through damage to the frontal lobes.*
- *Patients with mild to moderate alcoholism who have had two or more withdrawals performed worse on maze, vigilance and delay tasks.*

Researchers and clinicians know that patients undergoing alcohol detoxification are more likely to experience seizures if they have undergone previous episodes of detoxification. Prior research has also indicated that multiple withdrawals may lead to changes in brain functioning. A study in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* confirms previous findings of neurocognitive changes in alcoholics, extends those findings to individuals with mild to moderate alcoholism, and demonstrates a relationship of those changes to multiple withdrawals.

“Results from this study support previous findings of impaired frontal-lobe function in alcoholics,” said Theodora Duka, associate professor at the University of Sussex and first author of the study. “Our study adds to that by showing that such impairments can be found also in non-severe alcoholics. But its major contribution to the field is that the number of detoxifications that patients experience contributes significantly to these impairments.”

“Some clinicians tend to ignore the issue of multiple withdrawals, whereas other clinicians feel they’re important, having come to realize that patients who have had multiple withdrawals are much more likely to have more severe withdrawal subsequently, and probably not respond as well to medication to block the withdrawal symptoms,” said Robert Malcolm, professor of psychiatry, family medicine and pediatrics, and clinical investigator at the Center for Drug and Alcohol Programs, Medical University of South Carolina. “This study squarely points out the relevance of multiple withdrawals by demonstrating some alterations in neurocognitive functioning in this group of people.”

Study authors examined 85 volunteers divided into two groups: 42 abstinent alcoholics (24 males, 18 females) in inpatient treatment, and 43 social drinkers (23 males, 20 females) recruited from a university setting. The patient population was further divided into two populations based on information about prior, medically supervised detoxifications: patients with fewer than two experiences (n=36) and patients with two or more experiences (n=6). All of the subjects were asked to complete four types of tasks designed to measure executive function, which is responsible for supervising the production and execution of responses based on demands from the environment. The four tasks included a maze, which measured the ability to follow goals; a color-naming task; a vigilance task, which measured the ability to pay attention and disinhibit a pre-potent response; and a delay task, which measured the ability to wait before a response in order to receive a reward.

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REPEATED ALCOHOL DETOXIFICATIONS CAN IMPAIR COGNITIVE FUNCTION

Results indicate that repeated withdrawals from alcohol are associated with increased impairment of cognitive function, specifically, frontal-lobe damage. “The frontal lobes are extremely important for inhibiting behaviors,” said Malcolm, “and are also important for tasks that require attention.” The results showed that patients with two or more previous, medically supervised detoxifications performed worse than patients with less than two or no withdrawal experiences in the maze, vigilance and delay tasks.

“Compared to social drinkers,” said Duka, “the alcoholics were impaired in all the tasks except for the color-naming task. The age that patients started drinking, and the amount of alcohol they used to drink up to the last six months before treatment appeared also to play a role. Only measures of the delay task, the ability to wait before a response in order to receive a reward, appeared to depend solely on the number of detoxifications.”

These findings pertain to “mild to moderate alcoholics, not severe alcoholics. These were generally functioning people who, if they were seen in a clinician’s office, would not appear to be cognitively impaired, but yet they are,” added Malcolm.

“Another interesting finding of Dr. Duka’s is an association between multiple withdrawals and higher levels of nicotine or cigarette smoking,” said Malcolm, “which I think is a fascinating phenomenon and needs to be followed up on.”

Duka said her findings have implications not only for individuals who have experienced multiple withdrawals from alcohol, but also the clinician who treats them. “These individuals might be more difficult to treat,” she said. “When they are being helped to detoxify from alcohol, they may need extra support to prevent them from relapsing. It might even be sensible to wait a while before starting detox, if it helps to get the post-detox support organized.”

“The truth of the matter,” said Malcolm, “is that researchers really know very little about the effects of multiple withdrawals on cognitive function. This paper points out the relevance of clinicians asking patients about past withdrawals, the number of them, and how severe they were. Hopefully, it may influence clinicians to do further cognitive testing in order to get a sense of their patients’ capabilities for rehabilitation and present and future functioning. In other words, these findings represent a clue that some patients who have had multiple withdrawals might be impaired and might have trouble with their work and in their personal lives because of their impaired thinking processes.”

Article is based on the following published research:

Duka, T.,
Townshend, J.M.,
Collier, K.,
Stephens, D.N.
(October 2003).
Impairment in
cognitive functions
after multiple
detoxifications in
alcoholic inpatients.
*Alcoholism: Clinical
and Experimental
Research*,
27(10), 1563-1573.





BLOCKING SELECTED NEUROTRANSMITTER ACTIVITY MAY DECREASE ALCOHOL CONSUMPTION

- *Neuropeptide Y (NPY) is a neurotransmitter that is integral to neurobiological functions such as anxiety, pain, memory and feeding behaviors.*
- *Researchers have found that a compound which blocks NPY activity decreases both the onset as well as the repetition of alcohol consumption.*
- *These findings have important implications for the treatment of both alcohol abuse and dependence.*

Peptides are a class of neurotransmitters, chemicals used by brain cells to communicate with each other. Neuropeptide Y (NPY) is the most abundant and widely distributed peptide, and is involved in a variety of neurobiological functions including anxiety, pain, memory and feeding behavior. Although previous animal research has implicated NPY systems in alcohol abuse and alcoholism, findings published in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* are the first to show that a compound that blocks NPY activity may be useful for alcohol treatment.

“NPY is the most potent stimulant of feeding behavior known,” explained Clyde W. Hodge, associate professor in the departments of psychiatry and pharmacology at the University of North Carolina at Chapel Hill and corresponding author for the study. “For example, the primary brain region involved in control of eating is the hypothalamus. Animal studies have shown that repeated treatment of the hypothalamus with NPY produces dietary obesity in otherwise normal rats. We suspect that alcohol may usurp brain systems that evolved to perform other functions, such as eating, because these neural systems evolved long before humans discovered alcoholic beverages. Alcohol and drug abuse, therefore, can be considered disorders of consumption.”

“Since NPY is a signal molecule, it produces its effects via several NPY receptors in the brain, such as the NPY-Y5 receptors,” added Subhash C. Pandey, associate professor and director of Neuroscience Alcoholism Research in the Department of Psychiatry at the University of Illinois at Chicago. “This research suggests that alcohol-preferring mice may have higher levels of NPY-Y5 receptors in the brain. Other research suggests that these mice have lower NPY levels in the brain area involved in reward of alcohol drinking. It is also possible that both lower NPY levels and higher NPY-Y5 receptors in the brain may be associated with the excessive alcohol drinking behaviors of these mice.”

This study uses alcohol-preferring mice called C57BL/6 to examine the effects of the NPY-Y5 receptor antagonist L-152,804 on the onset and maintenance of alcohol self-administration. “Most of the known compounds that target NPY receptors do not cross the blood-brain barrier,” said Hodge. “L-152,804, however, is a novel compound that was recently shown to both cross the blood-brain barrier and block NPY-Y5 receptors.”

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BLOCKING SELECTED NEUROTRANSMITTER ACTIVITY MAY DECREASE ALCOHOL CONSUMPTION

Researchers housed 59 male C57BL/6 mice in standard Plexiglass cages (four per cage) with food and water always available. Mice were trained to self-administer either alcohol (10% v/v) or water during 16-hour sessions. After four months, the mice were injected systemically with L-152,804 (0, 10, 30 or 60 mg/kg) prior to the sessions.

Results indicate that not only does L-152,804 delay the onset of alcohol self-administration, which is considered an index of relapse potential, but it also seems to reduce the reinforcing or rewarding effects of alcohol.

“The process by which drug self-administration behavior becomes repetitive is called positive reinforcement,” said Hodge. “It reflects the tendency of all animals, human and non-human, to repeat responses that produce a desired outcome. In general, this process functions to sustain behavior that is essential to the individual or species, such as eating, drinking or reproduction. In this particular case, L-152,804 appeared to block the reinforcing effects of alcohol. When taken together, these results suggest that L-152,804 might reduce the motivation to start drinking as well as decrease the amount of alcohol consumed. Thus, L-152,804 might make relapse less likely and possibly dampen its consequences.

Both Hodge and Pandey said these results have clear implications for the medical management of alcohol abuse and alcoholism. “If these studies are replicable and consistently produce findings that alcohol preference and dependence are associated with increased NPY-Y5 receptors in the brain,” said Pandey, “then blocking these receptors with L-152,804 may be useful in treating alcoholism. Furthermore, since this receptor antagonist is able to delay the onset of alcohol-drinking behaviors in alcohol-preferring mice, it also has potential in preventing relapse to alcohol abuse.”

“Approved medications for alcoholism such as Naltrexone,” added Hodge, “may help prevent relapse but do not decrease drinking by chronic alcoholics who are actively drinking. L-152,804 has the potential to both prevent relapse and decrease active drinking. When you also consider the fact that L-152,804 can be administered orally, we believe that medications that block NPY actions at its receptors have great potential for the medical management of alcoholism.”



Article is based on the following published research:

Schroeder, J.P., Iller, K.A., Hodge, C.W. (December 2003). Neuropeptide-Y Y5 receptors modulate the onset and maintenance of operant ethanol self-administration. *Alcoholism: Clinical and Experimental Research*, 27(12), 1912-1921.



PROBING THE ROLE OF THE DELTA OPIOID RECEPTOR IN ALCOHOL CONSUMPTION

- *The body's endogenous opioid system has three classes of opioid receptors: mu, delta and kappa.*
- *Previous research showed that mice lacking the mu opioid receptor do not drink alcohol.*
- *A new study shows that mice lacking the delta opioid receptor drink more alcohol.*
- *The delta opioid receptor may also play a mediating role between stress and alcohol consumption.*

The body's endogenous opioid system has traditionally been linked with peptides such as enkephalins and endorphins, which influence the brain's reward pathway to act as the body's natural response to pain. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that the endogenous opioid system may also be important for the reinforcing properties of alcohol. Researchers discovered that "knocking out" the delta opioid receptor led to an increased state of anxiety as well as an increase in drinking.

"There are three classes of opioid receptor currently recognized," said Amanda Roberts, assistant professor of neuropharmacology at The Scripps Research Institute and lead author of the study. "They are the mu, delta and kappa receptors. We had previously shown that mice lacking the mu opioid receptor do not drink alcohol under several different experimental conditions." For the current study, Roberts and her colleagues used mice produced by co-author Brigitte L. Kieffer in France that had been genetically modified by having their delta receptor "knocked out."

"After becoming familiar with alcohol, mice lacking the delta receptor consumed more alcohol than their genetically intact counterparts (wild type mice) did," said Roberts, "suggesting that a decrease in delta receptor activity is associated with an increase in alcohol drinking behavior. This is a surprising finding as it suggests that, at least under certain conditions, the mu and delta receptors may act in an opposing manner to regulate alcohol consumption."

In addition to the endogenous opioid system's influence on the brain's reward pathway, it also plays an important role in the body's stress response. Alcohol researchers believe that stress and anxiety are important components of alcohol consumption. In fact, stress reduction is one of the most commonly reported psychosocial benefits of drinking alcohol. Another finding of Roberts' study supports a potential link among the endogenous opioid system, stress and alcohol consumption. The delta receptor knockout (KO) mice in this experiment exhibited increased anxiety prior to drinking and, in fact, seemed to use alcohol for its anxiolytic or calming effects.

"This suggests that the delta receptor," said Roberts, "while perhaps being important in directly modulating the activity of the brain's reward pathway, also may be a key player in mediating the link between stress and alcohol consumption."

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ROBING THE ROLE OF THE DELTA OPIOID RECEPTOR IN ALCOHOL CONSUMPTION

According to Tamara Phillips, professor of behavioral neuroscience at Oregon Health & Science University and the Portland VA Medical Center, the study's findings also have ramifications for those alcoholism treatment strategies that utilize opiate antagonists. Opiates are drugs derived from opium – like heroin and morphine – that act like chemicals the brain produces naturally, called endogenous (from within) opioids, which stimulate pleasurable feelings and suppress pain. Medications known as opiate antagonists bind with the brain's receptors for endogenous opioids, thus blocking the desired effects of heroin and similar drugs while having no effect themselves. Although alcohol is not an opiate-like substance, opiate antagonists like Naltrexone seem to block some of alcohol's rewarding effects.

“Drugs of abuse like alcohol,” explained Phillips, “appear to activate some of the same brain neurochemical pathways as those activated by natural rewards such as food, water, sweets and sex. A key neurochemical is dopamine. Dopamine pathways play a well-documented role in alcohol reward and reinforcement. Opioids are known to moderate the activity of dopamine pathways, and it is possible that alcohol addiction is partly associated with alterations in opiate receptor-mediated processes. Animal and human studies documenting reductions in alcohol consumption by treatment with Naltrexone, an opiate receptor antagonist drug, ultimately led to its clinical utilization for the treatment of alcoholism.” Phillips added that although Naltrexone is widely used in conjunction with clinical counseling, its success has been limited.

“Because this drug influences all three of the known opioid receptor subtypes: mu, delta and kappa,” she said, “a worthwhile endeavor is to examine the specific roles that each of the opiate receptor subtypes might play in alcohol addiction. Naltrexone has a greater tendency to interact with mu than with delta and kappa opiate receptors. It is possible that its success in alcoholism treatment is associated with its relative affinities for these receptor subtypes, and that a better treatment agent could be developed. This study, for example, shows the importance of the delta receptor in influencing voluntary alcohol consumption.”

Roberts and her colleagues plan to continue with their examination of the endogenous opioid system. They will more closely examine the brain regions and pathways responsible for the role of the mu and delta opioid receptors in alcohol's rewarding effects, as well as what role(s) the endogenous opioid system may play in addiction and relapse.



Article is based on the following published research:

Roberts, A.J,
Gold, L.H., Polis, I.,
McDonald, J.S.,
Filliol, D., Kieffer, B.L.,
& Koob, G.F.
(September 2001).
Increased ethanol
self-administration in
8-opioid receptor
knockout mice.
*Alcoholism: Clinical
and Experimental
Research*,
25(9), 1249-1256.



BEHAVIORAL SENSITIZATION: A NEW PERSPECTIVE ON ALCOHOLISM

- *Alcoholics may drink because they get a “bigger bang” each time they drink.*
- *This phenomenon is known as “behavioral sensitization.”*
- *Behavioral sensitization is the opposite of tolerance; it is even known as “reverse tolerance.”*
- *A neurochemical called MK-801 may block alcohol’s sensitizing effects.*

One of the ways by which people are believed to develop alcoholism is called “behavioral sensitization” to the effects of alcohol. This is another way of saying that each time someone drinks, they may find the alcohol more rewarding. In a recent study published in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)*, researchers explained how they may have found a way to “block” the increasingly rewarding effects of alcohol.

“What we’ve tried to show in this study,” said Rosana Camarini, the study’s lead author who is conducting post-doctoral research in neurology at the University of California–San Francisco, “is that it may be possible to block behavioral sensitization to alcohol by using NMDA receptor antagonists. The specific one we studied is called MK-801.”

Alcohol’s effects on the glutamate system are of particular interest to researchers. Glutamate acts as one of the brain’s endogenous (made within the body) excitatory systems. A subtype of glutamate receptors, the n-methyl-d-aspartate (NMDA) receptor, is highly sensitive to low doses of alcohol. Evidence indicates that alcohol may interact directly with the NMDA receptor complex. Indeed, NMDA receptors may be involved in sensitization to, tolerance of, and physical dependence on a variety of drugs, including opiates, nicotine, antidepressants and alcohol. NMDA receptor antagonists – in this case, MK-801 – appear to be able to “block” some of the pleasing effects of alcohol.

“This study provides evidence,” said Clyde Hodge, assistant professor of neurology at the University of California in San Francisco, “that MK-801 blocks one of the addictive properties of alcohol, its sensitizing effects. From a perspective of therapeutics, it means that NMDA receptors could be a valid target for treatment.”

To those familiar with the concept of tolerance, the phenomenon known as behavioral sensitization is intuitively confusing. Yet many aspects of the processes that underlie the transition from initial drinking to uncontrolled drinking remain unknown and under research. For example, studies of amphetamine and cocaine have shown that with repeated and intermittent administration both behavioral and neurochemical responses are progressively enhanced. This phenomenon, behavioral sensitization, contrasts with the well-known observation that repeated, frequent or continuous drug administration can lead to many diminished responses (tolerance). Indeed, behavioral sensitization is also called “reverse tolerance.” Despite the potential confusion, behavioral sensitization may help explain how substances of abuse can become addicting.

continued ~

B

EHAVIORAL SENSITIZATION: A NEW PERSPECTIVE ON ALCOHOLISM

“We believe that people may drink more and more because of the pleasurable and euphoric effects of alcohol,” said Camarini, “and these effects increase with time. In fact, there are theories that, after time, once this phenomenon is very well established in a person, it may actually change the responses in their gene expression. That is why behavioral sensitization is difficult to reverse.”

Researchers studied the effects of alcohol by measuring locomotor activity. They measured the distance that laboratory animals traveled following alcohol ingestion. Given independently, MK-801 stimulated locomotor activity, as did alcohol. When given together, however, the two substances diminished locomotor activity. This is how researchers determined that MK-801 might block the development of behavioral sensitization to alcohol as measured by locomotor activity.

“The results are not entirely anomalous,” said Hodge. “But it is a curious finding that a drug that increases locomotor behavior, and acts like alcohol, would block the locomotor-activating effect of alcohol.” Hodge said that a similar case of this phenomenon is the use of Ritalin for treating hyperactivity in children. “Ritalin is a stimulant,” he said. “Yet it is a general finding that stimulants will decrease behavior occurring at high rates.”

Both Camarini and Hodge admit that it’s difficult to distinguish when, in the continuum of addiction development, sensitization and tolerance may develop and/or co-exist. Hodge speculated that sensitization might occur early on in an individual’s exposure to a drug like alcohol, but noted that several ethical and practical considerations would impede testing that theory. A more procurable group would be alcoholics at risk of relapse.

“Sensitization may occur in relation to recent cessation of drinking,” said Hodge. “An alcoholic who has been alcohol-free for some time may start drinking again. MK-801 could be useful, in this case, to diminish the effects of drinking.”

Camarini and Hodge affirm the need for further research in this area, both to explore how something that acts like alcohol can block alcohol’s effects, and also how this finding can be turned into a drug that can help alcoholics.

“We don’t know if MK-801 can be used in the future as a prevention tool or as a reversal of alcoholism,” said Camarini, “but we do know that it makes alcohol less appealing to someone when they drink it.”

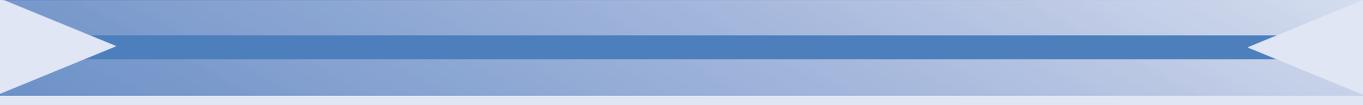


Article is based on the following published research:

Camarini, R.,
Frussa-Filho, R.,
Goldnadel-Monteiro, M.,
& Calis, H.M.
(March 2000).
MK-801 blocks the
development of
behavioral sensitization
to ethanol.
*Alcoholism: Clinical
and Experimental
Research*,
24(3), 285-290.



*Gender,
Ethnicity
& Culture*



GENDER, ETHNICITY & CULTURE

Articles in the *Gender, Ethnicity & Culture* Category

1. Women Who Drink May Be at Greater Risk of Cardiovascular Complications Than Men
2. Specifying Alcohol-Related Brain Damage in Young Women
3. African American Alcoholics: At Greater Risk for Immune Disorders?
4. Liver Cirrhosis Is No Longer a “Black” Disease
5. Ethnic Difference in DUI Arrests and Use of Health Care Services in California
6. Re-Examining Alcohol Problems Among American Indian Communities
7. The Genetic Complexities of Sensation Seeking Behavior in Alcoholic Men

WOMEN WHO DRINK MAY BE AT GREATER RISK OF CARDIOVASCULAR COMPLICATIONS THAN MEN

- *Chronic, heavy alcohol consumption can increase the prevalence of cardiovascular complications including hypertension, cardiomyopathy, arrhythmia and stroke.*
- *Some female alcoholics experience more severe cardiovascular effects from heavy drinking than male alcoholics; these effects are noted earlier and at lower consumption levels than those noted in men.*
- *Women who drink chronically may also be at risk for future cardiovascular complications.*

The cardiovascular effects of chronic, heavy alcohol consumption can include an increased prevalence of hypertension, cardiomyopathy, arrhythmia and stroke. Most of the studies to date, however, have focused on males, even though women appear to be more sensitive than men to alcohol's toxic effects on the heart. Research published in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* confirms that some female alcoholics experience more severe cardiovascular effects from heavy alcohol drinking than those observed in male alcoholics, and these effects are noted at an earlier stage of drinking and at a lower consumption level than those noted in men.

“This work adds to the growing body of literature that confirms what many researchers in the field have suspected,” said Nancy C. Bernardy, a research psychologist at the National Center for PTSD in White River Junction, Vermont. “The use of drugs, such as alcohol and nicotine, has a greater adverse impact on women than on men.” This phenomenon – where women need to drink a lesser amount of alcohol than men do, or for a shorter amount of time, to produce the same degree of damage – is referred to as “telescoping.”

“Additionally,” said Bernardy, also the first author of the study, “I think that this work adds to growing evidence that there are subtle differences in the cardiovascular systems of women in general compared to those of men. Women’s hearts are not just smaller versions of men’s. Their cardiovascular systems respond differently, and this is particularly true in response to stress and toxins like alcohol. Women need to know that they may be exposing themselves to a greater risk of heart disease than the risk noted in men by their behaviors as well as the way they handle stress.”

This study looked at 32 inpatient female alcoholics, abstinent for four weeks, and 16 female social drinkers. Researchers examined the participants’ blood pressure, heart rate, stroke volume and vascular resistance during rest and in response to two stress tests: a five-minute hand grip task, and a five-minute speech exercise. The alcoholics were then divided into subgroups according to their withdrawal blood pressures: those with transitory hypertension (tHT), occasional above-normal blood pressure that normalized after withdrawal, and those with normal blood pressure throughout withdrawal and treatment.

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WOMEN WHO DRINK MAY BE AT GREATER RISK OF CARDIO- VASCULAR COMPLICATIONS THAN MEN

“The women with tHT showed dysfunction across most of the cardiovascular measures,” said Candice Monson, assistant professor of psychiatry at Dartmouth Medical School. “The alcohol-dependent women who experienced hypertension related to detoxification also showed a protracted pattern of cardiovascular dysfunction after a period of abstinence from alcohol. This is in contrast to previous studies showing that men with tHT return to ‘normal’ resting cardiovascular functioning after a period of abstinence, and manifest cardiovascular dysfunction only when faced with an aversive stressor. Furthermore, this finding is congruent with recent studies showing that cardiovascular effects in women are more severe than in men, and emerge sooner with chronic drinking.”

Both Bernardy and Monson noted that these findings suggest that a subgroup of women may compromise, perhaps irreparably, their cardiovascular systems through chronic, heavy alcohol consumption.

“The short-term implication of this dysregulation may be evidenced as an increased risk for the development of hypertension,” said Bernardy, “with the long-term implication of an increased risk for the development of future cardiovascular disorders such as heart attacks, strokes, or cardiomyopathy.”

“This research is to be applauded for furthering our understanding of the consequences of women’s substance abuse,” said Monson. “For years, women’s alcohol use and its consequences has been sorely understudied and neglected. A one-size-fits-all, or perhaps more aptly put, a ‘male-size-fits-all’ approach has been applied to women. In fact, this study, along with other recent studies, shows that women’s alcohol use patterns and their consequences are different from men.”

Bernardy is hopeful that these findings will generate more research on the cardiovascular consequences of heavy drinking in women. “The average reader may be confused since she has heard that one or two drinks a day may be beneficial for her cardiovascular system. Although this appears to be true, we don’t know which of these social-drinking women may be prone to developing chronic heavy drinking down the road. Some of these women may experience fairly rapid health complications from alcohol misuse. That is the message that we need to convey.”



Article is based on the following published research:

Bernardy, N.C.,
King, A.C., Lovallo, W.R.
(September 2003).
Cardiovascular responses
to physical and
psychological stress in
female alcoholics with
transitory hypertension
after early abstinence.
*Alcoholism: Clinical
and Experimental
Research*,
27(9), 1489-1499.

SPECIFYING ALCOHOL-RELATED BRAIN DAMAGE IN YOUNG WOMEN

- *Women seem to have a heightened sensitivity to alcohol's toxic neurological effects.*
- *Thinking and memory abilities may be markedly affected.*
- *Researchers used functional magnetic resonance imaging (fMRI) to "visualize" brain activity in young women.*
- *Young, female alcoholics have significant aberrations in brain and cognitive function.*

A study in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)* uses a variant of magnetic resonance imaging (MRI) to closely examine brain function in young alcoholic women.

"Previous studies have shown that alcoholic women perform just as poorly as alcoholic men on thinking and memory tests," said Susan F. Tapert, first author of the study, "even though the women hadn't been drinking as long as the men had." Furthermore, added Tapert, also an assistant adjunct professor at the VA San Diego Healthcare System and the University of California at San Diego, recent research using MRI has found that alcoholic teens may have shrinkage of a brain part – called the hippocampus – that is critical for memory.

"We have done several studies comparing thinking and memory abilities in teens with and without drinking problems," Tapert continued, "and found that remembering information, solving spatial problems like working with maps or puzzles, and doing mental arithmetic were less accurate in heavy-drinking youth. With our brain imaging study, we wanted to understand what parts of the brain might explain these thinking and memory problems." Tapert and her colleagues used functional MRI (fMRI) to identify the areas of disturbed brain functioning.

The human brain is composed of approximately 90 percent water. Structural MRI is especially sensitive to the detection of water molecules, which means it can yield remarkably high-resolution images of the brain. Scientists can then manipulate image data to differentiate among the three principal tissue types in the brain: gray matter (cell bodies), white matter (fiber tracts connecting cell bodies), and cerebrospinal fluid (which fills cavities in the brain).

Functional MRI uses the same hardware as MRI but is more sensitive to changes in blood flow related to changes in cognitive, motor or sensory tasks performed by individuals while they are being scanned. Typically, fMRI reflects a change in activity between two tasks that differ in only one aspect. MRI provides a very clear picture of the brain so that the size and shape of brain parts can be examined. FMRI takes pictures of the brain every few seconds, so that researchers can paste together what Tapert calls a "movie" of activity in the brain while the subject is doing a mental task.

"FMRI allowed us to examine very subtle changes in blood and oxygen use in the brain while our subjects did tasks that are difficult for young heavy drinkers," said Tapert. After ensuring that all study participants had been abstinent from alcohol for at least 72 hours, researchers

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SPECIFYING ALCOHOL-RELATED BRAIN DAMAGE IN YOUNG WOMEN

tested their cognitive (or thinking) abilities and mood before the fMRI, and working memory abilities both before and during the fMRI.

Certain areas of the frontal and parietal lobes of the brain, even though they are physically distant from each other, are intimately connected through brain circuitry. A number of studies have shown that this brain circuit becomes active when subjects perform working memory tasks. In most people, working memory tasks that require spatial processing of visually presented material rely more heavily on right than left hemisphere function. In this study, the alcoholic women failed to show a “normal” pattern of activation while performing their visual spatial working memory task.

“Compared with the nonalcoholics,” explained Edith V. Sullivan, associate professor of psychiatry at Stanford University School of Medicine, “the young women with alcohol dependence appeared to engage their cortical systems less vigorously. In some cases, the brain systems activated by the alcoholic women were different from those activated by individuals with no alcohol problems.”

“The main finding,” said Tapert, “was that the alcohol-dependent women showed less activation in brain areas that are needed for spatial tasks like puzzles, maps and mechanics, and for working with information that is held mentally, like doing math inside your head or making sense of a lecture or set of complex instructions. The brain parts that showed the differences are in areas that we need for finding our way around, and working with all the information we are bombarded with in everyday life.”

“Before the advent of functional imaging technologies, we could only speculate what areas of the brain caused the performance deficits observed in life,” said Sullivan. “Now, fMRI enables us to identify with reasonably good precision circumscribed fields of brain activation occurring in conjunction with specific, experimentally controlled tasks. Previous studies that relied on behavioral testing had consistently reported alcoholism-related deficits in visuospatial nonverbal working memory. The Tapert study has demonstrated that even young women with alcohol dependence suffer significant aberrations in brain and cognitive function, and that this pattern of abnormalities is similar to that documented in older alcoholics with many years of abusive drinking.”



**Article is based
on the following
published research:**

Tapert, B.F.,
Brown, G.G.,
Kindermann, S.S.,
Cheung, E.,
Frank, L.R.,
& Brown, S.A.
(February 2001).
fMRI measurement of
brain dysfunction in
alcohol-dependent young
women.
*Alcoholism: Clinical
and Experimental
Research*,
25(2), 236-245.



A

FRICAN AMERICAN ALCOHOLICS: AT GREATER RISK FOR IMMUNE DISORDERS?

69

- *Alcoholism is known to compromise the immune system.*
- *African American alcoholics are at greater risk for certain infectious diseases.*
- *African American ethnicity, in conjunction with alcoholism, seems to signify a more compromised immune system.*
- *These immune changes may be the link to a greater risk for infectious diseases.*

Long-term alcohol dependence is known to compromise the immune system. Many alcoholics have more health problems than most people in general, and African American alcoholics seem to be at greater risk for a number of infectious diseases. A study published in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* has confirmed an association between African American ethnicity, long-term alcohol dependence and immune-disease risk.

“We know from epidemiological data that African American alcoholics are at greater risk for certain infectious diseases such as tuberculosis, hepatitis C and HIV,” said Michael Irwin, professor of psychiatry at San Diego Veterans Affairs Medical Center and the University of California, San Diego, and lead author of the study. One study found, for example, that among veterans with alcoholic liver disease, African Americans were 2.4 times more likely to have hepatitis C. “African American alcoholics also have increased mortality rates,” he added.

The study examined the effects of chronic alcoholism on three aspects of the immune system. The first was to measure the activity level of “natural killer cells,” a sort of first-line defense of cells in the body that kill other cells already infected by an invading virus. The second was to test the response level of natural killer cells that were artificially stimulated. The third was to look at the production of two types of hormone-like proteins called cytokines that regulate the intensity and duration of immune responses. Interleukin-6 (IL-6) is an inflammatory cytokine that essentially turns on the immune system. Interleukin-10 (IL-10) is an inhibitory cytokine that essentially turns off the immune system.

The findings indicated an across-the-board decrease in natural killer cell activity among all of the alcoholics, but the decrease was more pronounced in the African Americans. African American alcoholics also showed the greatest decline in natural-killer cell activity following artificial stimulation. Furthermore, the expression of IL-6 (the ‘on’ signal) was lower while the expression of IL-10 (the ‘off’ signal) was higher among African American alcoholics. Irwin called this finding a ‘double whammy.’ Not only do they have less production of signals that activate the immune system, but they also have more signals that turn off the immune system.” In summary, he noted, alcoholics have a compromised immune system, African American alcoholics show the greatest immune changes, and this may explain why African American alcoholics are at greater risk for infectious diseases.

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AFRICAN AMERICAN ALCOHOLICS: AT GREATER RISK FOR IMMUNE DISORDERS

“Showing that ethnic background makes a difference in terms of immune changes is a very important finding,” said Steven J. Schleifer, chair of the Department of Psychiatry at the University of Medicine and Dentistry of New Jersey - New Jersey Medical School. “There are increasing suggestions that many biological functions differ among ethnic groups, by gender, by age, and so on. Depending on your demographic background, your baseline biological function in some areas like the immune system could be altered.” In other words, he explained, two healthy people with different biological constitutions could respond to something that’s toxic to the immune system – like alcohol – in different ways.

“You may need the two risk factors, so to speak,” Schleifer explained, “to see any results. Neither one alone – alcohol itself or being African American – may have much of an effect. But if you have both elements, constitutional factors may make you more susceptible.”

Schleifer noted that too often studies will look at the outcome and consequences of alcoholism while not systematically controlling for influencing factors. “Many of these research studies,” he said, “don’t tend to carefully distinguish men from women, younger people from older people, people by ethnic differences, whether people have other medical problems or not, or whether they have concurrent use of substances other than alcohol.” He added that “Dr. Irwin has shown that you can’t ignore those factors, that something which could be benign in one group of individuals could be very toxic in another group.”

Irwin’s other research has examined the potential influence of depression, stress levels and disordered sleep on the immune system. He observed that some of the mechanisms which connect these atypical conditions to immune alterations may be very similar in nature.

Schleifer offered suggestions for future research. “First of all, we need to really ‘nail down’ what it is about the ethnic group that is putting them at risk. Could it be nutrition, socioeconomic status, general effects of poverty? Then we need to show that those people showing the most dramatic immune changes in laboratories are, in fact, those people at greatest risk of developing health problems in the real world. Ultimately, what we want to be able to do is not simply make general conclusions, but be able to identify particular individuals at greatest risk so that we can intervene.”



Article is based on the following published research:

Irwin, M., & Miller, C.
(April 2000).
Decreased natural killer
cell responses and
altered interleukin-6
and interleukin-10
production in alcoholism:
An interaction between
alcohol dependence and
African American
ethnicity.
*Alcoholism: Clinical
and Experimental
Research*,
24(4), 560-569.



LIVER CIRRHOSIS IS NO LONGER A “BLACK” DISEASE

- *Cirrhosis mortality rates have historically been higher among Black than White Americans.*
- *A new study has found that White Americans of Hispanic origin now have a greater risk of dying from cirrhosis than do African Americans.*
- *Among Hispanic decedents, the largest group was of Mexican ancestry.*
- *Drinking patterns, socioeconomic status and cultural beliefs are all contributing factors.*

In 1997, liver cirrhosis was the 10th leading cause of death in the United States, responsible for approximately 25,000 deaths. The disease is most frequently associated with heavy drinking. Historically, cirrhosis mortality rates have been higher among Black than White Americans. A study in the August issue of *Alcoholism: Clinical and Experimental Research (ACER)* is the first to document that White Americans of Hispanic origin have a risk of dying from cirrhosis that actually exceeds that of African Americans and is far higher than the risk for other whites.

“We’ve been looking at liver cirrhosis mortality numbers since the 1910 data year,” said Frederick S. Stinson, a survey statistician with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and lead author of the study. “However, it wasn’t until we examined the newly available death-certificate information on Hispanic origin that we made a surprising finding. White Hispanic males had the highest cirrhosis mortality rates. Among these, the largest group was of Mexican ancestry.” Many of these individuals had been born outside of the U.S. and had low levels of education.

“Death certificates contain a limited amount of information about each person who dies,” said Stinson. “The lower levels of education and immigrant status of many of these White Hispanic decedents suggest that they probably had lower levels of income, and may have had some difficulty reading or understanding English. This could lead to less access to health education and treatment, whether that’s treatment for an alcohol problem or access to medical care for cirrhosis treatment. Perhaps most importantly, there may also be some very, very important differences associated with alcohol consumption that are driving some of these numbers.”

“Some Hispanic groups,” explained Deborah A. Dawson, also a statistician with the NIAAA, “especially those of Mexican or Central American heritage, have a style of drinking that is marked by periodic consumption of extremely large quantities of alcohol. Doctors and other health care workers need to be aware of the increased risk of cirrhosis in this group in order to advise them of the risks that seem to be associated with this pattern of drinking.”

Dawson further explained that this pattern of drinking – which seems to increase the risk of liver damage – is somewhat less common among Hispanics of Caribbean (such as Cuban and Puerto Rican) origin, possibly because of differences in education and socioeconomic status. Among White Hispanics in the U.S., Mexican and Central American ancestry has become increasingly predominant over time. Among Black Hispanics, Caribbean ancestry still pre-

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LIVER CIRRHOSIS IS NO LONGER A “BLACK” DISEASE

dominates. The differences in drinking styles among various groups of Hispanics may help to explain why their origin increases the risk of cirrhosis mortality among White but not among Black Hispanics.

“The most important implication of these findings,” added Bridget F. Grant, second author and chief of the Biometry Branch of the NIAAA, “is that Hispanic Americans are in need of targeted prevention and intervention programs that take into account language and other cultural issues. We also need further research into the importance of heavy drinking occasions and not just overall volume of alcohol intake as a risk factor for cirrhosis mortality.”

“These findings have important prevention, policy development and treatment implications,” said Stinson. “They have relevance for health care workers, epidemiologists (people who study numbers) and policy makers.” Researchers at the NIAAA plan to continue with this research, seeking to determine if the risk for White Hispanics varies substantially from state to state.



**Article is based
on the following
published research:**

Stinson, F.S.,
Grant, B.F.,
& Dufour, M.C.
(August 2001).

The critical dimension
of ethnicity in liver
cirrhosis mortality
statistics.

*Alcoholism: Clinical
and Experimental
Research,*
25(8), 1181-1187.

ETHNIC DIFFERENCE IN DUI ARRESTS AND USE OF HEALTH CARE SERVICES IN CALIFORNIA

- *Hispanics in the United States traditionally “under-utilize” health and social services.*
- *Yet this same group, particularly Mexican Americans, tend to have more alcohol-related problems.*
- *In California, Mexican Americans have a proportionately high level of arrests for DUI offenses.*
- *DUI arrests and program referrals may provide a unique opportunity for otherwise lacking alcohol treatment.*

Hispanics in the United States have traditionally been considered an “underserved population” in relation to their use of health and social services, including alcohol treatment. Yet this same population – particularly Mexican Americans – tends to self report more episodes of heavy drinking and alcohol-related problems, and have higher rates of driving under the influence (DUI), than other ethnic groups. A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines what proportion of Mexican Americans arrested for DUI in one northern California county have severe alcohol problems, and what health and social services they have utilized.

“Despite higher rates of heavy drinking found among Mexican American DUI arrestees compared to whites,” explained Cheryl J. Cherpitel, a senior scientist with the Alcohol Research Group and author of the study, “Mexican Americans (both those with and without an alcohol use disorder) were less likely to use health and social services. These differences between Mexican Americans and whites were primarily due to the low rate of any services utilization among those Mexican Americans born in Mexico.”

Cherpitel explained that many Hispanics living in the United States, including Mexican Americans, have not had the opportunity to avail themselves of health care and social services. Lower utilization is also related to factors such as acculturation – including language barriers, low comfort with service providers, and an inability to negotiate the system – as well as a lack of insurance coverage. This underutilization of services has historically been most pronounced among migrant workers, who have not only lacked access to such services, but have also lacked access to standard housing and even proper sanitary services at the work site.

“Those born in Mexico may also have different expectations and perceptions regarding how to obtain services and relationships with providers,” said Cherpitel. “They may also be socially isolated due to language barriers. Additionally, it might be expected that those who do not have legal resident status in the U.S. would likely avoid contact with health and social services systems for fear of identification and deportation.” However, she noted, this latter point would not apply to her study’s findings, since any individual with an illegal status who was arrested for DUI would most likely be deported immediately, and never enter a DUI treatment program.

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*F*THNIC DIFFERENCE IN DUI ARRESTS AND USE OF HEALTH CARE SERVICES IN CALIFORNIA

In contrast to their low usage of health and social services, Hispanics – particularly Hispanic men – tend to have high levels of alcohol-related problems. Several studies by other researchers at the Alcohol Research Group demonstrate a disturbing pattern. The studies indicated that those who reported frequent heavy drinking during the previous year (defined as drinking once a week or more often, and having five or more drinks at one sitting at least once a week) were as follows: White males (12%) and females (2%) versus Hispanic males (18%) and females (3%). Those who reported three or more alcohol-related problems during the previous year (from a list of 29 social and dependence experiences) found: White males (11%) and females (4%) versus Hispanic males (16%) and females (5%). The mean number of drinks required to feel drunk showed that whites reported 6.3 while Hispanics reported 7.9. Comparable findings exist at some state levels. For example, a 1990 Department of Motor Vehicles study found that while Hispanics comprised 25 percent of the population in California, they accounted for 45 percent of DUI arrestees. According to Tom Greenfield, center director at the Alcohol Research Group, this problem continues to challenge policy makers.

“Since there tend to be high levels of DUI among the Hispanic group in California,” he said, “arrest for DUI, and mandatory referral to DUI programs, represent a crucial opportunity to address the higher-than-average alcohol-related problems seen in this group, treat their alcohol abuse and alcoholism, and perhaps help prevent later drunk driving offenses and other alcohol-related problems.” In addition, he noted, “disparities in health insurance have also been implicated in the service disparities that have been found, emphasizing the need to move toward universal health coverage that includes parity for alcohol-related treatment.”

Cherpitel reiterated that there were several caveats to her study’s findings. “Mexican Americans should not be considered a homogeneous group with respect to drinking patterns and health and social services utilization,” she said. “We found considerable differences between Mexican Americans born in Mexico and those born in the U.S., when compared to whites. Given this, future research on Mexican Americans should take into account the country of birth, which may be a more important variable to consider. Another few words of caution: these findings were obtained among those arrested, convicted and sent to a DUI treatment program. These individuals are not representative of the larger population of Mexican Americans or of whites in relation to demographic characteristics, drinking patterns and, possibly, health and social services utilization. Nor will a DUI-treatment-program clientele include those most likely to be underutilizers, those born in Mexico who are here illegally. Findings from this study are most likely conservative in relation to the under-utilization of health and social services by Mexican Americans compared to other whites.”

**Article is based
on the following
published research:**

Cherpitel, C.J.
(January 2001).
Differences in services
utilization between
White and Mexican
American DUI arrestees.
*Alcoholism: Clinical
and Experimental
Research*,
25(1), 122-127.



RE-EXAMINING ALCOHOL PROBLEMS AMONG AMERICAN INDIAN COMMUNITIES

- *Numerous stereotypes exist about American Indians' use of alcohol.*
- *New research examines alcohol dependence among Northern Plains and Southwest tribes.*
- *Although rates of alcohol dependence are higher than U.S. averages, they are not as high as previous research has indicated.*

Numerous stereotypes exist about American Indians' use of alcohol. However, a new study of alcohol dependence among two culturally distinct tribes in the United States – called Northern Plains (NP) and Southwest (SW) tribes in the report – has found that alcohol problems are not nearly as serious as some stereotypes may suggest. Results are published in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)*.

“Previous research has tended to report on only one tribe or to aggregate American Indian samples in ways that do not permit explicit examination of cultural issues,” said Paul Spicer, associate professor of psychiatry in American Indian and Alaska Native Programs at the University of Colorado Health Sciences, and first author of the study. “While no one study could do justice to the tremendous cultural diversity among contemporary American Indian tribes, we wanted to include two distinct tribal populations representing important variations in aboriginal subsistence adaptation, social organization, and religious/spiritual traditions in order to document possible cultural differences in alcohol dependence.”

“A lot of what was ‘known’ in the past about alcohol use among American Indians was anecdotal, stereotypical and fueled by bias,” added Fred Beauvais, senior research scientist at the Tri-Ethnic Center for Prevention Research at Colorado State University. “This manuscript helps to clarify that there is more abstinence from alcohol among American Indians than there is among non-Indians.”

Spicer and his colleagues analyzed data collected by the American Indian Service Utilization, Psychiatric Epidemiology, Risk and Protective Factors Project (AI-SUPERPFP) since 1997 from 3,084 NP and SW individuals living on or within 20 miles of their reservations. “Our goal was to describe reservation and near-reservation American Indian populations as opposed to urban Indian populations,” said Spicer, “as the former have not been included in sufficient numbers in national studies to permit inferences about their health status.”

Rates of *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)* alcohol dependence among the NP and SW tribes were then compared with U.S. averages collected by the National Comorbidity Survey (NCS).

“There are two major sets of findings in this paper,” said Spicer. “The first concerns prevalence rates, which indicate that alcohol dependence is a serious concern in these American Indian communities, but not nearly as dramatic as has been reported in previous research using non-random samples that may have provided biased estimates. The second concerns the

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R E-EXAMINING ALCOHOL PROBLEMS AMONG AMERICAN INDIAN COMMUNITIES

importance of cultural differences, both in terms of alcohol dependence and related to other factors such as gender, age and marital status.”

Although the study found higher rates of alcohol dependence among men in both tribes than in the NCS sample, NP women had lifetime rates of *DSM-III-R* alcohol dependence twice that of NCS women; whereas SW women had rates very similar to those of NCS women. Both Spicer and Beauvais said these findings warrant further investigation.

“Indian men are clearly accounting for the greatest proportion of the difference between Indian and non-Indian rates of alcohol use,” said Beauvais. “There is some speculation that disruption of traditional culture is a heavier burden for Indian men, thus they endure more stress and are likely to use more alcohol. The much lower rates of alcohol abuse among the SW women than the NP women is very intriguing, but there is no readily obvious explanation for this. It could be that there are cultural/historical reasons why the NP women are more at risk.”

He continues, “Women have often been characterized as ‘bearers of the culture’ and thus eschew alcohol since it interferes with their cultural responsibilities. It could be that in the NP, there has been such cultural disruption that culture no longer provides this deterrent. This explanation is, of course, speculative and must await further research. This is an example of why research is important. If the exact nature of the protective factors existent among the SW women could be determined, it would provide information for designing more effective prevention interventions.”

In summary, said both Spicer and Beauvais, although rates of *DSM-III-R* alcohol dependence found in the AI-SUPERPPF were generally higher than U.S. averages, they are not nearly as high as other studies using less stringent sampling methods have found.

“Most important is the finding that only a minority of American Indian people in these samples met the criteria for alcohol dependence,” said Spicer. “There are significantly higher levels of alcohol dependence in the Northern Plains for both men and women and in the Southwest for men, and these are worth continued serious attention, but the level of such problems is not nearly as high as stereotypes of the ‘drunken Indian’ might lead people to believe.”



Article is based on the following published research:

Spicer, P., Beals, J.,
Croy, C.D., Mitchell, C.M.,
Novins, D.K., Moore, L.,
Manson, S.M.,
American Indian Service
Utilization, Psychiatric
Epidemiology, Risk and
Protective Factors Project
Team.

The prevalence of
DSM-III-R alcohol
dependence in two
American Indian
populations.

*Alcoholism: Clinical
and Experimental
Research*,
27(11), 1785-1798.



THE GENETIC COMPLEXITIES OF SENSATION SEEKING BEHAVIOR IN ALCOHOLIC MEN

- *Researchers know that sensation seeking behavior is prevalent among men with a particular subtype of alcoholism.*
- *New research has found a genetic link between the DdeI polymorphism of the D1 dopamine receptor gene and sensation seeking among alcoholic patients.*
- *These findings are limited to male alcoholics.*

Previous research has found a significant degree of sensation seeking behavior in male patients with a particular subtype of alcoholism called Cloninger's Type I. A study in the August issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found for the first time an association between the DdeI polymorphism of the D1 dopamine receptor (DRD1) gene and sensation seeking among alcoholic men.

“Alcohol-dependence is a clinically heterogeneous disorder that arises from a combination of genetic and environmental biopsychological factors,” said Frédéric Limosin, a psychiatrist at the Albert Chenevier Hospital in Créteil, France and corresponding author for the study. “Substances such as alcohol that share a potential for abuse by humans also share an ability to enhance dopaminergic activity in mesolimbic mesocortical circuits, which are thought to be important for reward and reinforcement behaviors. Among the different candidate genes, those acting in the dopaminergic pathway may be specifically involved.”

Environmental factors may include personality characteristics such as impulsiveness or sensation seeking. “Experimental studies on animals have demonstrated that behavioral characteristics such as impulsivity, excessive or deficient behavioral inhibition, and a larger tendency to explore, may predict genetically determined excessive alcohol consumption in animals,” said Limosin.

Previous studies of both healthy subjects and alcohol-dependent patients have found associations between novelty seeking and polymorphisms of dopaminergic genes such as DRD2, DRD4, and DAT. Polymorphisms of the D1 receptor (DRD1) gene, however, have been much less examined in alcohol-dependence than other dopamine receptor genes.

For this study, participants comprised 72 alcoholic inpatients (39 men, 33 women) admitted to a psychiatric ward for alcohol withdrawal. All participants were assessed according to the *Diagnostic and Statistical Manual of Mental Disorders III - Revised (DSM-III-R)* criteria, genotyped using standard methods, and scored for sensation seeking behavior according to the Zuckerman scale (a 34-item self-report questionnaire designed to assess sensation seeking by focusing on four components: disinhibition, thrill seeking, novelty seeking and boredom susceptibility). Patients completed the Zuckerman scale at least one week after beginning the alcohol-withdrawal process.

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THE GENETIC COMPLEXITIES OF SENSATION SEEKING BEHAVIOR IN ALCOHOLIC MEN

Results indicate a limited association between the DdeI polymorphism of the DRD1 gene and sensation seeking among alcoholic males. “An essential part of our results is that the association revealed is limited to male subjects,” said Limosin. “This is in accordance with Cloninger’s biopsychological typology which describes Type I alcoholism as sex-specific, characterized by an earlier age at onset, a more severe course, with more social and somatic complications, more frequent paternal previous history of antisocial behaviors, and a personality profile with high levels of sensation seeking and low levels of harm avoidance and reward dependence.”

Limosin added that these findings have three main implications for alcohol research and treatment. “First,” he said, “in view of the heterogeneous results that are often found in association studies performed in alcohol-dependent patients, it may be relevant to restrict association studies with genetic polymorphisms to more homogeneous subgroups of patients. Our results, for example, contribute to a better understanding of a subgroup of alcohol-dependent men who are characterized by a higher level of sensation seeking that could be explained by a genetic factor of vulnerability, namely, the DRD1 gene DdeI polymorphism.”

“Second,” he added, “by focusing on the D1 dopamine receptor to improve our knowledge of the biochemical mechanisms involved in the vulnerability to alcohol-dependence, we may one day be able to develop new, highly targeted drugs. Third, it may be well worth our while to examine the impact of specific treatments, such as cognitive-behavioral techniques, on subgroups of alcohol-dependent patients who have particular personality traits.”

Limosin said he plans to continue searching for associations between genetic polymorphisms and personality traits, such as temperament dimensions, among alcoholics. “I think this is a particularly promising area of research,” he said, “because we know that personality dimensions are highly involved in the vulnerability to alcoholism. We’re just not sure to what degree they are involved.”

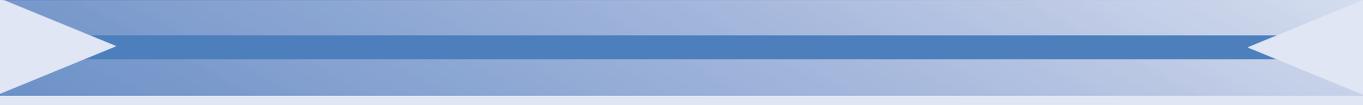


Article is based on the following published research:

Limosin, F., Loze, J.Y.,
Rouillon, F., Adès, J.,
Gorwood, P.
(August 2003).
Association between
dopamine receptor
D1 gene DdeI
polymorphism and
sensation seeking in
alcohol-dependent men.
*Alcoholism: Clinical
and Experimental
Research*,
27(8), 1226-1229.



*G*enetics &
Other Risk
Factors



GENETICS & OTHER RISK FACTORS

Articles in the *Genetics & Other Risk Factors* Category

1. A Neurogenetic Approach to Alcoholism
2. Untangling the Matrix of Risk Factors for Alcoholism
3. Using Brain Activity to Identify Risk for Disorders
4. Searching for Biochemical Markers in Children of Alcoholics
5. The Eyes Have It: Seeking Expressions of the Genetic Risk for Developing Alcoholism
6. On the Cutting Edge of Brain Gene Analysis
7. Genetic Contributions to Alcohol Sensitivity
8. Investigating a “Protective Gene” Against Alcoholism
9. Bridging the Gap Between Genetics and Motivations to Drink Alcohol
10. When Alcohol and Nicotine Interact
11. Exploring the Genetic Commonality of Alcohol and Tobacco Abuse
12. Abnormalities in Stress Hormone Response Among Alcoholics
13. Taste Testing May Help Identify Alcoholism Risk
14. A Sweet Tooth May Be a “Marker” for the Genetic Risk for Developing Alcoholism



A NEUROGENETIC APPROACH TO ALCOHOLISM

- *Researchers are integrating the fields of genetics and neurobiology to better understand the development of alcoholism.*
- *The neurotransmitter serotonin is a modulator or inhibitor of certain behaviors.*
- *Three behavior patterns are relevant to the development of alcoholism: disinhibition, negative mood states and a low response to alcohol.*
- *Pre-existing and alcohol-induced differences influence serotonergic neurotransmission.*

Scientists are moving beyond the knowledge that alcoholism is a disease. They are now integrating the previously disparate research fields of genetics and neurobiology to investigate how genetic influences may alter the function of neurotransmitters prior to and during the development of alcoholism. More specifically, a review in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the link between central serotonergic neurotransmission and three behavior patterns that are relevant for alcoholism: disinhibition (impulsive aggression), negative mood states (such as anxiety and depression) and a low response to alcohol.

“Several hypotheses have tried to explain the association between serotonergic dysfunction and alcoholism,” noted Andreas Heinz, associate professor of addiction research at the University of Heidelberg and lead author of the paper. “Sometimes, these hypotheses seemed to be contradictory. For example, it was not easy to understand why serotonergic dysfunction should be associated with depression *and* aggression, or what the impact of disposition versus the consequences of long-term alcohol intake might have on the serotonergic system.”

In this review, the neurochemical serotonin is the key player. Serotonin is an important modulator within the behavior inhibition system. The neurotransmitter is very likely influenced by genetics, early stress experiences, as well as alcohol itself. Serotonergic dysfunction has been linked to a number of psychiatric disorders, as well as the development and maintenance of excessive alcohol consumption and alcoholism. The authors believe that three behaviors or mechanisms in particular – disinhibition, negative mood states such as anxiety and depression, and a low response to alcohol – may explain the relationship between serotonin and alcoholism. They reviewed a number of primate and human studies to form an integrated perspective on serotonin and its role in the development of alcoholism.

David Goldman, chief of the Laboratory of Neurogenetics at the National Institute on Alcohol Abuse and Alcoholism, said that one of the key strengths of this approach to understanding alcoholism is its inclusive nature. “This article includes both the genetic influences, where there’s a biological substrate or tendencies inherent to the person, and also the secondary changes that alcohol induces in the function of this neurotransmitter system.”

Goldman noted that prior research had shown that people who are behaviorally disinhibited frequently have a lower turnover of serotonin. “But there has been inadequate attention paid to

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A NEUROGENETIC APPROACH TO ALCOHOLISM

the common pathway of neurobiological changes that occur once a person becomes an alcoholic,” he said. “There are many different reasons that a person might initially become an alcoholic. For example, they might drink because they are impulsive, because they are anxious, etc. ... but once they have begun, there is a common neurobiology experienced by all people who become addicted. These changes are induced in the brain regardless of what the pre-existing vulnerability was, and this review showed a common pattern of neurobiological change, at least as far as serotonin is concerned.”

“Serotonin seems to play two roles,” said Heinz. “One, an early deficit may result from genetic factors, as well as social stress, which can render subjects more tense, anxious and potentially aggressive. These subjects tend to drink more alcohol – most likely to calm down – and they have less negative effects from alcohol intake.”

Having fewer negative effects from drinking alcohol means the same thing as having a low response to alcohol; these are people who can ‘drink like a fish’ without getting drunk. Sons of alcoholics, for example, are often low responders and most likely to develop alcoholism themselves. “Two,” continued Heinz, “long-lasting alcohol intake may further disturb the serotonergic system and induce clinical depression, thus increasing the long-term relapse risk. A genetically defined subgroup of alcoholics may be specifically vulnerable to these effects.”

Additional studies of human alcoholics have found that long-term alcohol intake seems to further disturb serotonergic neurotransmission. “A reduction in the serotonin transporter,” said Heinz, “which recycles serotonin after it has been released from the nerve terminals, was correlated with clinical depression. This is, in turn, a predictor of an increased relapse risk when patients are followed for several years. In other words, the genetic constitution of the serotonin transporter may render some subjects more vulnerable to the neurotoxic effects of alcohol intake.”

“We are beginning to understand what some of the clinical subgroups of alcoholism and psychiatric diseases are. These subgroups are going to have different vulnerabilities and also different treatment responses,” noted Goldman.

“This review shows that social stress factors,” said Heinz, “especially early social separation, have long-term effects on the brain and on neurotransmitter systems that affect social behavior and the response to alcohol. There are also negative long-term consequences of alcohol intake, such as a loss of serotonin transporters, that may affect mood states.”

Article is based on the following published research:

Heinz, A., Mann, K.,
Weinberger, D.R.,
& Goldman, D.
(April 2001).

Serotonergic
dysfunction, negative
mood states, and the
response to alcohol.
*Alcoholism: Clinical
and Experimental
Research*,
25(4), 487-495.



UNTANGLING THE MATRIX OF RISK FACTORS FOR ALCOHOLISM

- *A family history of alcoholism places a person at greater risk of developing alcohol problems.*
- *Children of alcoholics tend to exhibit other types of behavioral and emotional problems.*
- *The neurotransmitter serotonin is believed to regulate many behaviors and emotions.*
- *Genetic variation in the serotonin transporter gene may partially determine overall levels of serotonergic function.*

Children of alcoholics (COAs) have a high risk of developing alcoholism, simply by virtue of their family history of alcoholism. Many studies have found that COAs also tend to exhibit high levels of behavioral and emotional problems. In the July issue of *Alcoholism: Clinical and Experimental Research (ACER)*, researchers explore the biochemical basis of two aspects of behaviors of undercontrol. Their findings indicate that behavioral disinhibition (BD), such as impulsive aggression and negative affect (NA), such as depression and anxiety, may be genetically influenced through the regulation of a neurotransmitter called serotonin (5-HT).

“Serotonin’s primary role appears to be that of an inhibitor,” explained Geoffrey R. Twitchell, postdoctoral fellow at the UCLA Integrated Substance Abuse Programs and lead author of the study. “Dysfunction in 5-HT neurotransmission has been found in individuals who exhibit problems with behavioral and affective control. For example, 5-HT deficits have been observed in antisocial alcoholics who exhibit BD, such as aggressiveness and difficulty controlling alcohol consumption. The relationship between 5-HT dysfunction and impulsive aggression in non-alcoholic groups has also been reliably documented. In addition, many studies have found 5-HT dysfunction in individuals who exhibit increased NA, as indicated by depression and anxiety. Depressed and highly anxious individuals are often treated with 5-HT enhancing medications such as selective serotonergic reuptake inhibitors.”

“Exactly how a serotonergic dysfunction relates to BD and NA is the realm of great speculation,” commented Robert O. Pihl, professor of psychology and psychiatry at McGill University. “Because serotonergic dysfunction seems related to an exceedingly wide range of behaviors, a likely explanation is that of a regulatory role for many biochemical systems in the brain. A speculative analogy has serotonin acting much like the maestro of an orchestra, able to meld disparate sections in order to produce music rather than cacophonous noise. Thus, without appropriate modulation – which we assume is supplied by serotonin – individuals will overreact to emotional stimuli.”

Knowing of the strong association between serotonergic dysfunction and behavioral disorders such as alcoholism, aggressiveness and depression, researchers wanted to further examine genetic variations in the serotonin transporter gene (5-HTTLPR). Genetic variation in 5-HTTLPR is related to efficiency in 5-HT reuptake, one aspect of 5-HT functioning. The long (LL) variation or genotype has been associated with an increased number and function of 5-HT transporters (the 5-HT structure that recycles synaptic 5-HT back into the pre-synaptic

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UNTANGLING THE MATRIX OF RISK FACTORS FOR ALCOHOLISM

neuron) when compared to the short (SS) or the short/long (SL) genotypes. An increased functionality of the 5-HT transporter has the effect of reducing the amount of 5-HT available in the synapse. Decreased synaptic 5-HT has the effect of decreasing overall 5-HT functioning.

Some psychiatric genetic studies had previously documented a relationship between the SS variant of 5-HTTLPR and alcohol dependence, depression, anxiety and the personality trait neuroticism (which is also a marker of NA). Some studies of alcoholics, however, have found a relationship between the LL variant of 5-HTTLPR and low levels of response to alcohol, alcohol dependence and antisocial alcoholism. For the current study, researchers examined 47 families classified by the fathers' alcoholism subtype. (The data were taken from a larger, ongoing longitudinal family study on risks for developing alcoholism and other problems.) The authors found that the LL genotype of 5-HTTLPR was associated with both BD and NA in COAs. In addition, significantly more LL than SS/SL genotype children reported they had already consumed alcohol.

"This finding," said Twitchell, "supports the hypothesis that behavioral and emotional problems in COAs, which put them at increased risk for later development of alcoholism, may be genetically regulated in part by the 5-HT transporter. In other words, the 5-HTTLPR genotype may serve as a marker for vulnerability for COAs."

"The results of this study are fascinating," said Pihl. "Although we have learned to cautiously view genetic studies that attempt to explain behavior; this one makes sense. It suggests an overactive transporter gene could result in a deficiency of serotonergic synaptic functioning. This is another strong piece of evidence in this evolving story. "However," he added, "there remain gaps in our knowledge. We continue to be in a state much like what Newton described when he said 'we are finding interesting pebbles while the great ocean of truth lays undiscovered before us.'"

Twitchell hopes to move beyond those 'pebbles' one day. "Our group plans to follow these children over time with complete psychosocial assessments at three-year intervals into adulthood," he said. "Our finding of higher rates of alcohol consumption in LL genotype children as young as a mean age of 10.88 years is important because it suggests that this liability manifests early in one's life course. Those with a family history of alcoholism may want to be aware of their increased risk and monitor their alcohol use accordingly."



Article is based on the following published research:

Twitchell, G.R.,
Hanna, G.L., Cook, E.H.,
Stoltenberg, S.F.,
Fitzgerald, H.E.,
& Zucker, R.A.
(July 2001).

Serotonin transporter
promoter
polymorphism
genotype is associated
with behavioral
disinhibition and
negative affect in
children of alcoholics.

*Alcoholism: Clinical
and Experimental
Research*,
25(7), 953-960.

U SING BRAIN ACTIVITY TO IDENTIFY RISK FOR DISORDERS

- *A P300 event-related potential (ERP) is a brief electrical wave in a person's electroencephalogram (EEG).*
- *The P300 is a measure of the way the brain pays attention to and discriminates between potentially important and non-important stimuli.*
- *It is believed that people with anxiety disorders are more likely to use alcohol to self-medicate their anxiety than people without anxiety disorders.*
- *P300 amplitude may distinguish the anxious people who are vulnerable to becoming alcoholic.*

Individuals who wish to identify their risk for developing alcoholism can undergo a noninvasive measure of brain electrical activity called P300 event-related potential (ERP), one of the few brain measures associated with risk for alcoholism. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the variation in P300 amplitude in individuals with co-existing alcohol use and anxiety disorders.

“We predicted,” said Mary-Anne Enoch, a staff scientist in the Laboratory of Neurogenetics at the National Institute on Alcohol Abuse and Alcoholism and lead author of the study, “based on the results of previously published studies, that alcoholics would have low P300, anxiety disorder subjects would have high P300, but we could not predict which way alcoholics with anxiety disorders would go.” Some of their findings were expected, while others were not.

“Even though our subjects had less severe forms of alcoholism and anxiety disorders, we nonetheless found that alcoholics had lower P300 amplitudes, and subjects with anxiety disorders had higher P300 amplitudes. When we looked at the subgroups, the results were much more dramatic. We found that it was the alcoholics with co-morbid anxiety disorders who had the lowest P300 amplitudes. Our study showed that the effects of alcoholism vulnerability on P300 amplitude wiped out or dominated the effect of anxiety vulnerability on P300 amplitude. It is often thought that people with anxiety disorders are more susceptible to alcoholism as they might tend to ‘self-medicate’. However, our results suggest that P300 amplitude may distinguish which anxious individuals are vulnerable to becoming alcoholic.”

“There are many different ways that someone can be at risk for developing alcoholism,” concurred Cindy L. Ehlers, associate professor of neuropharmacology at The Scripps Research Institute, “and one of them is to have an anxiety disorder. Alcohol is an anxiolytic (or anti-anxiety) agent. People who have anxiety can get relief from drinking. In fact, this is referred to as ‘relief drinking.’ While it may seem confusing that the group with both alcoholism and anxiety disorders have the lowest P300 amplitudes, it’s entirely plausible that someone with an anxiety disorder who does not develop alcoholism may have protective factors against the development of alcoholism that mediate their high risk. In other words, having a higher P300 may be a measure of a protective factor.” Which, alternately, means that having the lowest P300 may indicate the most severe of risk factors. Either perspective both supports and extends P300 research that began in the early 1980s.

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U SING BRAIN ACTIVITY TO IDENTIFY RISK FOR DISORDERS

An individual's electroencephalogram (EEG) – a recording of the continuous electrical activity going on in a person's brain – is like a distinctive fingerprint. Even when we're unaware of it, our brains are constantly on the alert for new stimuli or unusual changes in our immediate environment. If, for example, we are listening to the sound of rain and a clap of thunder interrupts, our brain will respond by producing a very brief electrical wave in our EEG. This is called an event-related potential (ERP). The maximum amplitude of the electrical wave occurs at around 300 milliseconds after the onset of the stimulus, which is why it is called the P300 ERP.

There exist a number of ways to measure ERPs in the laboratory. A subject might be shown the same picture on a computer screen again and again, but occasionally, and randomly, a different picture will appear and the subject will produce a P300 ERP in response to the rare stimulus. Or, a subject might listen to a stream of low-pitched sounds, interrupted by a high-pitched sound, to which their brain will respond with a P300 ERP. The more unusual or rare the stimulus, the larger the amplitude of the P300.

The P300 is a measure of the way the brain pays attention to and discriminates between potentially important and non-important stimuli. An individual inherits some aspects of their P300. Alcoholism is also heritable. Some alcoholics react differently to stimuli than do non-alcoholics; the amplitude of their P300 response tends to be lower than that of non-alcoholics. Alcoholics with a strong family history of alcoholism tend to have the lowest P300 amplitudes of all. Even some non-drinking children of alcoholics have low P300 amplitudes. This suggests that a low P300 is not caused by drinking but is inherited. It also suggests that a person with a low P300 may be at risk of becoming an alcoholic.

“Anxious individuals tend to be less relaxed,” said Enoch, “more alert and have heightened awareness. They are more likely to respond vigorously to changes in the environment. You could say that they are more ‘jumpy’. They would therefore be expected to produce bigger P300 amplitude responses. Studies have also shown that people who have an anxiety disorder, but are not anxious at the time of testing, have high P300 amplitudes, suggesting that high P300 may be a risk factor for anxiety disorders.”

“Alcoholism comes in many different forms,” said Ehlers, “because different people have different risks. Someone who has conduct disorder and is at risk for alcoholism probably has a different set of genes coding for this vulnerability than someone who has anxiety disorder and is at risk for alcoholism, even though they both have alcoholism.” She said that it is imperative to understand the different subgroups of alcoholism before discovering which genes are “coding” for particular disorders.

Article is based on the following published research:

Enoch, M.,
White, K.V., Harris, C.R.,
Rohrbaugh, J.W.,
& Goldman, D.
(September 2001).
Alcohol use disorders
and anxiety disorders:
Relation to the
P300 ERP.
*Alcoholism: Clinical
and Experimental
Research*,
25(9), 1293-1300.





SEARCHING FOR BIOCHEMICAL MARKERS IN CHILDREN OF ALCOHOLICS

- *Genetic factors contribute up to 40 percent to the risk of developing alcoholism.*
- *Environmental factors likely contribute the remaining risk.*
- *Those at most risk are children of alcoholics (COAs), but not all COAs become alcoholics.*
- *Biochemical markers or “biomarkers” may help identify specific individuals at highest risk.*

Individuals with a family history of alcoholism are themselves at greater risk of developing alcoholism, yet some children of alcoholics (COAs) develop the disease while others don't, even within the same environment. A study published in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that a hormone called beta-endorphin (B-E) may help identify which individuals have the particular genetic combination that places them most at risk of becoming alcoholics.

“Alcoholism, rather than a weakness of will,” said Janice C. Froehlich, professor of medicine at Indiana University School of Medicine and lead author of the study, “is a disease that has biological components to it. We know that alcoholism tends to run in families and that individuals with a family history of alcoholism are more likely to develop alcoholism themselves. However, not all children of alcoholics become alcoholic, in part, because not all family members will inherit a combination of genes that increases risk for alcoholism.” The challenge is to be able to identify specific individuals in families with alcoholism who are at the greatest risk. One approach is to study the response of B-E to alcohol consumption.

B-E is a hormone that is manufactured within the endogenous opioid system of the brain. It produces euphoria and acts like the body's own morphine, said Froehlich. Endorphin levels increase, for example, during childbirth, trauma and running (known as the “runner's high”). Endorphin levels also increase in response to alcohol drinking, and this hormone may contribute to feelings of well-being produced by alcohol.

“Prior work has shown that the beta-endorphin response to alcohol is greater and more prolonged in people with a family history of alcoholism,” said Froehlich. “This suggests that the beta-endorphin response to alcohol may possibly predict, in a high-risk family, which people will abuse alcohol and which people won't. But before a hormone can be used as a biomarker of genetic risk for alcoholism, it must be demonstrated that the hormonal response can be inherited. Our study demonstrated that the beta-endorphin response to alcohol is heritable.”

“This is the first report of the heritability of a hormonal response to alcohol,” said Froehlich. “When taken together with several other lines of evidence, the study suggests that the beta-endorphin response to alcohol may be a new biomarker that can be used to identify specific individuals who are at high genetic risk for developing alcoholism.”

Behavioral geneticists have used several approaches to study the influence of genetic and environmental factors on behaviors such as alcoholism, including adoption, twin, and

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SEARCHING FOR BIOCHEMICAL MARKERS IN CHILDREN OF ALCOHOLICS

genetic-marker studies. Adoption analysis is one of the more direct approaches. In the popular twin-studies approach, monozygotic or identical twins are compared with dizygotic or fraternal twins, both groups having been raised in the same environment. Identical twins share all of their genes whereas fraternal twins, like ordinary siblings, share approximately 50 percent of their genes. The genetic-marker approach seeks to identify those specific genes – out of the 50,000 to 100,000 genes that comprise the “human genome” or human genetic material – that may influence a person’s likelihood of developing alcoholism.

Using the twin-study approach, Froehlich’s paper adds to a growing body of research seeking to isolate a set of responses to alcohol that may be used as biomarkers to identify individuals who are at elevated genetic risk for developing alcoholism. One use of biomarkers is preventative. Researchers now believe there are at least two types of alcoholism, one of which is more affected by genetic factors than the other. Biomarkers could provide the basis for screening tests to allow early identification of those individuals who would benefit from early prevention. Biomarkers may also reveal information about the neurochemistry of alcoholism that can lead to the design of drugs to treat the disease.

Gary S. Wand, professor of medicine and psychiatry at Johns Hopkins University School of Medicine, believes Froehlich’s study makes at least two important contributions to the field. The first is finding that the B-E response to alcohol has a strong hereditary component; the second is further demonstrating the involvement of the endogenous opioid system in alcoholism. Wand himself studies the effects of opioid antagonists in the brains of nonalcoholic COAs.

“This is a novel, important study,” said Wand. “The findings highly suggest that people may be born with differences in their brain opioid function that lead them to this susceptibility. For more than a decade now, evidence has demonstrated that part of the biological vulnerability to alcoholism involves alcohol’s ability to activate opioid pathways within the brain.”

The next step will be to look at the predictive nature of the B-E response to alcohol, explained Froehlich. B-E will be examined in people in high-risk families before they become alcoholics, and they will then be watched over time to determine whether a larger B-E response to alcohol is highly correlated with the development of alcoholism. Wand believes that future studies will also need to investigate if opioid levels in the brain can be altered to reduce the chances of developing alcoholism.



Article is based on the following published research:

Froehlich, J.C.,
Zinc, R.W., Li, T-K.,
& Christian, J.C.
(March 2000).
Analysis of heritability
of hormonal responses
to alcohol in twins:
Beta-endorphin as a
potential biomarker of
genetic risk for
alcoholism.
*Alcoholism: Clinical
and Experimental
Research*,
24(3), 265-277.



THE EYES HAVE IT: SEEKING EXPRESSIONS OF THE GENETIC RISK FOR DEVELOPING ALCOHOLISM

- *Prior research indicates that the brain's response to alcohol is related to a genetic risk for alcoholism.*
- *New research examines high-velocity eye movements, called saccades, in individuals with and without a family history of alcoholism.*
- *Those with a family history of alcoholism have slightly but consistently slower saccadic eye movement than those without a history, yet appear to "adapt" more quickly to continued alcohol exposure.*

Genetic factors play a key role in the development of alcoholism. A family history of alcoholism does not, however, guarantee that individual offspring will develop the disease. In an effort to discover identifying "markers" of those at risk for alcoholism, researchers in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* evaluate the influence of a family history of alcoholism on the response of saccadic eye movements to alcohol.

Saccades are high-velocity eye movements made from one point to another, as in reading. Their main function is to bring the image of a target from the visual periphery onto the fovea centralis (center of the retina), where vision is most acute. The saccadic control system is sensitive to alcohol, and saccadic parameters provide reliable measures of alcohol's effects in a dose-dependent manner.

"The premise of our research is that the brain's response to alcohol is related to a genetically influenced risk for alcoholism," said Sean O'Connor, professor of psychiatry at Indiana University School of Medicine and corresponding author for the study. "We used a familial history of alcoholism as a proxy for genetic influence, since specific genes cannot yet be identified. Saccadic eye movements fulfilled all the criteria for a good measure of the brain's response to alcohol: they are known to be genetically influenced; they are a very reliable measure of brain function as most people will execute these movements in the same way day after day; they are quite sensitive to alcohol; and a lot is known about the systems of neurons that control the movements." O'Connor explained that associating response of saccades to alcohol with the genetic risk for alcoholism is the first step in seeking specific genes increasing that risk.

Researchers evaluated saccadic performance in 54 adults (27 males, 27 females) with a family history of alcoholism, and 49 adults (24 males, 25 females) without a family history of alcoholism. Participants were given alcohol and a placebo in a counter-balanced order. The alcohol was administered intravenously in order to achieve a breath alcohol concentration of 60 mg% in 20 minutes and to maintain it for 160 minutes. Saccadic eye movement was tested before each session (called baseline), and twice during the maintained level of intoxication.

The two groups showed significant overall differences in operational characteristics of the saccadic control system, both at baseline and when the brain was exposed to alcohol. Subjects with a family history of alcoholism were slightly, but consistently, slower than subjects without

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THE EYES HAVE IT: SEEKING EXPRESSIONS OF THE GENETIC RISK FOR DEVELOPING ALCOHOLISM

a history throughout the sessions, and appeared to “recover” baseline measures despite prolonged and constant exposure to alcohol.

“A key finding of our study is that the adaptive response of saccades to alcohol is associated with a family-history status known to be associated with a genetic influence on the risk for alcoholism,” said O’Connor. In other words, brain function among those with a family history of alcoholism returned towards “normal” despite continued exposure to alcohol.

“We are still trying to learn what is actually inherited that affects the risk of alcoholism,” said David Crabb, professor of medicine, biochemistry and molecular biology at Indiana University School of Medicine. “In other words, is the inherited risk related to brain control functions; to the inability to control drinking; or to the euphoria of drinking? We need to know this in order to devise therapies that address the actions of alcohol on the brain.” He called the study’s identification of brain functions (the control of eye movement at a subconscious level) that are both influenced by genetic factors (the family history of alcoholism) and show responses to alcohol “an incremental yet important step toward understanding genetic influences on alcohol’s effects on the brain.”

Crabb said these findings may one day have practical applications, such as developing a battery of easy-to-use measures of risk. “We could test children of alcoholics,” he said. “Perhaps combining the results of the eye movement tests in young people with other measures would predict their risk of alcoholism or other alcohol problems. If we could accurately tell people if they are at a higher or lower risk of alcoholism based on their test results, this could influence some people to reduce their drinking.”

O’Connor said it’s important for the field of alcohol research to continue to examine the question, “What does alcohol have to do with an increased risk for alcoholism?” His own research plans include quantifying the degree to which genes influence responses to alcohol, examining how other brain functions respond to alcohol, and expanding those studies to include experimental control of how quickly alcohol reaches and leaves the brain.



Article is based on the following published research:

Blekher, T.,
Ramchandani, V.A.,
Flury, L., Foroud, T.,
Kareken, D., Yee, R.,
Li, T.K., O’Connor, S.
(October 2002).

Saccadic eye
movements are
associated with a
family history of
alcoholism at baseline
and after exposure to
alcohol.

*Alcoholism: Clinical
and Experimental
Research,*
26(10), 1568-1573.

ON THE CUTTING EDGE OF BRAIN GENE ANALYSIS

- *Alcohol targets the central nervous system to produce its effects.*
- *Researchers have for the first time used a new technique called gene array technology to analyze brain gene expression in human alcoholism.*
- *Chronic alcohol abuse can change the molecular programming and circuitry of the frontal cortex.*
- *Thousands of gene products may now be analyzed simultaneously to ascertain the effects of complex diseases such as alcoholism.*

Alcohol's primary target is the central nervous system, where it influences neurotransmission to produce intoxication. Chronic alcohol abuse produces tolerance, dependence and neurotoxicity. Although changes in brain gene expression are believed responsible for these effects, research that appears in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* is the first to use an exciting new technique called gene array technology to study gene expression in human alcoholism.

"A critical question in addiction," said R. Adron Harris, director of the Waggoner Center for Alcohol and Addiction Research at the University of Texas at Austin and lead author of the study, "is how the reprogramming of the brain leads to long-lasting, severe, life-threatening dependence. This study provides insight regarding the molecular neurocircuitry of the frontal cortex that is altered in alcoholism. A key point here is that we study the superior frontal cortex. This is also called the 'executive cortex' because it is critical for judgement and decision making, tasks that are corrupted in addiction. Just as a computer virus can change the programming of specific functions, our data show that chronic alcohol abuse can change the molecular programming and circuitry of the frontal cortex."

All of our cells have exactly the same deoxyribonucleic acid (DNA), which means they all have the same genes. The reason that different cells can appear and work so differently with the same genes (giving us, for example, unique eyes, skin, hair, etc.) is that only some genes are used or "turned on" in each cell. This is called gene expression. The sequence of events is for DNA or genes to make ribonucleic acid (RNA), also called a "message," which is then used to make proteins. These proteins determine the appearance and function of each cell and, in turn, the proteins' existence depends on gene expression. Thus, gene expression is a normal function of all cells and is well regulated to avoid mistakes.

"Drugs can change gene expression and thereby disturb normal functions of the cell and tissue," explained Harris. "Alcohol can change gene expression in the brain and this is believed to be responsible for many of the hallmarks of addiction, such as tolerance, physical dependence, and craving as well as the consequences of chronic alcoholism, such as neurotoxicity (brain damage). The problem has been to find which genes are 'incorrectly' turned on or off in the brains of human alcoholics. This is because there are about 50,000 genes and any of these may

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ON THE CUTTING EDGE OF BRAIN GENE ANALYSIS

be important. Previously, it was impossible to analyze more than a handful of these genes. Gene array technology has now changed that.”

“Gene expression measurements that use arrays can simultaneously detect expression of thousands of gene products,” said Boris Tabakoff, chair of the Department of Pharmacology at the University of Colorado School of Medicine. “This is a novel and fruitful approach for understanding patterns of changes produced by various disease processes.”

A gene array is a small glass microscope slide that has thousands of different DNA samples attached to the glass. Knowing that DNA makes RNA, and wanting to know which genes have been turned on to make RNA, researchers measured the level of thousands of RNAs in the brain. RNA samples were extracted from post-mortem samples of superior frontal cortex of 10 alcoholics and 10 non-alcoholics, and measured by two different types of microarrays (the Affymetrix and Genome systems). Using two microarrays – a more complicated, challenging and expensive venture than just one – provided more complete gene coverage and enhanced the reliability and replication of the findings.

“The key,” said Harris, “is that RNA can be converted to a complimentary DNA called cDNA with a fluorescent or colored tag that will very selectively bind to or partner with its corresponding DNA. We can put a drop of this brain cDNA on the gene array and each spot of DNA that shows a colored tag will indicate that it is a gene that is turned on in the brain. Thus, each DNA element on the array has a color that reflects how much the gene is turned on in the alcoholic relative to the control.”

In this study, more than 4,000 genes in brain tissue were analyzed simultaneously. Of these, 163 (or roughly 4%) were found to differ by 40 percent or more between the alcoholics and non-alcoholics. The genes that seemed to change were those related to the generation of white matter in brain, and it was thought by the authors that the results may indicate that alcohol has a particularly damaging (or down regulating) effect on the generation of this white matter (which is called myelin). Myelin forms an insulation between information-carrying cells of the brain, and loss of white matter may result in cognitive deficiencies. These findings provide evidence for an extensive reprogramming of brain gene expression due to alcoholism.

Harris said, “This study is a beginning to unraveling the undesirable changes in the brain produced by chronic exposure to alcohol. Such studies will eventually result in new and better treatments for alcoholism and other addictions.”

Article is based on the following published research:

Lewohl, J.M.,
Wang, L., Miles, M.F.,
Zhang, L., Dodd, P.R.,
& Harris, R.A.
(December 2000).
Gene expression in
human alcoholism:
Microarray analysis
of frontal cortex.
*Alcoholism: Clinical
and Experimental
Research*,
24(12), 1873-1882.



G ENETIC CONTRIBUTIONS TO ALCOHOL SENSITIVITY

- *Sensitivity to alcohol's "incoordinating" effects seems to predict the later development of alcoholism.*
- *Individuals who seem resistant, or less sensitive, to alcohol's effects may drink more.*
- *Genetic differences contribute to alcohol sensitivity.*
- *Scientists have established an important link among genetics, a neurochemical messenger called adenosine 3':5'-cyclic monophosphate, and alcoholism.*

Understanding a disease such as alcoholism, like many other diseases, involves years of research dedicated to "teasing out" its multiple and interactive components. Scientists now know that alcoholism is influenced by both environmental and genetic factors. A study in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* looks closely at how genetic differences in the intracellular signaling capacity of a neurochemical messenger called adenosine 3':5'-cyclic monophosphate (cAMP) may relate to alcohol sensitivity and the later development of alcoholism.

"There are different theories as to the cause of alcoholism," said Shelli Kirstein, a graduate student in pharmacology, and Boris Tabakoff, chair of the Department of Pharmacology at the University of Colorado School of Medicine. Tabakoff is the senior author and Kirstein is the co-author of the paper. "One possibility involves differences in sensitivity. Less sensitive individuals may drink more because they do not receive the same cues of impending intoxication as individuals with a high sensitivity. Another possibility is that some individuals have the capacity to develop greater or more rapid tolerance and hence can drink more. Both low sensitivity and alcohol tolerance can lead an individual to drink more and become dependent on alcohol. It is not known how these two pre-existing conditions are related genetically and if being genetically programmed in one direction or the other is sufficient by itself to cause an individual to become alcoholic."

Alcohol can affect several different neurotransmitter receptors, causing them to couple to or activate intracellular signaling systems, such as adenylyl cyclases, which produces cAMP as a messenger. Signaling pathways can set the tone for alcohol's effects by either inhibiting (turning off) or potentiating (turning on) certain pathways. This study used different strains of specifically bred mice to examine what role cAMP signaling might play in setting the tone for alcohol sensitivity and tolerance. Sensitivity was measured as the ability to balance on a dowel following alcohol injections. This procedure mimics the "incoordinating" or disharmonizing effects that alcohol can have for some individuals. Tolerance was measured as the difference between sensitivity after the initial dose of alcohol and sensitivity after a subsequent dosing with alcohol.

"One key finding," said Tabakoff, "is that there is a genetic correlation between cAMP signaling in the cerebellum and initial sensitivity on the dowel test for ataxia." Ataxia is the inability to coordinate voluntary bodily movements. For example, a staggering drunk would appear ataxic.

continued ~

G ENETIC CONTRIBUTIONS TO ALCOHOL SENSITIVITY

“Also, there is a lack of correlation between initial sensitivity and tolerance, and there is a lack of genetic correlation between tolerance and cAMP signaling in the cerebellum or any brain region tested. Results from testing different strains of mice under similar environmental conditions reflect a genetic influence on the behavioral or biochemical phenotype investigated. Simply stated,” he added, “this means that a common gene or genes influence both initial sensitivity and cAMP signaling. Next, we would like to try to identify those genes.”

“The cAMP signaling system is much like the traffic controller at a large airport,” explained Richard Deitrich, professor of pharmacology at the University of Colorado School of Medicine. “It controls which systems are turned on or off in a given situation. That is, which planes or systems are allowed to take off or land, and which planes or systems are put into a holding pattern or not allowed to function. Alcohol, by its ability to affect these systems, is analogous to a malfunctioning radar system. Airport operations are slowed by a marginally malfunctioning system, or a low dose of alcohol, or completely disrupted by an acutely malfunctioning radar system, or a large dose of alcohol. In such cases, the airport has to be shut down, or the individual loses fundamental brain functions. In this study, the dose of alcohol was low and so the function of the animals was only partially disrupted. That is, they could still stagger around and were not unconscious.”

“Our results suggest those areas of the brain important for balance and coordination can be genetically programmed for sensitivity to alcohol’s incoordinating effects,” said both Tabakoff and Kirstein. “While the genes that influence this sensitivity are by no means the only genes that may predispose someone to alcoholism, they may influence sensitivity to certain effects of alcohol. This could make it easier to identify individuals at risk for alcoholism, as well as serve as an easily measured characteristic that contributes to the risk but does not explain the entire disorder.”

“This study is very relevant to understanding the underlying differences between those individuals who drink and do not become alcoholic, and those who drink and do become alcoholic,” said Deitrich. “The research shows that a combination of behavior, pharmacology, neurochemistry and genetics can be a powerful tool in investigating the basic mechanisms by which alcohol brings about its effects. Only by understanding these basic mechanisms can we design rational measures for the prevention or treatment of human alcoholism.”



Article is based on the following published research:

Kirstein, S.L.,
& Tabakoff, B.
(June 2001).
Genetic correlations
between initial
sensitivity to ethanol
and brain cAMP
signaling in inbred and
selectively bred mice.
*Alcoholism: Clinical
and Experimental
Research*,
25(6), 791-799.

INVESTIGATING A “PROTECTIVE GENE” AGAINST ALCOHOLISM

- *Alcohol dehydrogenase (ADH) is one of two important alcohol metabolizing enzymes.*
- *The ADH2*3 allele is a variant form of the gene that codes for the ADH enzyme.*
- *ADH2*3 has been documented only in people of African descent and certain Native American tribes.*
- *The ADH2*3 allele may be associated with a lowered risk for developing alcoholism.*

Many alcohol researchers believe that a person’s genetic predisposition interacts with their environment to produce his or her overall risk for alcoholism. In addition, ethnic differences in rates of alcohol use and abuse have been linked to differences in the genes that code for certain enzymes that break down alcohol. Two enzymes in particular – alcohol dehydrogenase (ADH) and mitochondrial aldehyde dehydrogenase (ALDH) – are highly involved in alcohol metabolism. The ADH2*3 allele (a variation of the gene) has been documented to occur only in persons of African descent and certain Native American tribes. A study in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* investigates if an association exists between the presence of ADH2*3 alleles in young African American adults and a family history of alcohol dependence.

“We know that alcoholism is hereditary,” said Cindy L. Ehlers, associate professor of neuropharmacology at The Scripps Research Institute and lead author of the study. “But we only have very limited information on what is inherited, and almost no information on what genes might be involved except in the case of alcohol metabolizing enzymes.”

Differences in alcohol metabolizing enzymes, and the genes that encode them, are the best understood factors that influence drinking behavior and the risk of alcoholism. Alcohol is metabolized principally in the liver by two enzymes that act sequentially. ADH converts alcohol to acetaldehyde, and aldehyde dehydrogenase (ALDH) subsequently converts acetaldehyde to acetate. Acetate is then metabolized by tissues outside of the liver. Individuals with a mutation in the gene that encodes for ALDH2 (predominantly of Far East Asian descent) instead accumulate acetaldehyde in the blood and tissues after drinking. These individuals experience a more intense response to drinking alcohol, notably facial flushing, headaches, palpitations, dizziness and nausea. Understandably, few individuals in the world who possess two defective ALDH2 alleles (thereby intensifying their response to alcohol) have developed alcoholism.

“The present study extends previous research to the ADH2*3 allele,” said Ehlers. “This gene codes for a form of the ADH enzyme which may provide more efficient or more rapid alcohol metabolism. In the past, it has been shown that African American women with this gene are less likely to have children with birth defects due to alcohol use during pregnancy. In fact, our results demonstrate that the ADH2*3 allele is associated with a negative family history of alcoholism. These findings suggest that, in this sample of young African American adults, the ADH2*3 allele may be associated with a lowered risk for the development of alcoholism.”

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INVESTIGATING A “PROTECTIVE GENE” AGAINST ALCOHOLISM

A positive family history of alcoholism is one of the most consistent and powerful predictors of a person’s risk for developing the disorder. For example, individuals with a positive family history of alcoholism (usually a father) have a four to five times greater risk for developing alcoholism.

“Having a biological relative such as a father or brother who is alcoholic increases the chances of an individual developing the disease. However, as with all genetic diseases, not all offspring or relatives get the risk genes, and all individuals live in different environments that affect risk,” explained David W. Crabb, professor of medicine, biochemistry and molecular biology, and chair of the Department of Medicine at Indiana University Medical Center.

It is this interaction between a genetic predisposition for alcoholism and environmental variables that continues to intrigue researchers. Most believe that it is a 50/50 interaction. “The variables that we believe are most important psychosocially,” said Ehlers, “are religion, family intactness, being employed and positive peer influences. These are called protective factors. Their opposite – that is, no religion, divorce, an absent parent or poor family ties, unemployment and negative peer influence – are considered risk factors. These factors, like genes, can differ somewhat between ethnic groups. For instance, acculturation stress is said to influence drinking in Hispanic second-generation adolescents. Among African Americans, religion is one key variable. However, studies have shown that it is not so much practicing a religion, but rather, attending religious services that is important. And this is particularly important in supporting alcohol abstinence.”

Although Crabb calls this study “long awaited,” he would like to see future studies compare the presence of the high-activity ADH2*3 allele between African American alcoholics and nonalcoholics. “We would predict that the frequency of ADH2*3 will be lower in the alcoholics than in the nonalcoholics,” he said. “Similar findings have been obtained with individuals with another high-activity ADH allele, ADH2*2, that is found in Asians and Jews.”

“All in all,” said Ehlers, “I think this finding definitely strengthens the case for the genetics of alcoholism. It also further delineates the importance of ethnic and cultural differences when looking at risk and protective factors for alcoholism.”



Article is based on the following published research:

Ehlers, C.L.,
Gilder, D.A., Harris, L.,
& Carr, L.

(December 2001).

Association of the
ADH2*3 allele with
a negative family
history of alcoholism
in African American
young adults.

*Alcoholism: Clinical
and Experimental
Research,*
25(12), 1773-1777.



B

BRIDGING THE GAP BETWEEN GENETICS AND MOTIVATIONS TO DRINK ALCOHOL

97

- *Genetic variation appears to influence drinking to relieve social anxiety and improve mood.*
- *People's alcohol expectations are known to influence their likelihood of developing alcohol problems.*
- *New research has found that a person's genetic makeup may influence their motivation to drink, leading to behaviors that increase the risk for alcoholism.*
- *Particularly important motivations involve drinking to relieve social anxiety and improve mood.*

Alcohol researchers already know that people who expect positive results from drinking – a better mood or social ease – are more likely than other drinkers to develop alcohol problems. Conversely, those who have negative expectations – queasiness, dizziness or fatigue – are less likely to develop alcohol problems. A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that a person's genetic makeup may influence their motivation to drink, which can, in turn, enhance behaviors that increase the risk for alcoholism.

“We were interested in learning if beliefs about alcohol provided a partial explanation for how risk for alcoholism is transmitted across generations,” said Carol A. Prescott, associate professor of psychiatry and psychology at the Virginia Institute for Psychiatric and Behavioral Genetics Virginia Commonwealth University and first author of the study. “This transmission could be either environmental, in that young adults model the drinking behavior and motivations of their parents, or through genetic mechanisms, meaning there are physiological reasons alcohol is perceived as more pleasurable by some people and this is transmitted from alcoholic parents to their offspring via genes.”

“Although there is much consensus that alcohol abuse and dependence are caused, in part, by genetic factors, there is less certainty concerning what is inherited and how that genetic vulnerability is manifested,” added Kenneth J. Sher, curators' professor of psychological sciences at the University of Missouri and the Midwest Alcoholism Research Center. “Drinking motives represent a possible genetic mediator of alcoholism risk in multiple ways. For example, if genetic variability predisposes someone to experience greater neuropharmacological reward from alcohol, it could lead to stronger motives to drink for positive reinforcement. Furthermore, genetic vulnerability to depression or anxiety could serve as the foundation for drinking to alleviate negative mood states. Thus, the study attempts to answer the question of how genetic risk might be related to the various reasons individuals report for why they drink.”

Prescott and her colleagues examined data gathered from 2,529 female and 3,709 male adult twins participating in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders. “The data from twin pairs are used to estimate the degree to which individual differences can be attributed to differences among people in their genetic, family environmental and individual-specific environmental causes,” explained Prescott.

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BRIDGING THE GAP BETWEEN GENETICS AND MOTIVATIONS TO DRINK ALCOHOL

The researchers used four scales to measure individual differences in drinking motives: drinking to manage mood states, to relieve social anxiety, in social situations and to improve mental functioning. They also determined lifetime alcohol abuse and/or dependence among the study participants through use of a structured interview that used criteria from the *Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV)*.

“The findings contribute to our understanding of how genetic risk results in alcoholism,” said Prescott. “It has long been known that alcoholism runs in families. Twin and adoption studies in the past 20 years have shown that this familiarity is in large part due to genetic factors shared by family members. But we don’t know very much about how differences among people in their DNA sequences result in differences in risk for drinking problems. This study provides evidence that one way in which genetic factors lead to alcoholism is that genetic factors influence drinking motives, in particular, drinking to alleviate social anxiety. Although motives are still a long way from DNA, they are one step closer to the biology than the clinical disorder of alcoholism.”

Prescott noted that there are several ways in which genetic factors may intersect with social drinking. “There is an overlap of the genetic factors which influence risk for alcoholism and those which influence drinking to relieve social anxiety,” she said. “Also, alcohol works on the brain in a way quite similar to anti-anxiety drugs, and there are genetic influences on how these drugs affect brain receptors. In addition, personality characteristics such as the need for social stimulation and ‘risk taking’ are in part inherited. People with these personality traits may be more likely to seek social activities which involve drinking and this in turn increases their risk for alcoholism.”

“It’s important to note that our results don’t prove that motives are causal, only that they are consistent with a causal explanation,” said Prescott. “Nonetheless, these findings have important implications for intervention. These results, in combination with others, suggest that drinking motives may have a causal influence on alcoholism. If so, this provides an important point of intervention among individuals at high risk. Motives can be measured prior to the development of drinking problems, and at-risk individuals can be taught strategies for reducing their social anxiety other than using alcohol.”



Article is based on the following published research:

Prescott, C.A.,
Cross, R.J., Kuhn, J.W.,
Horn, J.L.,
Kendler, K.S.
(January 2004).

Is risk for
alcoholism mediated
by individual differences
in drinking
motivations?

*Alcoholism: Clinical
and Experimental
Research,*
28(1), 29-40.

WHEN ALCOHOL AND NICOTINE INTERACT

- *A blood alcohol concentration (BAC) indicates both a level of intoxication and severity of toxicity.*
- *Nicotine can significantly reduce the peak BAC among newborn rodents.*
- *People who drink and smoke at the same time may consume more alcohol to achieve a desired level of intoxication.*
- *The more alcohol consumed to attain ‘intoxication’ in the presence of nicotine, the greater the build up of toxic agents in the system.*

Mixing alcohol with other drugs – over-the-counter, prescription, legal or illegal – is a recipe for damage. The concurrent use of aspirin and alcohol, for example, leads to more severe effects on fetal brain development than the use of alcohol alone. Heartburn medications such as Tagamet® and Zantac® slow the activity of a stomach enzyme that is responsible for breaking down alcohol, thereby leaving organ systems exposed to alcohol’s toxic effects for an extended period of time. Alcohol and cocaine together exert more cardiovascular toxicity than either drug alone; they also produce a compound called cocaethylene, similar to cocaine but more lethal. Now, a study in the July issue of *Alcoholism: Clinical and Experimental Research (ACER)* confirms the damaging interaction of alcohol and nicotine.

“Blood alcohol concentration is an important determinant for level of intoxication and severity of toxicity,” explained Wei-Jung A. Chen, assistant professor of anatomy and neurobiology at Texas A&M University System Health Science Center and lead author of the study. “Our results confirm that blood alcohol concentration can be significantly reduced in the presence of nicotine.” In a prior study, Chen and his colleagues found that high doses of nicotine lowered blood alcohol concentrations (BACs) among neonatal rats. In this study, they found that even low nicotine doses have an effect on BACs. In either case, the results indicate that people who drink and smoke at the same time will have to drink more if they want to feel any kind of intoxicating effect.

“In the alcohol field, we know that alcohol abusers generally ‘drink to effect,’” said Susan E. Maier, research assistant professor in the department of human anatomy, College of Medicine at the Texas A&M University System Health Science Center. “This means they drink until they feel an expected level of intoxication from alcohol. It is also known that smokers drink more alcohol than non-smokers, and that people who misuse alcohol are more likely to smoke than those who do not misuse alcohol. The findings from this study suggest a possible reason why this may occur. If nicotine lowers the BAC, more alcohol needs to be consumed in order to achieve that alcohol intoxicating effect. The consumption of sufficiently more alcohol to reach that ‘high’ may lead to adverse effects on organ systems other than the brain, such as the liver and the heart.”

The first step in the metabolism of alcohol is its conversion to acetaldehyde, which belongs to a class of compounds called aldehydes (such as formaldehyde, a disinfectant and preservative).

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WHEN ALCOHOL AND NICOTINE INTERACT

Acetaldehyde is a highly reactive and toxic chemical that can damage the cells of any living thing. Although nicotine reduces a person's BAC, possibly leading them to drink more, nicotine does not affect the levels of agents such as acetaldehyde. The level of acetaldehyde would likely continue to build up in the system and have an adverse effect on the brain, liver and heart.

"My research primarily concerns the effects of substance abuse on the developing brain," said Chen, "so most of my studies use newborn rat pups. This is the developmental stage that most closely represents the brain-growth equivalent of the human fetus during the third trimester. However, we have results from adult rats showing the same effects of nicotine on reducing the BAC." Although Chen was hesitant to equate the nicotine doses used in the rodent study to human use because of the confounding effects of a number of variables (metabolism, smoking habits, smoking preferences, etc.), he did comment on what would have been considered a medium nicotine dose in the study. "There is limited information in the literature," he said, "to suggest that 1.5 mg/kg/day administered to rats may be equivalent to a human smoking one pack of cigarettes in a day."

"The best discoveries in science," said Maier, "are those that come from serendipitous findings, and I believe that the results described in this study fall into that category. What we once thought was coincidence – that smokers drink more alcohol – has suddenly gained a plausible explanation from the results of this study. Despite a plethora of studies examining the effects of each drug alone on various parameters, it is not until the interactive effects of both drugs are examined, that exciting and important findings such as these reveal themselves."



**Article is based
on the following
published research:**

Chen, W-J.A.,
Parnell, S.E.,
& West, J.R.
(July 2001).
Nicotine decreases
blood alcohol
concentration in
neonatal rats.
*Alcoholism: Clinical
and Experimental
Research*,
25(7), 1072-1077.



***F*EXPLORING THE GENETIC COMMONALITY OF ALCOHOL AND TOBACCO ABUSE**

- *Alcohol and tobacco abuse often go together.*
- *Rodents selectively bred for high, low and control sensitivity to alcohol were tested for their sensitivity to nicotine.*
- *Rodents with high sensitivity to alcohol were also more sensitive to nicotine-induced locomotor activity depression than rodents with low sensitivity to alcohol.*
- *This suggests that common genes modulate, at least in part, the actions of alcohol and nicotine.*

Addiction researchers are both familiar with and intrigued by the strong connection between smoking and drinking. Recent human studies have suggested that one or more genes may play a critical role in increasing vulnerability to alcohol and tobacco addiction. A study in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* uncovers new evidence which supports the theory that common genetic factors influence sensitivity to both alcohol and nicotine.

“Numerous studies in the last several decades have confirmed that drinking and smoking are positively correlated,” said Christopher M. de Fiebre, assistant professor of pharmacology and neuroscience at the University of North Texas Health Science Center at Fort Worth and corresponding author for the study. “Nowhere is this association seen as clearly as in alcoholic populations. While the percentage of smokers in the general American population has decreased over the last several decades, the rate of smoking among alcoholics has remained at approximately 90 percent, a rate well above that seen in nonalcoholic populations. We knew that whether an individual develops alcoholism or becomes dependent on tobacco is mediated by both genetic and environmental factors. We hypothesized that common genetic factors were involved in modulating sensitivity to alcohol and nicotine and this, in turn, influenced the development of the co-abuse of these two agents.”

Male and female rats selectively bred for high (HAS), low (LAS) and control (CAS) sensitivity to alcohol were tested for nicotine sensitivity using several different measures. The HAS rodents were found to be more sensitive to one measure in particular – nicotine-induced locomotor activity depression – than the LAS rodents. Researchers also measured plasma and brain levels of nicotine and its primary metabolite, cotinine, as well as the binding of three nicotinic ligands in eight brain regions. Since no differences in plasma or brain nicotine levels were seen between the HAS and LAS rodents, the authors speculate that the HAS/LAS differences arise because of differences in the sensitivity of the central nervous system (CNS) to nicotine.

“The authors’ speculation is actually a very logical conclusion,” said Allan C. Collins, professor of pharmacology and behavioral genetics at the University of Colorado. “Many years of research done by many laboratories have demonstrated that mice, rats and humans may differ in behavioral reactions to a drug for two primary reasons: differences in drug pharmacokinetics,

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*F*EXPLORING THE GENETIC COMMONALITY OF ALCOHOL AND TOBACCO ABUSE

or differences in brain or CNS sensitivity.” The pharmacokinetics of a drug refers to the way it moves through the body, including its absorption into the circulation, its distribution to different parts of the body, its metabolism, and eventual elimination. “The authors measured the pharmacokinetic parameters via plasma and brain levels and found no difference,” continued Collins. “This leaves brain or CNS differences in sensitivity as the most likely explanation.”

“The key finding of this study is that there appears to be a commonality in the genes which modulate the actions of both nicotine and alcohol,” said de Fiebre. “Some, but not all, of the genes which modulate sensitivity to alcohol are probably the same as some, but not all, of the genes which modulate sensitivity to nicotine. Although we do not currently know which genes are responsible for modulating the actions of these two drugs ... we hypothesize that the overlap in genes controlling sensitivity to these two drugs may in part explain why smokers drink and drinkers smoke.”

“Which genes may be responsible for modulating the actions of alcohol and nicotine? The answer to this question remains largely unknown,” said Collins. “However, these findings add to the data which argues that common genes influence some of the behavioral actions of two of the most frequently abused drugs. It may be that studies that include both alcohol and nicotine may yield answers to questions that have remained unresolved for many years when the two drugs have been studied individually. Interestingly, Joe Medium and Sally Average have known for years that alcoholics are smokers. Yet this common knowledge has been, by and large, ignored by the scientific community. This paper will not change life as Joe and Sally know it, but it may help them to understand that there are biological or genetically determined reasons that contribute to individual differences in vulnerability to both alcohol and tobacco abuse.”



Article is based on the following published research:

De Fiebre, N.C.,
Dawson, Jr., R.,
deFiebre, C.M.
(June 2002).

The selectively bred
high alcohol sensitivity
(HAS) and low
alcohol sensitivity (LAS)
rats differ in sensitivity
to nicotine.

*Alcoholism: Clinical
and Experimental
Research,*
26(6), 765-772.



ABNORMALITIES IN STRESS HORMONE RESPONSE AMONG ALCOHOLICS

- *The reward and stress systems of the brain are closely interconnected.*
- *The euphoria caused by normal drinking is associated with the release of stress hormones.*
- *Alcoholism, in contrast, may be associated with a dysfunctional stress response.*
- *Some alcoholics may drink to relieve the prolonged elevation of the stress hormone cortisol.*

The brain's reward and stress systems are closely interconnected, both anatomically and functionally. For example, the euphoric response to alcohol that most people experience is related to the release of stress hormones, whereas a dysfunctional stress response may be associated with alcoholism. A study in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* has made two important findings related to this association. One, some recovering alcoholics with a lengthy abstinence may have a chronically subdued stress system. Two, their systems are hypersensitive to a neurotransmitter called serotonin, which is a key player in the body's stress response. The implication is that some alcoholics will respond differently than non-alcoholics to stressful situations that involve the brain's serotonin system.

Serotonin is an important neurotransmitter that influences most functions, including general motor activity, learning and memory, reproduction, the stress response, sleep and food intake. Disturbances in serotonergic activity have been linked with numerous behavioral disorders, including alcoholism, drug abuse and depression. Fenfluramine is a drug formerly used to treat appetite disorders by increasing serotonin activity in the brain. In this study, fenfluramine was given to recovering alcoholics in order to cause an acute increase of serotonin activity. This, in turn, is believed to cause increased activity in the limbic-hypothalamic-pituitary-adrenal (LHPA) axis – an interconnected system of brain structures and hormone-producing organs that becomes especially active when an individual is stressed – leading to the secretion of a steroid called cortisol from the adrenal glands.

“Our major finding,” said Robert M. Anthenelli, associate professor of psychiatry in the College of Medicine at the University of Cincinnati, director of substance dependence programs at the Cincinnati Veterans Affairs Medical Center and lead author of the study, “was that alcoholics who'd been abstinent for an average of more than four months had a two-fold greater cortisol response compared with non-alcoholics following administration of fenfluramine. This result was surprising because all other published studies of alcoholics with shorter lengths of abstinence found they had a blunted or unchanged stress response following serotonergic stimulation. We also found that the stress hormone response in recovering alcoholics did not return to baseline levels as quickly as it did in age- and race-matched non-alcoholic comparison subjects. In other words, it appears that some of our recovering alcoholic subjects had difficulty turning off the fenfluramine-induced stress response.”

When an individual either perceives (psychological stress) or is faced with an actual threat (physical stress), the brain sets into action a cascade of signals intended to help respond to the threat. The end product of that cascade is the release of the stress hormone, cortisol, which

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BNORMALITIES IN STRESS HORMONE RESPONSE AMONG ALCOHOLICS

produces numerous effects throughout the body and brain. These effects include mobilizing more glucose for the body to use as energy to respond to the threat, raising blood pressure and suppressing the immune system. The stress response also triggers the sympathetic nervous system to increase heart rate and dilate the pupils (known as the fight-or-flight response). After mobilizing resources to meet the challenge, a reversed order of the process returns the body to a level of homeostasis (or non-stressed levels). Although stress response is important for survival, chronic stress or alterations in this response may contribute to various diseases.

“When stressors are short-lived,” explained Stephen Woods, professor of psychiatry and neuroscience at the University of Cincinnati, “the LHPA axis is very effective at ensuring that the body functions optimally until the situation changes for the better. When stress is more chronic, continued stimulation of the LHPA axis can have detrimental effects throughout the body.” This study, he said, clearly showed that abstinent alcoholics stimulated with fenfluramine (mimicking a stress-related increase of serotonin) had high blood cortisol levels for a significantly longer period of time than other individuals.

“While the Anthenelli report does not speculate on what some of the specific consequences of this might be,” said Woods, “it is reasonable to speculate that there are physical consequences. Whether this change in the LHPA axis response to a serotonin challenge is related to brain damage, or alteration resulting from former consumption of large amounts of alcohol, is not known. An interesting clue, however, is the authors’ recognition that the elevated cortisol response is reminiscent of what has been observed in individuals who have never before experienced alcohol, but who are considered high risk for developing alcoholism. One possibility, therefore, is that the prolonged elevation of cortisol following fenfluramine is characteristic of certain alcoholism-prone individuals and can be observed either before they ever drink or after a prolonged period of abstinence.”

“Based upon these findings,” said Woods, “one could go out on a limb and speculate that one reason some individuals have a tendency to imbibe more and more when exposed to alcohol, and eventually become alcoholic, is that a ‘defect’ in their LHPA response to serotonin is ‘corrected’ by alcohol. Remember that a prolonged cortisol response has undesirable consequences in the brain or throughout the body. Individuals who have such a prolonged response might find that it is remedied in the presence of alcohol. If this were the case, alcohol would provide a greater degree of reward value for them than for individuals who do not have the same ‘defect.’”

Article is based on the following published research:

Anthenelli, R.M.,
Maxwell, R.A.,
Geraciotti Jr., T.D.,
& Hauger, R.
(May 2001).

Stress hormone
dysregulation at rest
and after serotonergic
stimulation among
alcohol-dependent
men with extended
abstinence and controls.
*Alcoholism: Clinical
and Experimental
Research*,
25(5), 692-703.



TASTE TESTING MAY HELP IDENTIFY ALCOHOLISM RISK

- *Individuals with a family history of alcoholism are considered at-risk for developing the disorder.*
- *Not all family members, however, will develop alcoholism.*
- *Scientists are searching for “markers” to help pinpoint which individuals are most at risk.*
- *Taste perception of sour and salty solutions may be one such marker.*

Individuals with a family history of alcoholism are known to be at greater risk of developing the disorder than those without such a family history. In order to pinpoint these individuals, researchers are searching for “markers” of alcoholism risk. Both animal and some human studies have shown an association between sweet preference and excessive alcohol intake. A study in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* extends this research, finding that individuals with a positive paternal history (PHP) of alcoholism rate salty solutions as less pleasurable and sour solutions as more intense and less pleasurable than individuals with a negative paternal history (PHN) of alcoholism.

“Administering taste tests to offspring of alcoholics, those who have not yet developed alcoholism, is a way to examine taste perception without the possible interference of taste alterations that might occur in heavy drinkers,” said Henry R. Kranzler, professor of psychiatry at the University of Connecticut Health Center and corresponding author for the study. “As research in this area has moved from evaluating alcoholics to assessing offspring of alcoholics, new studies have also expanded the investigation of taste perception to include salty, sour and bitter tastes.”

“Taste preference is an innate reaction that may be detected within minutes after birth,” added Alexei B. Kampov-Polevoy, assistant professor of psychiatry at Mt. Sinai School of Medicine. “The most consistent finding that links taste preference and alcohol consumption [has been in animals] such as rats, mice and monkeys, that are prone to [both] excessive consumption of alcohol – in quantities sufficient for the development of physical dependence – and sweet solutions, sometimes quadrupling their normal daily fluid intake.” To date, however, not all studies of alcohol and sweet preference have yielded consistent findings.

For this study, researchers recruited 112 non-alcoholic participants (62 females, 50 males) between the ages of 18 and 40 from other studies of alcoholism risk and through advertisements. Family history interviews were used to identify psychiatric disorders and alcohol dependence among first-degree family members. Of the 112, 45 were considered PHP (32 females, 13 males), 67 were PHN. All participants were given a series of salty and sour solutions in varying concentrations, and asked to rate each for intensity and pleasantness.

“PHP individuals rated the salty solutions as less pleasurable than PHN subjects,” said Kranzler. “They also experienced the sour stimulus as more intense and less pleasurable than PHN subjects. These findings extend previous research by demonstrating the phenomenon of different

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TASTE TESTING MAY HELP IDENTIFY ALCOHOLISM RISK

taste characteristics among a larger and more diverse sample, and also support preliminary results from a study in Poland. We interpret these findings as evidence of unique taste perception among individuals with a paternal history of alcoholism compared to those without such a history.”

“We evaluated a group of nonalcoholic offspring of alcoholic fathers,” Kranzler said. “Participants were screened to exclude those who had ever experienced any alcohol, drug, and psychiatric disorders. In light of that, there are two possible explanations for our findings. First, these results could indicate that PHP individuals who are protected from alcoholism possess unique taste characteristics which contribute to this protection, that is, decreased pleasantness of salt and increased perception of intensity of sour. Alternatively, certain groups of individuals with a paternal history of alcoholism may inherit genetic alterations in taste characteristics that put them at increased risk for alcoholism. The implication of the latter explanation, altered taste characteristics, has yet to be fully explored in relation to alcoholism risk.”

Taste characteristics may interact with other factors in the development of alcoholism, said Kranzler. “Sweet-taste sensitivity has been linked to impulsiveness and other related behavioral factors associated with alcoholism,” he said, “but salty and sour taste differences are not as easily linked to such markers. We know that a decreased sensitivity to the intoxicating effects of alcohol appears to put one at risk of developing alcoholism. Perhaps salty and sour taste characteristics exert indirect independent effects that may be more important in the acquisition of drinking behavior, while decreased sensitivity to alcohol’s intoxicating effects may influence the maintenance of drinking behavior.”

Kampov-Polevoy’s research has also uncovered a connection between taste characteristics and other factors, finding that combining a sweet preference test and a personality profile can predict alcoholic versus non-alcoholic status with “fair” sensitivity and “good” specificity. “These data indicate that the sweet preference itself may not be sufficient for prediction of alcoholism in humans,” said Kampov-Polevoy. “However, if combined with some personality traits, it has a better predictive value regarding alcoholism,” he said.



Article is based on the following published research:

Sandstrom, K.A.,
Rajan, T.M., Feinn, R.,
Kranzler, H.R.
(June 2003).

Salty and sour taste
characteristics and risk
of alcoholism.

*Alcoholism: Clinical
and Experimental
Research,*
27(6), 955-962.



A SWEET TOOTH MAY BE A “MARKER” FOR THE GENETIC RISK FOR DEVELOPING ALCOHOLISM

- *Prior research has found an association between a liking for sweets and alcohol intake.*
- *New research indicates that a liking for sweets precedes alcoholism.*
- *A liking for sweets among individuals with a family history of alcoholism may serve as a “marker” for the genetic risk for developing alcoholism.*

Although both animal and human research has found an association between a liking for sweets and alcohol intake, it has been unclear if a liking for sweets among humans was caused by years of drinking or was linked to a genetic predisposition for alcoholism. Findings published in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* indicate that a liking for sweets precedes alcoholism and may in fact serve as a “marker” for the genetic risk for developing alcoholism.

“Previous research has established that in mammals such as mice, rats and monkeys, the preference for and consumption of sweet fluids are strongly correlated with voluntary alcohol intake,” said Alexei B. Kampov-Polevoy, assistant professor of psychiatry at Mt. Sinai School of Medicine and first author of the study. “It is thus possible to measure the amount of sweet solution that an animal drinks per day and accurately predict how much alcohol it will drink if given a chance.”

Kampov’s prior research also showed that alcoholic patients prefer stronger sweet solutions than do non-alcoholics. “However,” said Kampov, “it was not clear whether the increase in sweet preference was caused by a long history of drinking or if a higher sweet preference existed before the onset of alcoholism and somehow reflects predisposition for this disease. Our present manuscript is focused on resolving this issue.”

Researchers recruited 163 social drinkers from a university setting, dividing them into two groups: 81 (27 males, 54 females) had a paternal history of alcoholism; 82 (38 males, 44 females) did not. Each study participant rated a series of sucrose solutions for intensity of sweetness and palatability.

“Because humans consume their food based on both biological and environmental factors,” said Kampov, “we study the hedonic or pleasurable response to various concentrations of the sugar solutions. This trait is much less controlled by environmental factors. People may regulate the amount of sweet foods they consume, but they usually have less concern about their hedonic reaction to various sweet tastes. Thus, this test better reflects the biological reaction to sweet taste.”

Individuals with a paternal history of alcoholism were two and a half times more likely to like sweets than those who did not have a paternal history of alcoholism. “This finding indicates that sweet-liking precedes alcoholism,” said David Overstreet, associate professor of psychiatry with the Bowles Center for Alcohol Studies at the University of North Carolina at

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A SWEET TOOTH MAY BE A “MARKER” FOR THE GENETIC RISK FOR DEVELOPING ALCOHOLISM

Chapel Hill. “This suggests that the association previously reported is unlikely to be due to differential histories of alcohol exposure. This finding adds further weight to the hypothesis for the association between the liking for sweets and the genetic risk for alcoholism. However, it does not provide definitive proof.”

The present study produced some unexpected results as well: individuals with a paternal history of alcoholism disliked the tastes of the two weakest sucrose concentrations, while individuals without a paternal history of alcoholism rated the tastes as neutral.

“This finding may provide a mechanistic explanation of the association between sweet preference and risk for alcoholism,” explained Kampov. “Pleasurable reactions to both alcohol and sweet substances are regulated by the same mechanism, namely, the brain’s opioid system. Activation of this system results in increased consumption of both alcohol and sweets, while blockade of this system causes the opposite effect. The latter is used in medicine when opioid antagonists such as Naltrexone are prescribed to alcoholics to reduce their drinking. We believe that children of alcoholics have a genetic abnormality of the brain opioid system, which leads to an increased sensitivity to the rewarding effects of alcohol. The same abnormality of the brain opioid system may also lead to a preference for stronger sweet solutions.”

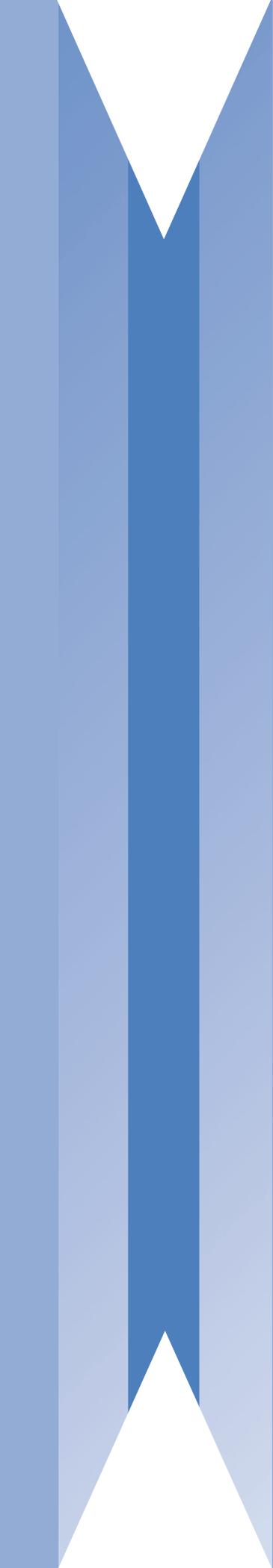
“These studies imply that a person whose relatives are alcoholics may be at greater risk for developing alcoholism if he or she likes sweets,” said Overstreet. “By demonstrating that a liking for sweets is dependent on the family history of alcoholism in young individuals, this paper has provided one further step in developing ‘sweet-liking’ as a marker for alcoholism.”

Overstreet suggested that future research be long-term in nature. “The current study could follow these individuals for a period of five or 10 years and repeat the assessments,” he said. “If the liking of sweets is predictive of the later development of alcoholism, then sweet-likers with a positive family history of alcoholism will exhibit more ... problems related to alcohol drinking. Another area that could be explored is conducting the sweet test in even younger individuals. It is not uncommon for children of alcoholics to have started heavy drinking during their teenage years. Being able to advise and counsel individuals at risk before alcohol abuse has started may help prevent its onset and/or progression.”



Article is based on the following published research:

Kampov-Polevoy, A.B.,
Garbutt, J.C.,
Khalitov, E.
(November 2003).
Family history of
alcoholism and
response to sweets.
*Alcoholism: Clinical
and Experimental
Research*,
27(11), 1743-1750.



*M*ental
Health



MENTAL HEALTH

Articles in the *Mental Health* Category

1. Alcoholics Have Blunted Responses to Psychological Stressors Such as Public Speaking
2. Alcoholics With Antisocial Personality Disorder Have Blunted Emotional Reactivity
3. Childhood Abuse May Predict Social Phobia, Agoraphobia and Post Traumatic Stress Disorder Among Adult Alcoholics
4. Searching for Anxiety Relief in Alcohol Can Be Dangerous
5. Suicidal Behavior Among Alcoholics
6. Adult Alcoholism and Attention Deficit Hyperactivity Disorder Are Connected
7. Alcohol Impairs Executive Cognitive Functioning Much Longer Than Expected
8. Alcohol Damages Day-to-Day Memory Function



ALCOHOLICS HAVE BLUNTED RESPONSES TO PSYCHOLOGICAL STRESSORS SUCH AS PUBLIC SPEAKING

- *Researchers measured the cardiovascular responses of alcoholics and nonalcoholics to the psychologically stressful act of public speaking.*
- *Alcoholics had blunted heart-rate responses to public speaking even though they reported similar anxiety responses to the nonalcoholics.*
- *This suggests a disconnection between perception of threat and the resulting physiological responses among the alcoholics.*

Secretion of a stress hormone called cortisol and activation of the sympathetic nervous system are components of the classic “fight or flight” response to danger. A common source of cortisol release and increased cardiovascular activity is public speaking. A study in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* builds upon previous work by comparing the cardiovascular responses of alcoholics and nonalcoholics to the psychological challenge of public speaking in relation to the physical challenge of standing (orthostasis).

“Since cortisol is central to our ability to handle stress,” said William R. Lovallo, director of the Behavioral Sciences Laboratories at the Veterans Affairs Medical Center in Oklahoma City and corresponding author for the study, “we were surprised several years ago when we found that patients with alcohol dependence had cortisol responses that were absent or greatly attenuated. It didn’t matter if the patient was asked to hold a hand in ice water, squeeze a hand-exercise device until it hurt, do mental arithmetic problems, or perform in a public-speaking simulation. Due to this cortisol response deficit, we suspected that these patients might also have a reduced fight or flight response. Most persons see public speaking as socially threatening, and they respond with the primitive fight or flight mechanism.”

Before testing alcoholics for their responses to a public-speaking task, researchers first needed to establish if their sympathetic nervous system was able to respond at all. “This would tell us if their blunting was specific to psychological stressors like public speaking,” said Lovallo, “or due to a generalized autonomic deficit.”

He and his colleagues examined 20 alcohol-dependent subjects, abstinent for 21 to 28 days, and 10 age-matched nonalcoholics. All subjects were males between the ages of 22 and 55 years. The researchers used impedance cardiography and dynamap blood pressure monitoring to assess the participants’ heart rate, stroke volume, cardiac output, total peripheral resistance, mean arterial pressure, systolic blood pressure and diastolic blood pressure during orthostasis and public speaking. Self-reported mood was also assessed during these two tasks.

Cardiovascular responses to orthostasis were similar for the two groups. However, the alcoholics had blunted heart-rate responses to public speaking even though they reported similar

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ALCOHOLICS HAVE BLUNTED RESPONSES TO PSYCHOLOGICAL STRESSORS SUCH AS PUBLIC SPEAKING

anxiety responses to the nonalcoholics. This suggests a disconnection between perception of threat and resulting physiological responses among the alcoholics.

“The similar cardiovascular responses to orthostasis among the alcohol-dependent patients indicate that their autonomic nervous systems were working normally,” said Lovallo. “Yet when we asked them to prepare and memorize a short speech and then deliver the speech to a video camera, the patients reacted with little or no change in heart rate, and of course, they failed to have a cortisol response. The patients reacted as if the social challenge of public speaking had no special meaning for them. So, the sympathetic nervous system in the patients looked normal, but their response to a psychological stressor was almost absent. When faced with a socially meaningful stressor, neither part of their fight-flight mechanism was working.”

“Emotion is the product of cognitive and physiological processes,” observed Ralph E. Tarter, professor of pharmaceutical sciences and psychiatry at the University of Pittsburgh. “Although speculative, the results of this study point to a physiologic-cognitive disconnection as a potential mechanism underlying the disturbed emotional experience of alcoholics. For example, although speculative, it could perhaps help explain why alcoholics appear outwardly unconcerned about their alcoholism when in fact their life is chaotic. This is commonly referred to as ‘denial.’ However, we need further research to delineate the extent to which deficient interpretation of cognitive and physiological processes is responsible for certain of the emotional tendencies of alcoholics.”

“Psychological stressors are usually events in our environment that have no ability to hurt us directly, in the way that cold, hunger or a predator can hurt us. So, why do we react as if we were in real danger when we are only giving a talk to an audience, and a fake audience at that? We process these kinds of events in our frontal cortex, the part of the brain that allows us to imagine things and to project ourselves into the future. This brain region has extensive connections with our limbic system, the primitive brain areas responsible for emotions and stress responses. Our results suggest that some aspect of this frontal-limbic connection has been altered in patients recovering from severe alcohol dependence, which has implications for their social functioning and comprehension,” said Lovallo.



Article is based on the following published research:

Panknin, T.L.,
Dickensheets, S.L.,
Nixon, S.J.,
Lovallo, W.R.
(June 2002).
Attenuated heart rate
responses to public
speaking in individuals
with alcohol
dependence.
*Alcoholism: Clinical
and Experimental
Research*,
26(6), 841-847.



ALCHOLICS WITH ANTISOCIAL PERSONALITY DISORDER HAVE BLUNTED EMOTIONAL REACTIVITY

- *Emotional reactivity refers to how people respond to pleasant and unpleasant events.*
- *New research has found that adult male alcoholics with antisocial personality disorder (ASPD) have abnormally low emotional responsiveness.*
- *Researchers speculate that the blunted responses found in this subgroup of alcoholics may be related to poor inhibitory abilities, which may, in turn, facilitate the development of alcoholism.*

Emotional reactivity refers to how people respond to both pleasant and unpleasant events, including ones that cause physical and mental stress. A study in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found abnormally low emotional responsiveness among adult male alcoholics with antisocial personality disorder (ASPD). Study authors say these findings may reflect dysfunction in brain regions that govern how humans relate to their environment and make adaptive decisions, which may in turn facilitate the development of alcoholism through maladaptive, disinhibited behavior.

“Despite their often subtle nature, emotional reactions hold a central position in determining how the brain regulates behavior,” said Robert Miranda, Jr., a National Institute on Alcohol Abuse and Alcoholism Postdoctoral Fellow at Brown University and first author of the study. “Through integration with cognitive processes, emotional reactions play an important role in learning and memory, evaluating variable environmental contingencies, and motivating adaptive behavior. There is considerable variability among individuals in terms of how emotionally reactive we are to different types of situations and events. These differences may indicate vulnerability to certain psychiatric conditions, such as mood and anxiety disorders and addictions. In the case of antisocial behavior and addictions, there may be diminished reactions to cues that signal aversive events, including punishment.”

Individuals who do not experience the appropriate amount of anxiety or negative emotion when threatened are unlikely to alter their behavior in response to the threat, said Peter R. Finn, professor of psychology at Indiana University in Bloomington. “Psychopaths, for example, are a subset of people with ASPD who show hyporesponsiveness to aversive stimuli. This study looks at reduced or hyporeactivity to aversive stimuli as evidence for poor inhibition, which may result in increased vulnerability to a wide range of problems including criminal, alcohol and/or drug problems. In other words, this hyporesponsivity may be manifesting itself in the antisocial behavior as well as the excessive use of alcohol.”

Researchers examined 62 males, divided into three groups: 24 were alcohol dependent; 17 were alcohol dependent and had ASPD; and 21 “controls” were neither alcohol dependent nor had ASPD. All of the participants completed self-report questionnaires, clinical interviews,

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LCOHOLICS WITH ANTISOCIAL PERSONALITY DISORDER HAVE BLUNTED EMOTIONAL REACTIVITY

and had their eye-blink electromyograms measured to acoustic startle probes while viewing color photographs rated as pleasant, neutral and unpleasant. (The startle response is a defensive reflex that is evoked when a person is presented with an abrupt event, such as a loud, unexpected noise. The reflex – in this case, the eye blink – is influenced by emotional states. It is “normally” larger when an individual is presented with unpleasant pictures, sounds or odors, and smaller when presented with pleasant stimuli.)

“We found that persons with co-existing alcoholism and ASPD are different from alcoholics without ASPD and non-ASPD, non-alcoholic controls in their responsiveness to emotional cues,” said Miranda. “The control and non-ASPD alcohol-dependent groups showed the normal linear increase in the eye-blink component of the startle reflex from pleasant to neutral to unpleasant stimuli. In contrast, alcoholics with ASPD did not show the typical increase of startle in response to the unpleasant stimuli or the decrease in response to pleasant stimuli. In short, their emotional responses appeared to be blunted. Importantly, all three groups rated the photographs similarly, ruling out the likelihood that response differences were due to altered subjective experiences of the photographs.”

Finn said these findings have both immediate and future applications. “Alcoholics tend to get into trouble a lot,” he said. “Yet these individuals simply may not be as affected by the prospects of negative outcomes, and may, in fact, have problems inhibiting their behavior to avoid such outcomes.”

Miranda agrees. “Conduct disorder (CD), the childhood predecessor to ASPD, is the most robust psychiatric risk factor for adolescent alcohol and drug use,” he said. “Numerous studies point to a consistent relationship between conduct problems in early and middle childhood and later drug use. Furthermore, the behavioral patterns exhibited by children and adolescents with CD may be a marker for underlying deficits in emotional reactivity and related impairment in frontal-limbic processes.”

Although a number of studies have identified a strong relationship between child and adolescent conduct problems and drug use, Miranda added, little research has targeted the underlying mechanisms that might explain this association. He said future research would attempt to do just that.



Article is based on the following published research:

Miranda Jr., R.,
Meyerson, L.A.,
Myers, R.R.,
Lovallo, W.R.
(December 2003).
Altered affective
modulation of the
startle reflex in
alcoholics with
antisocial personality
disorder.
*Alcoholism: Clinical
and Experimental
Research*,
27(12), 1901-1012.



CHILDHOOD ABUSE MAY PREDICT SOCIAL PHOBIA, AGORAPHOBIA AND POST TRAUMATIC STRESS DISORDER AMONG ADULT ALCOHOLICS

- *Many alcoholics report coexisting psychiatric disorders such as social phobia, agoraphobia, and post traumatic stress disorder.*
- *New research indicates that childhood abuse – sexual, physical or both – may play a role in the later development of coexisting psychopathologies among alcoholics.*

Findings published in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* have uncovered the important role that an environment of childhood abuse – sexual, physical or both – appears to play in the development of psychiatric comorbidity among alcoholic patients.

“Our findings clearly indicate that childhood abuse – more specifically, sexual abuse and combinations of sexual and physical abuse – is an important factor for the presence of comorbid anxiety disorders in treated alcoholics, particularly regarding social phobia, agoraphobia and post traumatic stress disorder,” said Willemien Langeland, a freelance trauma researcher at the University of Amsterdam and the Vrije Universiteit in Amsterdam, as well as first author of the study.

Langeland added that compared with other environmental risk factors, childhood sexual and “dual” abuse contribute independently to a more severe clinical profile, that is, more comorbid diagnoses in abused versus non-abused alcoholic patients. “This has not been previously demonstrated in treated alcoholics,” she said. “In addition, more severe and intrusive forms of early sexual abuse as well as early multiple traumas are associated with a more complex symptom constellation that includes dysthymia (a chronic mood disorder) and suicidality.”

“This study and a few others clearly show that seeing alcoholics only as people having an alcohol problem should be a thing of the past,” said Onno van der Hart, professor of psychopathology of chronic traumatization in the department of clinical psychology at Utrecht University in the Netherlands. “Very often the alcohol dependency or abuse is an indissoluble part of a history of childhood maltreatment or other adverse life events or conditions, as well as a range of other mental health problems. Insight into such complex patterns will lead to the realization that the simple treatment goal of ‘stopping drinking’ makes sense only when the overall treatment is geared toward this more complex system of problems.”

Researchers collected data during eight months (September 1994 - May 1995) from 155 alcoholics (122 males, 33 females) applying for treatment in a center for substance-use disorders. All study participants were assessed for demographics and treatment history through use of the European Addiction Severity Index. Numerous childhood stressors were indexed by the Structured Trauma Interview, and lifetime diagnoses of major depression, dysthymia, panic

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CHILDHOOD ABUSE MAY PREDICT SOCIAL PHOBIA, AGORAPHOBIA AND POST TRAUMATIC STRESS DISORDER AMONG ADULT ALCOHOLICS

disorder, social phobia, agoraphobia, generalized anxiety disorder and post traumatic stress disorder (PTSD) were assessed with the Composite International Diagnostic Interview. Participants were also asked about lifetime suicide attempts.

Alcoholic patients who reported childhood abuse – sexual, or sexual and physical – also reported social phobia, agoraphobia and PTSD more often than patients with no history of abuse. “Our study suggests a distinct pattern of psychiatric comorbidity associated with childhood abuse in treatment-seeking alcoholics,” said Langeland. “These findings point to the need for greater clinical attention to the role of childhood stressors in the evaluation and treatment of alcoholic patients. They also underline the importance of routine assessment of childhood trauma and possible trauma-related disorders in individuals presenting to alcohol-treatment services. Usually, standard or routine screening procedures do not include possible trauma-related symptoms such as PTSD, leading to underdiagnosis of this disorder.”

Although this study’s sample size of men was much greater than the sample size of women, Langeland said it is likely that gender may influence the way that alcohol problems and a co-occurring psychiatric disorder are related. “For example,” she said, “there is some evidence that women may be at higher risk than men to [develop] the form of comorbidity in which PTSD develops first.”

In addition, said Van der Hart, “it may well be that many female patients with alcohol dependence or abuse seek treatment in, or are referred to, more general mental-health centers. Perhaps their comorbid disorders, such as depression and anxiety disorders, as well as their trauma history (females report higher degrees of sexual abuse history), are more in the foreground, with the alcohol problems regarded as part of this overall clinical picture.”

“Given the fact that a considerable proportion of alcoholics report a history of childhood trauma and adverse events that include childhood physical and/or sexual abuse, as well as maternal dysfunction, which may point to neglect,” added Van der Hart, “studies should investigate whether the use of substances may be a form of coping or self-soothing. In addition, future studies, like the current one, should not only focus on one type of trauma, such as childhood sexual abuse, but should take the whole range of adverse life events and conditions into account.”

Article is based on the following published research:

Langeland, W.,
Draijer, N.,
& van den Brink, W.
(March 2004).
Psychiatric comorbidity
in treatment-seeking
alcoholics: The role of
childhood trauma and
perceived parental
dysfunction.
*Alcoholism: Clinical
and Experimental
Research*,
28(3), 441-447.



SEARCHING FOR ANXIETY RELIEF IN ALCOHOL CAN BE DANGEROUS

- *Practically everyone experiences some degree of anxiety in his or her life.*
- *Anxiety sensitive (AS) individuals have a fear of anxiety symptoms.*
- *Many people with alcohol problems have higher AS levels than “normal” drinkers.*
- *High AS individuals appear to be more “soothed” by alcohol than low AS individuals.*

People with high anxiety sensitivity (AS) have a fear of anxiety symptoms. Feeling common anxiety symptoms such as “butterflies in your stomach,” rapid breathing or an increased heart rate in the face of a stressful situation tends to amplify their anxious response. A study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* investigated if high AS individuals are more soothed by alcohol than low AS individuals after being exposed to a stressful situation.

“People diagnosed with alcohol problems exhibit significantly higher levels of anxiety sensitivity than non-clinical populations,” said Alan B. MacDonald, a doctoral candidate in psychology at Dalhousie University and one of two first authors of the study. “Just as everyone experiences some degree of anxiety in their lives, almost everyone has some degree of anxiety sensitivity. However, people who have high anxiety sensitivity are people on the upper end of the continuum.” MacDonald estimates that approximately 16 percent of the population has high AS.

“Anxiety sensitive individuals are people who have a fear of anxiety, basically,” said Robert O. Pihl, professor of psychology and psychiatry at McGill University. “It’s kind of an anticipatory type response. This study helps us understand why these individuals are highly likely to become alcohol abusers.”

Although prior research has clearly demonstrated a link between alcohol problems and high AS, it has not established causality. This is, does high AS contribute to alcohol abuse or is it the other way around? This study examined volunteer undergraduate students with high or low AS who did not have, or were not yet diagnosed with, an alcohol problem. Participants were asked to hyperventilate for three minutes to induce anxiety-like symptoms. Following hyperventilation, participants were asked to report on three aspects of their experience: fearful thoughts, such as losing control; negative feelings, such as nervousness; and body sensations, such as an increased heart rate. Two doses of alcohol (high and low) were then administered.

Following the hyperventilation exercise and while completely sober, high AS participants reported significantly more fearful thoughts and negative feelings than the low AS participants. They also reported experiencing these negative thoughts and feelings more intensely than their low AS counterparts. After ingesting alcohol (both the high and low doses), high AS individuals showed much greater reductions in their fearful thoughts and negative feelings than the low AS participants. The high AS individuals not only found the alcohol more “soothing” (in that they experienced a greater reduction in their worries and concerns) than did their low AS counterparts, but this soothing effect became more pronounced the more they drank.

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SEARCHING FOR ANXIETY RELIEF IN ALCOHOL CAN BE DANGEROUS

MacDonald said that “coping” as a reason for drinking is a well-known marker for future alcohol abuse. “Our findings support the idea that high AS individuals may drink to cope with unpleasant sensations associated with anxiety, which could in turn lead to alcohol abuse,” said MacDonald. “Moreover, the more they drink, the greater the benefit they experience in terms of avoiding these unpleasant sensations. This may explain why high AS individuals report drinking to excess more frequently than the regular population.”

Although it might be said that people with high AS experience more benefits or positive effects from the stress-response dampening properties of alcohol, developing a dependency on alcohol is a potential downside. High AS individuals could become highly motivated to drink as a means of avoiding or reducing the anxiety sensations that they find so uncomfortable.

“Our findings have opened a small window into why some people may learn to abuse alcohol,” said MacDonald. “Knowing why leads to knowing what to do about it. We know that about one in seven readers of this article may have a high degree of AS. We are not saying that all people with high AS will necessarily go on to abuse alcohol, but it does appear that they are a high-risk group. If a reader recognizes that they may have high AS, perhaps they should think twice about using alcohol to feel better about their anxiety symptoms.”

MacDonald believes the study’s findings have implications for both prevention and treatment programs. “There is something unique about anxiety sensitivity, rather than anxiety per se, which may lead to future alcohol problems. Also, we need to study how well people are able to stay abstinent with or without treatment of anxiety sensitivity.” He suspects that treatment of high AS may enhance this population’s ability to stay abstinent from alcohol.

Indeed, Pihl believes it is imperative to be as specific as possible when looking for the different reasons why people abuse alcohol and other drugs. “We can’t look at these individuals as one kind of ubiquitous mass,” he said. “When someone talks about alcoholism, that doesn’t really explain anything. That doesn’t tell you ‘why.’ There are multiple reasons why things happen, and it’s important to understand these reasons before you get into any kind of treatment. Treatment should be specific to the ‘why.’”



Article is based on the following published research:

MacDonald, A.B.,
Baker, J.M.,
Stewart, S.H.,
& Skinner, M.
(November 2000).
Effects of alcohol on
the response to
hyperventilation of
participants high and
low in anxiety sensitivity.
*Alcoholism: Clinical
and Experimental
Research*,
24(10), 1656-1665.

SUICIDAL BEHAVIOR AMONG ALCOHOLICS

- *Alcoholics have a much higher rate of death by suicide than do members of the general population.*
- *Those alcoholics with a history of suicide attempts appear to have a significantly more severe course of alcohol dependence than other alcoholics.*
- *The fathers, mothers and siblings of alcoholics who had attempted suicide also showed a significantly higher prevalence of suicide attempts.*

Contemplating suicide is very common, according to a 1997 article in the *New England Journal of Medicine*. In fact, up to one third of the general population has thought about suicide at some point in their lives. The strongest predictor of suicide is psychiatric illness; more than 90 percent of people who commit suicide have diagnosable psychiatric illnesses at the time of death – usually depression, alcohol abuse or both. The lifetime risk for suicide completion among alcohol-dependent individuals has been reported to be almost 10 percent, which is five to 10 times greater than that found among the general population. A study in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* seeks to identify risk factors for suicide attempts among a large family-based sample of alcoholics from the Collaborative Study on the Genetics of Alcoholism (COGA).

“We found that alcohol-dependent individuals with a history of suicide attempts had a significantly more severe course of alcohol dependence,” said Marc A. Schuckit, principal COGA investigator at the University of California-San Diego site, also of the Veterans Affairs Medical Center and corresponding author for the study. “They also had a higher prevalence of both independent and substance-induced psychiatric disorders, as well as other substance dependence.” Schuckit speculated that increased alcohol intake by this subgroup of alcoholics may have led to more severe problems, which may have then resulted in brain dysfunction, neuropsychological changes and subsequent judgment impairment, an increased likelihood of mood swings and alcohol-related violent behavior. All of these factors could have contributed to life problems, as well as suicide attempts.

For this COGA investigation, 3,190 alcoholic men and women were given semi-structured, detailed interviews. Information about suicidal behavior, socioeconomic characteristics, psychiatric comorbidity, substance-use disorders and characteristics of alcohol dependence were obtained from the alcohol-dependent probands (original subjects of the study), their relatives, and controls (families without a history of alcohol dependence).

Of the total number of alcoholics, 522 (more than 16 percent), had a history of ever having attempted suicide; whereas 2,668 (close to 84 percent), did not. First-degree relatives (fathers, mothers and siblings) of individuals who had attempted suicide also showed a significantly higher prevalence of suicide attempts than other alcoholics, but – according to previous research – no enhanced rate of alcohol dependence, psychiatric comorbidity or other sub-

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SUICIDAL BEHAVIOR AMONG ALCOHOLICS

stance-use disorder. This suggests that suicidal behavior may be transmitted in families independent of alcohol dependence, psychiatric disorders or other substance-use disorders.

“Is there a suicide gene? Probably not,” said Robert M. Anthenelli, associate professor of psychiatry in the College of Medicine at the University of Cincinnati and director of substance dependence programs at the Cincinnati Veterans Affairs Medical Center. “But that’s beyond the scope of this paper’s findings. What this finding does is give some support for the idea that ‘suicidality’ or suicide attempts seem to run in families. However, family studies rarely do a good job of teasing out nature versus nurture, or genetics versus environment. What this study does nicely is show that a suicidal trait seems to exist independent of substance abuse disorders as well as other psychiatric disorders.”

Anthenelli added that the size of the study makes the associations found between suicidality and alcohol dependence more meaningful and believable than similar findings in previous, smaller studies. “Another strength is the percentage of women included, almost 40 percent,” he said, “which a lot of other studies are not always able to achieve.” In fact, he said, some of the gender differences in the findings were notable.

“The odds ratio of alcoholic women making a suicidal attempt was 2.86,” he said. “This means that an alcoholic woman has almost a three-fold greater likelihood of attempting suicide than a male alcoholic. That’s powerful. It also fits well with the knowledge that women in the general population make more suicide attempts than men, even though men have a higher completion rate.”

Schuckit plans to continue with the investigation of suicidality among alcoholics in order to better understand and prevent suicide attempts and completions among this subgroup. “The underlying theme of this paper,” said Schuckit, “and of the COGA studies in general, is that alcohol-dependent individuals who drink will likely have mood problems. Those that drink a lot will have major problems.”



Article is based on the following published research:

Preuss, U.W.,
Schuckit, M.A.,
Smith, T.L., Danko, G.P.,
Buckman, K.,
Bierut, L., Bucholz, M.N.,
Hesselbrock, M.N.,
Gesselbrock, V.M.,
& Reich, T.
(April 2002).
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individuals with
and without suicide
attempts.
*Alcoholism: Clinical
and Experimental
Research*,
26(4), 471.

A **ADULT ALCOHOLISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER ARE CONNECTED**

- *Attention deficit hyperactivity disorder (ADHD) symptoms include inattention, motor hyperactivity and impulsiveness.*
- *ADHD is five to 10 times more frequent among adult alcoholics than among the normal population.*
- *Investigation of the serotonin transporter gene (5-HTT) and the 5-HT_{2c} receptor Cys23Ser polymorphism does not support a genetic commonality of ADHD and alcoholism.*

Attention deficit hyperactivity disorder (ADHD) symptoms include inattention, motor hyperactivity and impulsiveness. Roughly half of the adults who report ADHD symptoms also report a co-existing substance abuse disorder. New findings published in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* have identified a distinct phenotype or “profile” of individuals with co-existing ADHD and alcoholism. Although prior studies have suggested a genetic commonality of ADHD and alcoholism, the study found no significant contribution of two specific candidate genes, the promoter polymorphism of the serotonin transporter gene (5-HTT) and the 5-HT_{2c} receptor Cys23Ser polymorphism.

“Our results indicate that individuals with persisting ADHD symptoms in adulthood seem to be at high risk of developing an alcohol use disorder,” said Monika Johann, medical doctor and research associate at the University of Regensburg and first author of the study. “Moreover, there is evidence for a highly increased severity of alcohol dependence in subjects with ADHD.”

Researchers examined 314 adult alcoholics (262 males, 52 females) as well as 220 unrelated healthy control subjects, all of German descent. Each participant was assessed for psychiatric disorders, such as substance-use disorders (including alcoholism), ADHD and antisocial personality disorder (ASPD). Patients with a history of major psychiatric disorders, including depression and schizophrenia, and those with addictions to drugs other than alcohol and nicotine, were excluded from the investigation. Genotyping was performed without knowledge of diagnostic status, with a focus on the 5-HTT promoter and the 5-HT_{2c} Cys23Ser polymorphism.

“Prior neuroendocrine challenge studies with a drug called fenfluramine in subjects with ADHD or alcoholism revealed similar differences in the serotonergic neurotransmission when compared to normal subjects,” explained Johann. “The usual response to fenfluramine administration is a measurable increase in the circulating prolactin. This usual increase is blunted in subjects with ADHD or alcoholism. The main structures responsible for the fenfluramine-induced prolactin release are the 5-HTT and the 5-HT_{2c} receptors. Therefore, both seemed plausible as overlapping sources of genetic liability of ADHD and alcoholism.”

Neither of them, however, appear to be genetic risk factors in the sample examined. “Our data

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demonstrate that the 5-HTT promoter and the 5-HT_{2c} Cys23Ser polymorphism do not contribute to the putative common genetic predisposition for ADHD and alcohol dependence,” said Johann. “However, several other candidate genes have yet to be investigated.”

Nonetheless, the findings do indicate a distinct phenotype, a way to measure an observable trait or behavior. Adult alcoholics with ADHD had a significantly higher daily and record intake of alcohol per month, an earlier age of onset of alcohol dependence, a higher frequency of thoughts about suicide and a greater number of court proceedings .

Despite the lack of support for a common genetic predisposition, “the data show once again that to have ADHD means to be at high risk for developing alcohol dependence,” said Ema Loncarek, a medical doctor and clinician at the psychiatric clinic of the University of Regensburg. “Dr. Johann’s findings of a phenotype are very close to what we see in drug addicts with ADHD, and what has been described before by other authors. ”

Johann described in more detail the phenotypic variations she and her colleagues found. “Within this group of alcoholics, subjects with ADHD in adulthood are five to 10 times more frequent than in the normal population,” she said. “Compared to alcoholics without ADHD, alcoholics with ADHD in adulthood were at least four years younger at onset of alcoholism, drank about 50 grams pure alcohol more per day during the previous month, had a nearly twofold higher rate of first-degree positive family history of alcoholism, had a nearly three times higher frequency of antisocial personality disorder, had a nearly seven times higher frequency of court proceedings, and had a more than two times higher frequency of suicidal thoughts.”

Both Johann and Loncarek spoke of a need for the development and evaluation of specialized treatment programs that address “phenotypical specifics” as well as co-existing disorders such as alcoholism and ADHD. While pharmacological remedies, they noted, have been extensively evaluated for the treatment of ADHD in childhood, little attention has been given to substance abusing individuals with ADHD in adulthood.”

“ADHD seems to be highly underestimated in adulthood,” said Johann, “yet seems to be an important risk factor for the development of alcohol dependence.”



Article is based on the following published research:

Johann, M., Bobbe, G.,
Putzhammer, A.,
Wodarz, N.
(October 2003).
Comorbidity of alcohol
dependence with
Attention deficit
hyperactivity disorder:
differences in phenotype
with increased
severity of the
substance disorder,
but not in genotype
(serotonin transporter
and
5-hydroxytryptamine-
2c receptor).
*Alcoholism: Clinical
and Experimental
Research*,
27(10), 1527-1535.

A

LCOHOL IMPAIRS EXECUTIVE COGNITIVE FUNCTIONING MUCH LONGER THAN EXPECTED

- *Executive cognitive functioning (ECF) includes cognitive abilities such as abstract reasoning, planning and the capacity to govern self-directed behavior.*
- *Researchers have found that ECF is more impaired during the descending limb of the blood alcohol concentration curve, when people no longer feel stimulated by alcohol.*
- *These findings indicate that intoxication effects last much longer than previously believed.*

Executive cognitive functioning (ECF) encompasses a number of higher order cognitive abilities, such as attention, abstract reasoning, organization, mental flexibility, planning, self-monitoring and the ability to use external feedback to moderate personal behavior. A study in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* has confirmed that not only does alcohol impair ECF but, surprisingly, this effect is more pronounced on the descending rather than the ascending trajectory (or limb) of the blood alcohol concentration (BAC) curve.

“Executive functioning is basically a metaphor for frontal lobe functioning,” explained Robert O. Pihl, professor of psychology and psychiatry at McGill University and first author of the study. “This area of the brain, the prefrontal cortex, arguably defines us as a species; it is roughly 120 percent larger in humans than in our closest primate relatives. In fact, some Russian neurophysiologists refer to it as the area of the brain that pulls the past, the present and the future together. In other words, it puts things in context.”

“Research on alcohol’s effects on ECF is important primarily because it sheds light on the relationship between intoxication and aggression,” added Jordan B. Peterson, associate professor of psychology at the University of Toronto. “Approximately 50 percent of murderers are intoxicated at the time of their crime. The same holds true of their victims.”

Study participants (n=41) were divided into two groups: 21 subjects were given 1.32 ml of 95 percent alcohol per kg of body weight mixed with orange juice; the remaining 20 were given a placebo. Participants were randomly assigned to either an ascending or descending limb group. (When people drink alcohol, stimulation is initially prominent, while blood alcohol levels are rising during the ‘ascending limb’ of the blood alcohol concentration [BAC] curve. During the ‘descending limb’ of the BAC curve, when blood alcohol levels are falling, sedation becomes the prominent experience.) All of the participants were given six tests of ECF when a breath measure of their BAC reached 0.08.

Intoxicated participants on both limbs demonstrated ECF impairment. However, the descending alcohol limb group showed greater ECF impairment than their ascending limb counterparts, particularly in spatial functioning.

“Our results were unexpected,” said Pihl. “Based on prior research, we had expected cognitive deficiencies to be greater on the ascending limb. Although ‘intoxication’ clearly lasts a long

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ALCOHOL IMPAIRS EXECUTIVE COGNITIVE FUNCTIONING MUCH LONGER THAN EXPECTED

time, you don't have the same feedback of feeling intoxicated on the descending limb. You have a different perception of what your decrements are when you 'feel' intoxicated and energized versus when you think, 'Hey, I'm getting sober.' Yet our findings show that even when you're at the same blood alcohol level on the downward limb, you have more pronounced deficits."

This finding has important ramifications for behaviors such as driving, Pihl added. "People who think they've waited their two hours before driving home may need to actually wait six hours. Or else, maybe at the time when you least expect it, you're the most vulnerable."

"The subjective effects that alcohol drinkers pursue are most likely experienced during the short, ascending limb," said Peterson. "Conversely, the descending limb lasts a very long time. This means that the drinker in the process of re-attaining sobriety is likely to be more dangerous, for example, than the drinker who is still imbibing. As the authors point out, this may also be relevant with regards to impaired driving: it could be that the drinker at a BAC of 0.08 is less qualified to drive while immediately recovering from a drinking episode than while actively drinking."

Peterson praised Pihl's lab for its investigation of relatively high-dose alcohol administration – research that has become increasingly difficult in recent years. "However, such high doses appear absolutely necessary to produce the kind of cognitive effects reported in this manuscript," he said. "Furthermore, they are clearly in keeping with the levels of intoxication that drinkers reach when drinking for pleasure in bars and at parties." He suggested that future research examine how long the detrimental descending-limb cognitive effects last. "Are drinkers back to baseline cognitive function once their BACs fall to 0.04, for example, or are they still substantively impaired? Have they returned to baseline the next day, after sleeping through the sobering-up process, even if they still feel some hangover effects?" he asked.



Article is based on the following published research:

Pihl, R.O.,
Paylan, S.S.,
Gentes-Hawn, A.,
Hoaken, P.N.S.
(May 2003).

Alcohol affects executive
cognitive functioning
differentially on the
ascending versus
descending limb of
the blood alcohol
concentration curve.
*Alcoholism: Clinical
and Experimental
Research*,
27(5), 773-780.

A

LCOHOL DAMAGES DAY-TO-DAY MEMORY FUNCTION

- *Researchers know that heavy alcohol use damages retrospective memory.*
- *New research shows that heavy alcohol use also damages day-to-day memory, which includes prospective memory (remembering to do things at some future point in time) and everyday memory (remembering to complete daily activities).*
- *This damage occurred within drinking limits suggested by U.K. government guidelines.*

Research has shown that heavy alcohol use clearly damages retrospective memory, that is, the learning, retention and retrieval of previously presented materials. Less is known about the effects of alcohol on day-to-day memory function, specifically, prospective memory (remembering to do things at some future point in time) and everyday memory (remembering to complete daily activities). A study in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* uses Internet-based methodology to find that heavy alcohol consumption has a negative impact on day-to-day memory.

“Prospective memory impairments include things like forgetting to send someone a birthday card on time, or forgetting what you’re going to say in the middle of a sentence,” said Jonathan Ling, a senior lecturer in psychology at the University of Teesside in the United Kingdom and first author of the paper. “Everyday memory failures include telling someone a story that you’ve told them before, or forgetting where things are normally kept. Obviously we all forget things from time to time, however, heavy users of alcohol make noticeably more of these mistakes than either non- or low-users of alcohol.” Ling added that most of what is known about heavy drinkers’ retrospective memory function is based on laboratory research, and even less is known about alcohol’s effects on normal memory-related tasks that people perform from day-to-day.

For this study, researchers collected data from 763 participants (465 female, 298 males) using a specially created Web site on the University of Westminster Web server. Memory was assessed using two self-report questionnaires: the Prospective Memory Questionnaire (PMQ), and the Everyday Memory Questionnaire (EMQ). The PMQ has three sub-scales that measure short-term habitual PM, long-term episodic PM and internally-cued PM. Respondents also self-reported their level of use of alcohol and other drugs by responding to the UEL (University of East London) Recreational Drug Use Questionnaire.

The results indicate a dose-dependent effect of alcohol use on day-to-day memory function. “We found that heavy users of alcohol reported making consistently more errors than those who said that they consumed little or no alcohol,” said Ling. “A typical heavy user of alcohol reported over 30 percent more memory-related problems than someone who reportedly did not drink, and almost 25 percent more problems than those who stated they drank only small amounts of alcohol. More specifically, those participants who reported higher levels of alcohol consumption were more likely to miss appointments, forget birthdays and not pay bills on time. Deficits in everyday memory included problems with remembering whether they had done something like locking the door or switching off the lights, or forgetting where they put items like house keys.”

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LCOHOL DAMAGES DAY-TO-DAY MEMORY FUNCTION

Colin R. Martin, a lecturer in mental health in the Department of Health Sciences at the University of York and honorary consultant psychologist to the Addiction Service and National Monitoring and Evaluation Center of the Salvation Army, said these results “contribute to the increasing evidence that a diverse range of memory impairment is associated with excessive alcohol consumption. The underlying mechanisms responsible for memory deficits associated with excessive alcohol consumption are multi-factorial and, in many areas of specific deficit, continue to be currently poorly understood. This study is important because it extends our knowledge of alcohol-related memory impairment to everyday situations that most people can identify with, in contrast to laboratory-based memory tasks.”

“We also found a significant increase in reported memory problems by people who claimed to drink between 10 and 25 units each week in comparison to non-drinkers,” added Ling. One unit of alcohol is the equivalent of 10 ml of ethanol; roughly half a pint of beer or one small glass of wine. Current U.K. guidelines for maximum safe units per week are 21 units for women and 28 units for men. “This is an important finding, as it indicates that even if people are using alcohol within the limits suggested by U.K. government guidelines, these individuals still report experiencing memory problems.”

Martin concurred. “Interested readers may wish to reflect on the relevance of government recommended safe drinking limits, since decreased memory performance was observed even within what is generally acknowledged as safe drinking levels,” he said. “Recommended levels may be safe for the liver, but we can’t be sure that they represent safe limits for optimum brain function.”

Martin suggested that the role of deficits in day-to-day memory performance should be explored and extended to those individuals receiving treatment for alcohol-dependency problems. “Memory deficits are common in individuals who are receiving inpatient and community treatment for alcohol dependency,” he noted, “yet assessment of everyday memory performance in this group has yet to be established. This is particularly important because a number of the counseling and relapse prevention therapies and strategies used in this group are reliant on a fundamentally intact memory system.”



Article is based on the following published research:

Ling, J.,
Heffernan, T.M.,
Buchanan, T.,
Rodgers, J.,
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Parrott, A.C.
(June 2003).
Effects of alcohol
on subjective ratings
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everyday memory
deficits.
*Alcoholism: Clinical
and Experimental
Research*,
27(6), 970-975.



*P*harmacology



PHARMACOLOGY

Articles in the *Pharmacology* Category

1. Searching for New Detoxification Strategies
2. Fine-Tuning Naltrexone Treatment for Alcoholics
3. Searching for New Medications to Treat Alcoholism
4. Using Naltrexone to Treat Alcoholics With a “Mediterranean Drinking Pattern”
5. Behavioral Therapies Plus Pharmacotherapies Can Add Up to Success
6. An Anti-Nicotine Drug Reduces the Rewarding Effects of Alcohol
7. Promising New Treatment Options for People with Co-Existing Alcohol Use and Psychiatric Disorders

SEARCHING FOR NEW DETOXIFICATION STRATEGIES

- *Alcohol withdrawal syndrome (AWS) can range from no symptoms to a life-threatening event.*
- *In the United States, anti-anxiety agents called benzodiazepines are the primary treatment for AWS, yet they can also be abused.*
- *In Europe, anticonvulsants are commonly used to treat AWS.*
- *Researchers have found that an anticonvulsant agent called divalproex sodium can significantly reduce the amount of benzodiazepine needed for treating AWS.*

Alcohol withdrawal syndrome (AWS) can range from no symptoms to agitation and intense anxiety to tremors, seizures, delusions, fatal increases in body temperature, and cardiovascular collapse. Benzodiazepines provide an alcohol-like effect, relieving AWS symptoms by substituting for the alcohol that is no longer present in the system. However, benzodiazepines are similar enough to alcohol to have significant potential for intoxication, abuse and even dependence. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the viability of an anticonvulsant agent called divalproex sodium as an alternative to benzodiazepines for treating AWS.

“Alcohol, benzodiazepines and divalproex sodium all enhance gamma-aminobutyric acid (GABA) neurotransmission, one of the brain systems that becomes unbalanced during alcohol withdrawal,” said Joseph P. Reoux, a psychiatrist with the Veterans Affairs Puget Sound Health Care System and lead author of the study. “More specifically, certain anticonvulsants appear to prevent the nervous system hyperexcitability that develops during alcohol withdrawal. Although an anticonvulsant like divalproex sodium enhances the same brain inhibitory system that alcohol and benzodiazepines do, it does not have the euphoria, abuse potential or as high of a risk for cognition impairment that can occur with benzodiazepines. It also has anti-kindling properties, and tends to be better tolerated than carbamazepine (another anticonvulsant that can be used to treat alcohol withdrawal).”

“Kindling” occurs when the nervous system develops increased sensitivity to a stimulus such as withdrawal from alcohol. (Enhanced withdrawal responses are referred to as a kindling effect because of their similarity to the kindling of brain seizures.) When a nerve cell is repeatedly exposed to a stimulus that is initially too small to cause full nerve excitement, it can become more sensitive, or kindled, to the stimulus and begin to react at lower thresholds. This sensitivity persists over time and can become stronger with continued exposure to the stimulus. The concept of neuronal kindling is used to understand what clinicians may see during alcohol withdrawal: symptoms tend to become worse over time in people who repeatedly expose their brains to withdrawal from alcohol. Certainly kindling can complicate addiction by contributing to an individual’s unwillingness to forego alcohol, even when its ingestion is no longer a source of pleasure.

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SEARCHING FOR NEW DETOXIFICATION STRATEGIES

Researchers gave a primarily male inpatient population either 500 mg of the divalproex sodium formulation of divalproex sodium (also called valproate) or a placebo three times a day. Because the study participants were already experiencing withdrawal symptoms at a level that is normally medicated, they were also given a baseline dose of oxazepam (a benzodiazepine sedative) to ease their discomfort, as well as additional oxazepam if and when the severity of their withdrawal symptoms warranted it. During the seven-day study period, divalproex sodium reduced the amount of the oxazepam needed to adequately treat alcohol withdrawal. Adding divalproex sodium to the treatment regimen also appeared to stop the withdrawal symptoms from becoming worse when compared to giving oxazepam alone.

“The findings certainly support the idea that valproate is a viable treatment option for AWS,” said Reoux, “although it would be more correct to say that this study showed that using divalproex sodium significantly reduces the amount of benzodiazepine needed for the treatment of AWS. One of the more important aspects of this study is that it was scientifically rigorous. Previous studies of valproate for AWS were not randomized double-blind placebo controlled trials, so this study provides the strongest evidence to date supporting the use of valproate in the treatment of alcohol withdrawal.”

The anticonvulsant valproate has been available in Europe for treating AWS since the 1960s, but has only been marketed in the U.S. since 1978. In the U.S., benzodiazepines comprise the drug regimen of choice, despite their potential for abuse.

“Many medications are used differently in other places,” explained Richard K. Ries, a professor of psychiatry and addictions at the University of Washington. “Much of this has to do with what clinicians are used to doing. Sometimes this also has to do with pharmaceutical company marketing. Or sometimes it’s due to what the Federal Food and Drug Administration allows. For example, many meds are available in Europe well before they are available here, which has been true of many of the anticonvulsants.”

Ries is intrigued by the study’s findings because of the potential for valproate to become a new detoxification strategy. “AWS is an immense problem which affects patients in medical, surgical, and psychiatric settings as well as in addiction treatment populations,” he said. “Yet there is a paucity of research documenting new and better ways to deal with it. This pilot study makes a good attempt to address this and highlights the need for more research.”

Article is based on the following published research:

Reoux, J.P.,
Saxon, A.J.,
Malte, C.A., Baer, J.,
& Sloan, K.

(September 2001).
Divalproex sodium in
alcohol withdrawal:
A randomized
double-blind
placebo-controlled
clinical trial.

*Alcoholism: Clinical
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Research,*
25(9), 1324-1329.



FINE-TUNING NALTREXONE TREATMENT FOR ALCOHOLICS

- *Naltrexone has proven to be highly effective for many in recovery, but it does not work for everyone.*
- *A recent study has found that individual metabolism may be a factor in Naltrexone's effectiveness.*
- *Its effectiveness can, in turn, be partially determined by measuring blood levels for Naltrexone and its major metabolite, 6-beta-naltrexol.*

Naltrexone is a medication that decreases the rewarding effects of drinking and reduces the craving for alcohol that often leads people to relapse. Yet despite its effectiveness for many recovering alcoholics, it does not work for everyone. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that Naltrexone's effectiveness may be influenced by individual metabolism, and that this may be detected by measuring blood levels for the medication's major metabolite, 6-beta-naltrexol.

"Determining blood levels may be useful for patients who are not helped by the standard Naltrexone dose," explained Mary E. McCaul, associate professor at Johns Hopkins University School of Medicine and lead author of the study. "This study demonstrates the importance of adjusting Naltrexone dosage to ensure that an adequate blood level of 6-beta-naltrexol is achieved. If an individual does not achieve a therapeutic effect at the standard Naltrexone dose of 50 milligrams per day, he or she may want to discuss a dose increase with the prescribing physician."

McCaul explained that drugs can have agonist and/or antagonist properties. Agonists activate a receptor to achieve their effect. Antagonists block the receptor from being activated by another endogenous (produced within the organism) or exogenous (produced outside the organism) chemical, but do not produce any activity of their own. Naltrexone is an opioid antagonist. This means that Naltrexone blocks the opioid receptor from being activated, but does not cause any psychoactive effects for the person taking the medicine.

Naltrexone was first developed in the 1970s as a compound to block heroin and other opioid agonists from activating the receptors for opiates like heroin. In the mid-1980s, Naltrexone was approved for the treatment of heroin addiction. In the late 1980s, researchers began to suspect that drinking alcohol was pleasurable because it released endogenous morphine-like molecules. Joseph R. Volpicelli, associate professor and senior scientist at the Treatment Research Center at the University of Pennsylvania, was one of those original researchers.

"The reward system in the brain involves several neurotransmitters," said Volpicelli, "one of which is the opioid neurotransmitter system." Activation of this system – by alcohol consumption, for example – is associated with pain relief, calming and euphoria. "When opioids are stimulated," he said, "that in turn causes an increase in the neurotransmitter called dopamine." Dopamine activity in the brain center, called the nucleus accumbens, is thought to be key

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FINE-TUNING NALTREXONE TREATMENT FOR ALCOHOLICS

to reward and experiencing the high of a variety of different drugs such as cocaine, amphetamines and nicotine. “What happens is that the brain gets a ‘taste’ of having endorphins or dopamine released, and it wants more of it,” Volpicelli continued. “So first use is like an appetizer for the brain, particularly for people who have a family history of alcoholism and may have a genetic susceptibility for becoming addicted to alcohol.”

Preclinical research has shown that animals treated with an opioid antagonist such as Naltrexone decrease voluntary consumption of alcohol in the laboratory. In human clinical trials, Naltrexone decreases alcohol consumption, slows the onset of relapse, and reduces craving for alcohol in recently abstinent alcohol-dependent patients. Yet researchers couldn’t determine why some alcoholics were helped and others were not, despite their equal commitment to quit drinking. McCaul’s findings may help resolve this mystery.

“This paper is especially important on two fronts,” said Volpicelli. “First, it begins to identify that, for at least blocking the pleasure associated with drinking, doses higher than 50 milligrams may be helpful for some people. There seems to be a huge individual variability in how Naltrexone is metabolized, so those people who may be the more rapid metabolizers may benefit from higher doses of the medication.” He explained that the usual 50-milligrams-per-day dose of Naltrexone for treatment of alcoholism was based on the dosage formerly given to heroin addicts. “Furthermore,” he said, “this study also shows us that we can measure blood levels and know if a person needs a higher dose. We can now dose people specifically to get the best level of beta-naltrexol in their system in order to have the best clinical effect.”

McCaul is planning to continue her studies in this area. “Currently,” she said, “we are using positron emission tomography to scan brain opioid receptors to determine the extent of opioid receptor blockade by Naltrexone. This may vary among individual patients as a function of possible genetic differences, effects of chronic alcohol consumption, and differences in Naltrexone blood levels. We expect that those patients with greater receptor blockade will experience greater alcoholism treatment effectiveness than patients with lower blockade. If so, this will help further elucidate the mechanisms of Naltrexone’s effectiveness in alcoholism treatment.”

“McCaul’s study as well as other studies showing how alcohol affects the brain are very important,” said Volpicelli. “They provide more evidence that alcohol addiction is a medical disease, and medicines like Naltrexone can be helpful in helping people recover.”



**Article is based
on the following
published research:**

McCaul, M.E.,
Wand, G.S., Rohde, C.,
& Lee, S.M.
(September 2000).
Serum 6-beta-naltrexol
levels are related to
alcohol responses in
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*Alcoholism: Clinical
and Experimental
Research*,
24(9), 1385-1391.

SEARCHING FOR NEW MEDICATIONS TO TREAT ALCOHOLISM

- *Naltrexone is a prescription medication taken by mouth that helps reduce drinking in alcoholics.*
- *Naltrexone is quickly metabolized in humans by the liver to a metabolite called 6-beta naltrexol.*
- *Researchers have provided the first direct evidence that 6-beta naltrexol may itself effect alcohol consumption.*
- *These results suggest that 6-beta naltrexol is a potential new medication for alcohol dependence.*

Since its 1994 approval by the Federal Food and Drug Administration, Naltrexone remains the sole prescription medication used to reduce drinking in alcoholics. Naltrexone is taken by mouth and quickly metabolized in the liver to a number of different compounds or metabolites that can be measured in blood or urine. Naltrexone's major metabolite is called 6-beta naltrexol. A study in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines if 6-beta naltrexol itself can reduce alcohol consumption.

“Although 6-beta naltrexol is a metabolite that can be measured in human plasma and urine after administering Naltrexone,” explained Margaret R. Rukstalis, assistant professor of psychiatry at the University of Pennsylvania-VA Treatment Research Center and lead author of the study, “it is not known if 6-beta-naltrexol is independently pharmacologically active in reducing alcohol consumption. Studies have shown that high plasma levels of 6-beta naltrexol are critical in preventing relapse to alcoholism. Yet human plasma levels of both Naltrexone and 6-beta naltrexol are highly variable following standardized oral doses of Naltrexone. This is probably related to individual differences in the ability of the liver to metabolize Naltrexone.”

First and foremost, as noted by Raymond Anton, professor of psychiatry and scientific director of the Alcohol Research Center at the Medical University of South Carolina, “alcohol works on cells in the brain. Alcohol alters the function of these cells immediately. While most people's cells return to normal once the alcohol is removed/metabolized, some people (those at risk for developing alcoholism) are likely to have their cells more permanently changed. If this occurs again and again during episodes of intoxication, the cells begin to depend on alcohol. This dependency is manifested in a change in chemical signalling between the cells.”

The reward system in the brain involves several neurotransmitters, one of which is the opioid neurotransmitter system. Activation of this system by alcohol consumption, for example, is associated with pain relief, calming and euphoria. When opioids are stimulated, that causes an increase in the neurotransmitter called dopamine. Dopamine activity in the brain center, called the nucleus accumbens, is thought to be key to reward and experiencing the “high” of a variety of different drugs, including alcohol.

SEARCHING FOR NEW MEDICATIONS TO TREAT ALCOHOLISM

Drugs can have agonist and/or antagonist properties. Agonists activate a receptor to achieve their effect. Antagonists block the receptor from being activated by another endogenous (produced within the organism) or exogenous (produced outside the organism) chemical, but do not produce any activity of their own. Both Naltrexone and 6-beta naltrexol are opioid antagonists. This means that they block the opioid receptor from being activated.

“Repeated alcohol exposure in some individuals,” continued Anton, “may increase the cellular release of heroin/opiate-like chemicals called endorphins and enkephalins. This could lead to higher pleasure or a craving for alcohol. Drugs like Naltrexone and 6-beta-naltrexol specifically block this effect of alcohol, so that in individuals that have this type of alcohol dependency, the drug counteracts the alcohol effect.”

Rukstalis said, “Previous studies in humans have shown that plasma levels of 6-beta naltrexol following Naltrexone administration were two to 10 times as high as Naltrexone. Naltrexone is typically given in 50-mg tablets. The dose range of 6-beta naltrexol we tested was comparable to levels of 6-beta naltrexol found in humans following a 50-mg oral dose of Naltrexone.”

In the study, researchers compared the amount of alcohol drinking by rats given 6-beta naltrexol to the amount of alcohol drinking by rats given salt water. They found that alcohol drinking by the rats decreased as the doses of 6-beta naltrexol increased. “These results suggest that 6-beta naltrexol is a potential new medication to treat alcohol dependence,” said Rukstalis.

Both Rukstalis and Anton are optimistic about the future possibilities of 6-beta naltrexol as a treatment for alcoholism. “Naltrexone is so quickly metabolized by the liver that for many people,” said Rukstalis, “there is much more 6-beta naltrexol in the blood than Naltrexone. Currently, Naltrexone is the only way to obtain 6-beta naltrexol. In the future, giving patients 6-beta naltrexol directly may lead to higher and more consistent therapeutic levels compared to the variable levels seen with Naltrexone. Six-beta naltrexol may be easier to give and more effective than currently available medications that help prevent alcohol relapses in alcoholics.”

Anton added, “One nice thing about Naltrexone, even now, is that it needs to be taken only once a day, which is very important for medication compliance, especially in an alcoholic population who may be ambivalent about taking medications to begin with. If 6 beta-naltrexol shows promise, it could potentially be given every other day, or maybe produced in a skin-patch or a long term (depot) injectable format.”



**Article is based
on the following
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U SING NALTREXONE TO TREAT ALCOHOLICS WITH A “MEDITERRANEAN DRINKING PATTERN”

- *Naltrexone has been used to treat alcoholism in the United States for close to a decade.*
- *Initial studies of Naltrexone’s effectiveness examined alcohol-dependent individuals who drank primarily on holidays and weekends.*
- *Researchers in Spain examined Naltrexone’s effectiveness on alcohol-dependent individuals who drank throughout the week.*
- *Fewer Naltrexone-treated subjects relapsed to heavy drinking than placebo-treated subjects.*

Many of the original studies of Naltrexone’s effectiveness examined alcohol-dependent patients with a “Scandinavian drinking pattern,” that is, greater drinking on holidays and weekends. Conversely, individuals with a “Mediterranean drinking pattern” tend to regularly consume alcohol during the week, particularly with meals. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* is among the first to examine the effectiveness and safety of Naltrexone for the treatment of alcoholism among Spanish patients with a Mediterranean drinking pattern.

“Years ago,” said José Guardia, a consultant at the Hospital de la Santa Creu i Sant Pau in Barcelona, Spain and lead author of the study, “there was a clear difference between drinking patterns in the northern and southern countries of Europe. The Anglo-Saxon/Scandinavian tendency was to drink more on holidays and weekends. In France, Italy, Spain and other Mediterranean countries, wine was usually consumed with meals. However, when everyday consumption becomes heavy, and after a long period of time, severe withdrawal and organic consequences of chronic alcohol toxicity are probable. We wanted to see if there would be differences in using Naltrexone for the treatment of alcohol dependency in this population.”

Drugs can have agonist and/or antagonist properties. Agonists activate a receptor to achieve their effect. Antagonists block the receptor from being activated by an endogenous (produced within the organism) or exogenous (produced outside the organism) chemical. Naltrexone acts as an opioid antagonist within the opioid neurotransmitter system, which is a part of the brain’s reward system. When opioids are stimulated, levels of the dopamine neurotransmitter are increased, leading to the “high” that is associated with a variety of drugs. Naltrexone blocks the opioid receptor from being activated. It was first developed in the 1970s to block heroin from activating the receptors for opiates, later becoming approved for the treatment of heroin addiction in the mid-1980s. In the late 1980s, researchers began to suspect it might have uses for the treatment of alcohol addiction.

For the Guardia study, subjects were 202 alcohol-dependent patients (151 males, 51 females),

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U SING NALTREXONE TO TREAT ALCOHOLICS WITH A “MEDITERRANEAN DRINKING PATTERN”

18 to 60 years of age, who were seeking outpatient treatment from seven different treatment centers in Spain. Patients were randomly assigned to 12-weeks of treatment with either 50 mg/day of Naltrexone (n=101) or an identical-looking placebo (n=101). Patient treatment also included a psychosocial intervention, consisting of a weekly session of supportive group therapy, a weekly visit with the study physician and a nurse intervention three times a week. Following treatment, researchers evaluated the relapse rate, alcohol consumption levels, craving, adverse effects, changes in the biochemical markers of heavy drinking and possible toxicity among the final tally of 192 patients considered eligible for evaluation.

Of the Naltrexone-treated subjects, only 7.9 percent (n=8) relapsed to heavy drinking. (Heavy drinking was defined as more than five drinks per day for men, more than four drinks per day for women, or more than five drinking days per week for both genders.) Of the placebo-treated subjects, 18.8 percent (n=19) relapsed to heavy drinking. The adverse effects known to be associated with Naltrexone use (nausea, headache, abdominal discomfort, sleepiness) were low among those treated, confirming previous studies of Naltrexone’s safety and tolerability.

“The most significant finding of our study was that Naltrexone-treated alcohol-dependent subjects showed a reduced relapse rate to heavy drinking,” said Guardia, “in comparison with those patients treated with a placebo. These results demonstrate the synergistic effects of combining pharmacotherapy with psychosocial intervention. We know that alcoholism is a recoverable disease. These results show that when alcohol-dependent patients get the appropriate psychosocial intervention plus pharmacotherapy for a suitable amount of time, they can overcome this addictive disease.”

“These results open up the possibility for European alcohol-dependent patients to receive treatment with Naltrexone,” said José Pérez de los Cobos, a psychiatrist with the Addictive Behavior Unit at the Hospital de la Santa Creu i Sant Pau. In fact, since this study was conducted, Naltrexone has been authorized for the treatment of alcoholism in Spain. “Furthermore,” he added, “once we understand the effectiveness of Naltrexone, we can go on to explore its limitations. That way, future research can examine how combining Naltrexone with other medications, and even more effective psychosocial interventions, can treat alcoholism.”

Article is based on the following published research:

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BEHAVIORAL THERAPIES PLUS PHARMACOTHERAPIES CAN ADD UP TO SUCCESS

- *Alcoholism treatment can include behavioral therapies and/or pharmacotherapies.*
- *A new study examines the effectiveness of combining communications, cue exposure and coping skills training with Naltrexone in a treatment program.*
- *Patients who took Naltrexone during aftercare were more alcohol-resistant than placebo recipients.*
- *Patients who received communications, cue exposure and coping skills training were less likely to relapse than education/relaxation training recipients.*

There is no singular approach to treating alcoholism. Treatment professionals can choose from an array of behavioral therapies and pharmacotherapies. However, behavioral therapies may have limited effectiveness because they do not address underlying brain processes at the neurotransmitter level. Conversely, pharmacotherapies may have limited success because they do not address the individual's need to develop coping skills, confidence about staying abstinent in risky situations, and the appropriate responses to high-risk stimuli. A study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* combines elements from both approaches – Naltrexone, communication skills training (CST) and cue exposure combined with urge-specific coping skills training (CET) – into a comprehensive program and then assesses its effectiveness.

“It is generally recognized that a pharmacotherapy should not be used alone without providing some behavioral treatment or counseling,” said Peter M. Monti, professor of medical sciences and director of the Center for Alcohol and Addiction Studies at Brown University and lead author of the paper. “However, behavioral treatments are often used without pharmacotherapy for alcoholism. The usual reasons are that the patient does not want to use a medication, the counselor or treatment program does not believe that the medication would be useful for the patient, or the patient is not eligible for the medication for medical reasons.”

In this study, researchers looked at the effects of prescribing Naltrexone versus a placebo during the 90 days after alcoholics completed a two-week daily alcohol treatment program. The two-week program consisted of either CST/CET training, or educational discussions and relaxation training.

“Alcoholics who took Naltrexone for at least two months of the 90 days that they were prescribed it, drank alcohol significantly less heavily as compared to alcoholics who were given a placebo,” said Monti. “While Naltrexone did not affect whether alcoholics had any drinks at all, alcoholics using Naltrexone had fewer heavy drinking days, had fewer drinks if they drank, and had fewer urges to drink. The beneficial effects of Naltrexone lasted only while the alcoholics were taking Naltrexone, suggesting that it would be helpful to prescribe Naltrexone for longer than 90 days.”

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EHAVIORAL THERAPIES PLUS PHARMACOTHERAPIES CAN ADD UP TO SUCCESS

Naltrexone acts as an opioid antagonist within the opioid neurotransmitter system, which is a part of the brain's reward system. When opioids are stimulated, levels of a neurotransmitter called dopamine are increased. Dopamine activity is thought to be key to experiencing the "high" of a variety of different drugs, including alcohol. Naltrexone decreases the rewarding effects of drinking and reduces the craving for alcohol that often leads people to relapse.

"One thing that is new about this study," said Stephanie O'Malley, professor of psychiatry at Yale University School of Medicine, "is the sequencing of therapies. The behavioral interventions were provided during day hospital treatment, while the pharmacotherapy occurred after discharge when the patient had brief contacts with a physician for 12 weeks. The results suggest that Naltrexone may be a useful aftercare strategy that, in conjunction with new communication skills and strategies for coping with urges, will help patients maintain their improvements in the long term."

Patients who received the communications, cue exposure and coping skills training were significantly less likely to report a relapse day than patients who received the education/relaxation training. Furthermore, CST/CET patients also reported fewer heavy drinking days at six- and 12-month assessments.

CST is designed to help alcoholics develop more healthy social networks in order to make relapse to drinking less likely. This is necessary for primarily two reasons: alcoholics often damage their family relationships, and many of their friends also drink heavily. Alcoholics are taught communications and conversation skills that can be used to improve their close relationships, such as learning to accept criticism and resolve conflicts gracefully, and to increase their sober friendships.

CET is designed to help alcoholics practice "bringing down" the urge to drink when they are in high-risk situations. For example, patients practice thinking about specific effects that sobriety would have for them (such as spending more time with their children), and by thinking of specific things they could do to minimize the urge to drink (such as calling a sober friend or playing basketball). These methods are individualized for each person's needs. Many treatment programs currently use some form of coping skills training, and to a lesser degree communication skills training, however, the cue exposure treatment approach is not currently used in the United States.



Article is based on the following published research:

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AN ANTI-NICOTINE DRUG REDUCES THE REWARDING EFFECTS OF ALCOHOL

- *Mecamylamine is a drug that blocks the effects of nicotine in the brain.*
- *Mecamylamine is believed to reduce the rewarding effects of cigarette smoking.*
- *A new study has found that mecamylamine also reduces self-reported stimulant and euphoric effects of alcohol in humans, as well as their desire to drink more.*

Mecamylamine is a central nicotinic receptor antagonist that is believed to reduce the rewarding effects of cigarette smoking. Scientists have suspected for some time that common mechanisms may be involved in both nicotine and alcohol reward. Furthermore, prior research has suggested that mecamylamine blocks the reinforcing effects of alcohol in animals. A new study, published in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)*, has found that mecamylamine reduces the self-reported stimulant and euphoric effects of alcohol in humans, and also decreases their desire to drink more.

“Of all the drugs that act in the brain to produce their rewarding effects,” said Harriet de Wit, associate professor in the department of psychiatry at the University of Chicago and corresponding author for the study, “alcohol has some of the most complex and varied effects on neurotransmitter receptor systems. One of the receptor systems where alcohol may act is the nicotinic acetylcholine (NACH) receptor system, the same system where nicotine acts. By acting at these NACH receptors, alcohol also increases the activity of another neurotransmitter system, the dopamine system, which is where most drugs are thought to produce their rewarding effects. We hypothesized that mecamylamine would block the effects of alcohol on the NACH receptors which would, in turn, reduce the activity of the dopamine system, resulting in a dampening of the rewarding effects of the alcohol.”

Researchers recruited 27 (14 males, 13 females) non-smoking social drinkers to participate in six laboratory sessions lasting roughly four hours each. At the beginning of each session, study subjects received either a placebo or one of two doses of mecamylamine (7.5 or 15 mg), followed two hours later by either an alcohol (0.8 g/kg) or a placebo beverage. For two hours following beverage consumption, physiological and subjective-effect measures were taken at 30-minute intervals. The physiological measures included heart rate and blood pressure; subjective effects included stimulation and euphoria.

“Our findings extend previous observations made in animals,” said de Wit, “that alcohol produces its mood-altering effects, in part, through actions on the nicotinic receptor system. These findings also fit nicely with observations that alcohol users are often also smokers, and smokers tend to drink more than non-smokers. This suggests that these associations may have a biological basis, that is, they reflect shared actions on some of the same receptor systems.”

Only one other published human study, by authors Ola Blomqvist and Henry Kranzler, has previously examined the effects of mecamylamine on subjective responses to alcohol. The

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AN ANTI-NICOTINE DRUG REDUCES THE REWARDING EFFECTS OF ALCOHOL

present study expanded on their findings by testing another dose of mecamylamine, and by including a placebo beverage as a control condition.

“Clearly this study extends our findings,” said Kranzler, a professor in the department of psychiatry at the University of Connecticut Health Center, “and provides another step in linking preclinical animal findings with the effects of alcohol in humans. The study sample is also larger, which helps to validate our initial findings. It should be noted, however, that as with our study, the humans were healthy subjects, so additional work is needed to evaluate the clinical significance of these findings in heavy drinkers. It is likely, based on other research, that these effects can be extended to heavy drinkers.”

Researchers also found some unexpected gender differences in the results. “First, we found that male subjects reported more of a stimulant effect from the alcohol than the females,” said de Wit, “regardless of whether they were pretreated with mecamylamine. Second, mecamylamine reduced the stimulant effects of alcohol more in men. Third, women reported more effects from the mecamylamine alone, specifically, self-reported feelings of sedation.” Both de Wit and Kranzler cautioned, however, that these differences may be due to gender differences in pharmacokinetics.

“We gave the women the same amount of alcohol as we gave to the men,” said de Wit, “and there is evidence that women attain a higher concentration of alcohol because of differences in body composition. This could have accounted for some of the sex differences we saw in responses to alcohol. We also gave the same dose of mecamylamine to men and women. Although doses of most drugs – except alcohol – are usually not adjusted for sex or body weight, it is possible that the greater response to mecamylamine in the women could be related to their smaller size.”

“Developments in the pharmacotherapy of alcoholism have been limited by the paucity of agents with demonstrated effects on alcohol reinforcement,” said Kranzler. “This study, in conjunction with other research findings, shows that the nicotinic cholinergic system is a promising one for evaluation as a pharmacotherapeutic target in alcoholism.” Kranzler cautioned that “mecamylamine is not particularly well tolerated in high doses ... however, other, possibly more selective drugs that are active at the nicotinic receptor are becoming available, and may provide better tolerability.”



**Article is based
on the following
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Chi, H., de Wit, H.
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*Alcoholism: Clinical
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PROMISING NEW TREATMENT OPTIONS FOR PEOPLE WITH CO-EXISTING ALCOHOL USE AND PSYCHIATRIC DISORDERS

- *The United States has typically separated services for mental health from those associated with addictions.*
- *A selective serotonin reuptake inhibitor (SSRI) called paroxetine shows promise in the treatment of social anxiety in alcohol-dependent subjects.*
- *Researchers have found that an anticonvulsant mood stabilizer called sodium valproate, may be useful for both stabilizing mood states and decreasing alcohol use among bipolar alcoholics.*

Individuals who have co-existing alcohol use and psychiatric disorders must overcome a number of significant hurdles on their way to recovery: multiple health and social problems, double the stigma, a poor response to traditional treatments, a lack of joint treatment options, and a chronic cycle of treatment entry and re-entry. Symposium proceedings published in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)* examine treatment options for this group.

“The United States has typically separated services for mental health from those associated with addictions,” said Charlene E. Le Fauve, symposium organizer and health scientist administrator at the National Institute on Alcohol Abuse and Alcoholism. “Because of this separation, when a person with comorbid disorders enters one type of care, they are inadequately treated for the other condition. If one disorder goes untreated, both usually worsen and additional complications occur, which can include serious medical problems.”

Symposium speakers at the June 2003 Research Society on Alcoholism meeting in Fort Lauderdale, Florida presented findings from recent trials and clinical studies:

- A selective serotonin reuptake inhibitor (SSRI) called paroxetine shows promise in the treatment of social anxiety in alcohol-dependent subjects.

“Since this was the first study to examine the effectiveness of paroxetine in this dual-diagnosis population,” said Le Fauve, “we need to see if the results can be replicated by other researchers before we can determine how promising the results are.”

- Response to SSRIs among people with co-existing alcohol dependency and depression seems to depend on various factors, including the severity of the depression, whether the depression is primary or secondary to the alcohol use, alcoholic typology (Type A or B) and gender.

“When someone is severely depressed, addicted to alcohol, needs inpatient mental health treatment, and has a history of attempting suicide,” explained Le Fauve, “SSRIs are effective at

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PROMISING NEW TREATMENT OPTIONS FOR PEOPLE WITH CO-EXISTING ALCOHOL USE AND PSYCHIATRIC DISORDERS

improving the depression and decreasing alcohol consumption. Whereas, for alcoholics who do not need inpatient treatment because their symptoms of depression are mild to moderate, SSRIs are not very effective at treating both disorders. On the other hand, a heavy drinker who does not require formal addiction treatment may take SSRIs and notice that they will substantially reduce their alcohol intake.”

Research indicates that gender may also play a role in the effectiveness of SSRIs, in that women with both alcohol and depressive disorders tend to respond better than men. In addition, the type of alcoholic receiving SSRIs – Type A versus Type B – can influence its effectiveness. Type As become alcoholics at a later age, have less severe symptoms or fewer psychiatric problems, and have a better outlook on life than Type Bs.

“Type B alcoholics are considered to be more severe and at greater risk for poor health outcomes,” said Le Fauve. “Type B alcoholics also significantly worsen when they are treated with SSRIs when compared to Type A alcoholics. Clearly, SSRIs will not be the best method of treatment for all people who have both depression and alcoholism.”

- In the first study of its kind, researchers found that an anticonvulsant mood stabilizer called sodium valproate, used previously to treat bipolar disorder, may also be useful for both stabilizing mood states and decreasing alcohol use among bipolar alcoholics.

- Researchers have also found that treatment with the antipsychotic clozapine is associated with a decrease in alcohol and other substance use in patients with schizophrenia.

“Atypical or ‘novel’ antipsychotics are generally safer and better tolerated than older or typical antipsychotic medicines,” explained Le Fauve. “Emerging studies suggest that atypical antipsychotics can also be effective for a broad range of psychiatric syndromes beyond the primary indication of schizophrenia. So, it is not entirely surprising that a new atypical antipsychotic such as clozapine ... may be a useful treatment modality for a broad range of non-psychotic conditions, including alcoholism.” Le Fauve noted that researchers are just beginning to unravel the complexities of how to treat people with comorbid mental illness and alcohol use disorders.



Article is based on the following published research:

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*P*hysical
Health



PHYSICAL HEALTH

Articles in the *Physical Health* Category

1. Alcohol Abuse May Increase Susceptibility to HIV Infection
2. Alcohol and Cancer
3. Can Heavy Alcohol Use Lead to Some Kinds of Cancer?
4. Alcohol May Hasten the Progression of Cancer
5. Is There a Link Between Alcohol and Allergies?
6. How to Build Strong Bones: Get Milk, Lose the Booze
7. Alcohol, Sodium Sensitivity and Blood Pressure
8. Alcohol's Effects on Testosterone
9. Moderate Alcohol Consumption After Meals Can Decrease Levels of Insulin
10. Chronic Alcohol Abuse Damages Regulating Hormones

A LCOHOL ABUSE MAY INCREASE SUSCEPTIBILITY TO HIV INFECTION

- *Alcohol abuse among people with the human immunodeficiency virus (HIV) is significant.*
- *Researchers used simian immunodeficiency virus (SIV) infection of rhesus monkeys to examine the combined effects of chronic, binge alcohol consumption on the primary stage of SIV/HIV infection.*
- *Binge drinking appears to increase the host's susceptibility to SIV/HIV infection.*

Alcohol abuse among people with the human immunodeficiency virus (HIV) is significant. One study found that 41 percent of HIV-infected patients met the criteria for alcoholism. Although alcohol abuse and HIV infection individually compromise immune function, the consequences of both conditions together is poorly understood. A study in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* used simian immunodeficiency virus (SIV) infection of rhesus monkeys to examine the combined effects of chronic, binge alcohol consumption on the primary stage of SIV/HIV infection. Researchers found that alcohol consumption may increase susceptibility to SIV/HIV infection.

“The prevalence of alcohol abuse among HIV-infected people is at least twice that found in the general population in the United States,” said Gregory J. Bagby, Kai and Earl Rozas professor of physiology at Louisiana State University Health Sciences Center and first author of the study. “Several studies indicate that individuals who abuse alcohol engage in risky behaviors such as unprotected sex with multiple partners. By itself this behavior would increase the chances of becoming infected with HIV. What is not known is whether alcohol intoxication or chronic alcohol consumption alters susceptibility to infection upon exposure to HIV beyond the behavioral effects of alcohol.”

Twenty-two male rhesus monkeys, four to six years of age, were given either alcohol or sucrose for four days per week for three months. The alcohol doses were individualized in order to achieve plasma alcohol concentrations of 230-250 mg/100ml (roughly the human equivalent of 6 to 10 drinks) for a five-hour period. After three months, seven alcohol-treated and seven sucrose-treated monkeys were infected with SIV; four alcohol-treated and four sucrose-treated monkeys were not. Blood samples were drawn prior to alcohol/sucrose infusions, one month prior to SIV infection, and then on days 6, 13, 20, 27, 42 and 61 post-SIV infection.

“This study had two primary purposes,” said Bagby. “First, we wanted to develop an animal model to study the interactive effects of alcohol on HIV disease transmission, pathogenesis, progression and anti-viral therapy. We adapted the primate model, using SIV, which infects rhesus monkeys in the same way that HIV infects humans and produces a disease that is very similar to the human disease that leads to an immunosuppressed state and AIDS. The second purpose was to examine the effects of alcohol consumption on what is called the primary stage of infection. This stage is extremely difficult to study in humans because it is rare to be able to identify infected people this early.”

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LCOHOL ABUSE MAY INCREASE SUSCEPTIBILITY TO HIV INFECTION

Approximately one week after SIV infection, there was a 64-fold increase of the SIV virus in the blood of the alcohol-treated monkeys compared to the sucrose-treated monkeys. “This most likely means that either more cells are infected with virus at this early stage or that infected cells are producing more virus,” said Bagby. “If more cells are infected, it means that the alcohol increased infectivity of cells or increased the number of susceptible cells.”

Alcohol consumption also enhanced lymphocyte turnover (as assessed by expression of the cell cycle protein marker Ki67) in SIV-infected monkeys during the early stage of infection, which may have contributed to the observed increase of virus in the blood.

When a body becomes infected with a pathogen or virus, explained Bagby, certain cells in the immune system become activated and start dividing or proliferating. “The cell cycle marker Ki67 increases in cells that are proliferating,” said Bagby. “So an increase in this protein indicates that the immune system is responding to an infection. The cells that are produced are specifically designed to eradicate the infection. Furthermore, the increase in immune-cell production during a viral infection is accompanied by an increase in the number of cells that die. ‘Lymphocyte turnover’ refers to this increase in the numbers of cells that are produced and subsequently die.”

“The well-documented immune-weakening effects of both alcohol and HIV infection underscore the importance of understanding the potential interactions between these two common immune suppressive factors,” said Shirish Barve, associate professor in the department of medicine at the University of Louisville Medical Center. “The present work by Bagby and [colleagues] has established the much-needed animal model that could be effectively used in the study of HIV disease. Due to its similarity to HIV infection, [this] model [could] be extremely important in addressing and understanding the clinically relevant issues concerning the susceptibility of alcoholics to acquiring HIV infection and the effect of alcohol on the rate of HIV-disease progression in alcoholics.”

Bagby and his coauthors intend to continue studying the effects of alcohol on HIV disease transmission, pathogenesis, progression and therapy. “Our next study will examine the longitudinal effects of alcohol on SIV disease progression,” said Bagby. “We will look at the effects of alcohol and SIV infection on disease progression, muscle wasting and behavioral deficits.”

Article is based on the following published research:

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*Alcoholism: Clinical
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A LCOHOL AND CANCER

- *Drinking alcohol is linked to a greater risk of tumors in the esophagus, mouth, larynx and liver.*
- *Alcoholics also have a greater incidence of genetic damage than normal.*
- *A new study has found that alcohol contributes to the destructiveness of certain carcinogens.*
- *Acetaldehyde, the first product of alcohol metabolism, appears to play a key role in the damage.*

Cancer, the often-deadly process during which normal body cells are transformed into malignant ones, likely involves change in the genetic material of the cells known as deoxyribonucleic acid (DNA). Oncogenes are those genes that regulate cell growth, proliferation and repair of tissues. Oncogenes are also the targets of carcinogenic agents such as asbestos, ultraviolet rays of the sun and cigarette smoking. A study in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* investigates if alcohol exposure can increase the cytotoxicity (cell destructiveness) of known carcinogenic agents that could, in turn, damage DNA and lead to mutation or cancer.

“We are bombarded by potential carcinogenic agents every day in our environment,” said Richard A. Deitrich, professor of pharmacology at the University of Colorado Health Science Center. “Most of these do not cause cancer, but given a boost from alcohol, some of them may.”

“Epidemiological studies have shown that drinking alcohol is associated with an increased risk of tumors in the esophagus, mouth, larynx and liver,” noted David B. Couch, associate professor of pharmacology and toxicology at the University of Mississippi and lead author of the study. “Blood cells of alcoholics also have a greater incidence of genetic damage than do members of the general population. It has been unclear, however, if alcohol itself causes these effects. The key finding of our study was to show that, in the model system used, alcohol exposure could produce effects consistent with inhibition of the base excision repair pathway.” In other words, alcohol appears to contribute to genetic damage by impairing DNA repair processes.

Researchers tested the survival capabilities of Chinese hamster ovary A10 cells by exposing them to alcohol, genotoxicants (substances that can damage DNA through mutation or cancer) and non-DNA reactive cytotoxic agents. A10 cells were chosen because they have been engineered to express alcohol dehydrogenase (ADH), which is known to convert alcohol to acetaldehyde (AcHO). AcHO belongs to a class of compounds called aldehydes (such as formaldehyde, a disinfectant and preservative), and is well-known as a highly reactive and toxic compound that can damage the cells of any living thing. Normally when people drink, alcohol is converted to AcHO in the liver. It is then rapidly metabolized to acetate, which is then further metabolized by tissues outside of the liver.

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A LCOHOL AND CANCER

The specific genotoxicants used in the experiment were 1-methyl-3-nitro-1-nitrosoguanidine, ethyl methanesulfonate, 4-nitroquinoline-N-oxide, ICR 170 and mitomycin C. Also used was 6-thioguanine, which damages DNA but not directly. The non-DNA reactive compounds used were ouabain, cycloheximide and colchicine. In addition, an inhibitor of ADH called 4-methylpyrazole was given to some of the A10 cells in order to establish if alcohol or its metabolite acetaldehyde was responsible for cell damage.

“The major finding of this study is that alcohol causes an increase in the mutagenicity (the capacity to induce mutations) of agents that damage DNA,” said Deitrich. “This is as a result of the metabolism of alcohol to acetaldehyde. In fact, it is clear that acetaldehyde is the major culprit in the effects noted here. The presumption is that it is acetaldehyde itself that is causing the damage, but it could be other aldehydes as well. For example, acetaldehyde may interfere with the normal cellular mechanisms designed to inactivate endogenous aldehydes, those produced in normal cellular function or those produced as a result of alcohol’s production of oxidative damage.”

“Acetaldehyde is highly reactive,” added Couch. “It can react with amino groups on proteins, which could potentially interfere with the function of the protein. Of course, acetaldehyde can also react with other cellular constituents, including DNA.”

Couch and Deitrich both noted that, even though researchers have known for a long time that alcohol increases the risk of cancer, relatively little attention has been paid to the genotoxic implications of exposure to alcohol. Deitrich had several suggestions for future research directions, some of which Couch and his colleagues already plan to pursue.

“It would seem reasonable to dissect the mechanism(s) by which DNA damage takes place,” said Deitrich. “For example, what specific DNA damage is done, and why can’t the cells repair this damage? What implications does this research have for about half of the Asian population who lack the ability to efficiently metabolize acetaldehyde? Does this relate to their greater risk of liver damage if they do drink? What implications does this have for alcoholics who are treated with Antabus (containing disulfiram) which increases the level of acetaldehyde in the body if they drink? What implications does this have for these people even if they do not drink, since Antabus inhibits the metabolism of endogenous aldehydes as well?” He added, “Perhaps the most important future research would be to demonstrate that acetaldehyde levels that are found in the normal range after alcohol consumption will also cause this damage.”

**Article is based
on the following
published research:**

Couch, D.B.,
& Baker, R.C.
(March 2002).
Ethanol-enhanced
cytotoxicity of
alkylating agents.
*Alcoholism: Clinical
and Experimental
Research*,
26(3), 381-385.



CAN HEAVY ALCOHOL USE LEAD TO SOME KINDS OF CANCER?

- *A significant proportion of Asians lack the aldehyde dehydrogenase-2 (ALDH2) gene.*
- *Acetaldehyde is produced in saliva while drinking alcohol.*
- *ALDH2-deficient individuals who drink heavily appear unable to eliminate salivary acetaldehyde.*
- *These same individuals have much higher rates of digestive tract cancers.*
- *Findings suggest that salivary acetaldehyde may be carcinogenic.*

In the June issue of *Alcoholism: Clinical and Experimental Research (ACER)*, researchers explore a potential association between high rates of alcohol use and high rates of upper digestive cancers. They used a unique group to investigate their hypothesis: individuals who lack the aldehyde dehydrogenase-2 (ALDH2) gene.

Alcohol is metabolized principally in the liver by two enzymes that act sequentially. Alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde; aldehyde dehydrogenase (ALDH) converts acetaldehyde to acetate. Acetate is then metabolized by tissues outside of the liver. As much as 50 percent of Chinese and Japanese people lack the aldehyde dehydrogenase-2 (ALDH2) isoenzyme, a deficiency which allows acetaldehyde to accumulate in the blood and tissues after drinking. These individuals experience an unpleasant response to drinking alcohol, such as facial flushing, headaches, palpitations, dizziness and nausea. They also seem to have significantly higher rates of digestive tract cancers.

“We need to remember that ALDH2-deficient individuals number in the hundreds of millions,” said Mikko Salaspuro, chairman of Alcohol Diseases at the University of Helsinki, a specialist in internal medicine and gastroenterology at the Helsinki University Central Hospital and lead author of the study. “Accordingly, ALDH2 deficiency is quantitatively the most important gene mutation potentially exposing humans to an increased risk of cancer.” Salaspuro explained that high rates of digestive tract cancers among this population may be associated with high levels of salivary acetaldehyde, an association that provides strong evidence that salivary acetaldehyde is carcinogenic in humans.

Parotid glands are the main saliva-producing organs. Located next to each ear, they are connected by a duct to the upper gingival area under the upper lip. Most people produce approximately 1.5 liters of saliva per day. Usually taken for granted until it’s compromised, saliva is a clear, alkaline, semi-viscous liquid which helps in the digestion of food, and helps to keep exfoliated epithelial cells, most bacteria and food particles away from the teeth. Salaspuro’s study proposes that the parotid glands are able to metabolize alcohol into acetaldehyde.

Oral microflora may also produce acetaldehyde. Every individual has about 300 hundred different bacterial species in their mouth. That number increases exponentially in saliva, even more on tooth surfaces and even more on gingival scrapings. Everyone develops their oral

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CAN HEAVY ALCOHOL USE LEAD TO SOME KINDS OF CANCER?

microflora within a few weeks after birth. Many live and grow in people's mouths on a platonic basis, but some are harmful, such as those producing tooth cavities or those producing acetaldehyde.

The study found that ALDH2-deficient Asians were exposed to two to three times higher salivary acetaldehyde levels than either Caucasians or Asians with normal ALDH every time they drank, and for as long as they had elevated blood alcohol levels. The ALDH2-deficiency seemed to prevent those subjects from eliminating salivary acetaldehyde. Those with the normal ALDH enzyme were able to remove the acetaldehyde, likely formed in the parotid gland, before it was secreted to their saliva. Which is not to say that normal ALDH levels completely protect heavy drinkers from salivary acetaldehyde; Salaspuro noted that Caucasians that drank heavily for a number of years had much higher rates (20 fold) of esophageal cancer.

"At higher salivary ethanol concentrations," he said, "even the individuals with normal ALDH can achieve carcinogenic acetaldehyde levels in the saliva." Salaspuro said his study's findings are important on several different levels. "We all produce potentially carcinogenic acetaldehyde in our saliva when we drink. The higher the acetaldehyde levels in the saliva, the higher the risk of digestive tract cancer. A person's risk is enhanced if, one, they drink a lot; two, if they are ALDH2-deficient; three, if they smoke or have bad oral hygiene, both of which increase the potential to produce acetaldehyde from alcohol; and four, if they have individual oral microflora characteristics that place them at higher risk."

Ting-Kai Li, distinguished professor at the Indiana University School of Medicine, agrees. "There's a high degree of suspicion or probability that acetaldehyde, which comes from alcohol, is carcinogenic, and this may be a mechanism in the higher rates of cancer among ALDH2-deficient heavy drinkers. It's not a one-to-one relationship, but it may increase the risk."

Salaspuro noted that before dietary means and cholesterol-lowering drugs were discovered, individuals with an inherited inability to remove normal blood cholesterol in their livers often died before they reached 30 years of age. He added, "Our findings open a new area, both for screening and preventive research, with respect to gastrointestinal tract cancer. I hope we will be able to one day use our findings about microbially produced acetaldehyde for the prevention of some types of cancers."



Article is based on the following published research:

Väkeväinen, S.,
Tillonen, J., Agarwal,
D. P., Srivastava, N.,
& Salaspuro, M.
(June 2002).

High salivary
acetaldehyde after a
moderate dose of
alcohol in ALDH2-
deficient subjects:
Strong evidence of the
local carcinogenic action
of acetaldehyde.
*Alcoholism: Clinical
and Experimental
Research,*
24(6), 873-877.



A LCOHOL MAY HASTEN THE PROGRESSION OF CANCER

- *Alcohol consumption is known to compromise the body's immune system.*
- *A new study investigates the effects of alcohol consumption on mice with melanoma.*
- *Melanoma-bearing mice who received alcohol had a significant loss in body fat.*
- *The loss in body fat appears to facilitate "wasting" which, in turn, shortens survival time.*

Alcohol, the socially acceptable drug, acts upon virtually every organ system and causes a variety of physiologic and behavioral alterations. Its ability to compromise the body's immune system has been linked to the development of infectious diseases such as tuberculosis, as well as oral cancer (including the oral cavity, pharynx, larynx and esophagus), liver cancer and possibly breast cancer in women. A study in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that individuals with cancer who drink excessively may be placing themselves at risk of a more rapid death from cancer.

"Some studies have shown that alcohol consumption increases cancer metastasis," said Gary G. Meadows, director of the Cancer Prevention and Research Center at Washington State University, "while other studies have shown that alcohol consumption decreases metastasis. Thus, there is a lot more work needed in this area." Meadows, the Dorothy O. Kennedy distinguished professor, is also the corresponding author for the study.

For the study, pathogen-free female mice were divided into a number of study groups, each containing 20 mice. These included nontumor, water-consuming mice; nontumor, alcohol-consuming mice; with-tumor, water-consuming mice; with-tumor, alcohol-consuming mice; with-tumor, pair-fed mice that had their alcohol calories replaced with maltose-dextrin; and with-tumor, pair-fed mice that did not have their alcohol-derived calories replaced with maltose-dextrin. The mice were given water or 20% w/v alcohol in their drinking water for three weeks to six months. Some were then inoculated with melanoma cells subcutaneously into the right dorsal hip. The mice continued to consume water or alcohol, and researchers gathered a variety of biochemical data at various time periods following tumor inoculation, including body weight, body water content, tumor weight and carcass fat content.

"Alcohol consumption caused a loss in body fat in the mice with melanoma," said Meadows, "and this was associated with a decrease in survival of the melanoma-bearing mice. This could be important because cancer patients often lose a lot of weight near the end of life even if they are able to maintain their food intake. It is commonly thought that this weight loss accelerates the progression of the cancer and shortens survival. The weight loss for cancer patients is in body protein as well as body fat. However, the interesting thing about the loss of body weight in our study is that it was from fat, not protein."

"Although often regarded as socially unacceptable, fat serves a useful purpose as energy storage for the body," said Carl Waltenbaugh, professor of immunology at Northwestern University Medical School. "Chronic alcohol consumption increases leptin, a fat-cell

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A LCOHOL MAY HASTEN THE PROGRESSION OF CANCER

(adipocyte) derived hormone that has multiple biological effects, including the ability to change lipid metabolism. Eventually, an alcoholic's body utilizes fat as a primary energy source, resulting in 'wasting' or rapid loss of body weight. Once fat reserves are exhausted, the body must rely more and more upon alcohol as an energy source. At the same time, alcohol depresses immune function, especially natural killer cells that are responsible for tumor cell elimination. This study shows that chronic alcohol consumption shortens cancer survival time for tumor-bearing patients. For alcoholics without known cancer, loss of natural killer cells means that a first line of defense is missing in these individuals, thus increasing their susceptibility to cancer in the future.

Waltenbaugh suggested that future research determine if alcohol presents a confounding factor for more cancers than melanoma, what amount and duration of alcohol consumption causes this effect, whether or not abstinence from alcohol might affect tumor progression/weight loss, and if leptin antagonists might increase chances of survival.

"Other studies have shown that abnormal leptin levels also alter immune function," he said. "Yet alcohol-induced augmentation of leptin is new to science. Elevated leptin levels and diminished immune function in alcohol-consuming individuals suggest a potential cause for increased susceptibility to infection in these individuals." Conversely, he said, this association may also allow scientists to develop ways to protect alcoholics from infection.

Another possibility for future leptin research, according to Meadows, is related to the finding that the tumor-bearing mice lost weight and fat without losing muscle mass (body protein).

"We are planning more studies in the future to see how alcohol influences fat metabolism," said Meadows. "We are very interested in finding the mechanism for the fat loss in the tumor-bearing mice, because this could lead to a new way to promote fat loss in obese people without the accompanying loss in muscle mass during dieting. In particular, we are interested in the effects that alcohol has on leptin, which also has a role in controlling obesity."



Article is based on the following published research:

Nunez, N.P.,
Carter, P.A., &
Meadows, G.G.
(May 2002).

Alcohol consumption
promotes body weight
loss in melanoma-
bearing mice.

*Alcoholism: Clinical
and Experimental
Research,*
26(5), 617-626.



IS THERE A LINK BETWEEN ALCOHOL AND ALLERGIES?

- *Immunoglobulin E (IgE) is a molecule involved in allergic diseases.*
- *Serum IgE levels are influenced by genetics, allergen exposure and some environmental factors.*
- *A new study investigates if alcohol may be one such environmental factor.*
- *Low to moderate alcohol consumption was found to be associated with increased IgE levels.*

Immunoglobulin E (IgE) is a molecule involved in allergic diseases. Atopy – the genetic predisposition to develop IgE antibodies against some antigens in the environment – affects as much as 30 percent of the population, and is believed to be increasing in frequency. In addition to the influence of genetics and allergen exposure, serum IgE levels can also be increased by a number of factors that include parasitic and other infections, neoplasms (abnormal tissue growth) and exposure to certain environmental factors. A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* investigates if alcohol may be one such environmental factor.

“In prior studies we observed that alcoholics have increased IgE values,” said Arturo González-Quintela, associate professor of internal medicine at the Complejo Hospitalario Universitario de Santiago, Spain and corresponding author of the study. “In the present study, we focused on the possible influence of minor quantities of alcohol intake, that is, ‘normal consumption’ or what is considered below the range of alcohol abuse. To our knowledge, this is the first study to focus on the association of low to moderate alcohol intake and both total and specific serum IgE levels.”

A total of 460 patients (251 males, 209 females) were recruited from an adult allergy clinic in Spain. Based on skin-prick tests to common aeroallergens, 325 (71%) were classified as atopic and 135 (29%) as non-atopic. Most of the atopic patients (253 or 78%) were allergic to house dust mites. Using 10 grams as a measure of one drink, 260 patients (57%) were found to consume a median of 30 grams of alcohol per week and 200 patients (43%) were considered abstainers. Total serum IgE was measured in all patients and serum specific IgE (for specific allergies) were measured in atopic patients.

“Our research found that regular alcohol intake higher than 70 grams per week (or more than one drink per day) was associated with increased total serum IgE levels in the patients studied,” said González-Quintela. “In patients allergic to house dust mites, regular alcohol intake was associated with increased serum levels of specific IgE against these mites.”

“These findings do not merely support the suggestion that alcohol simply is a risk factor for developing allergies,” observed Thomas R. Jerrells, professor of pathology and microbiology at the University of Nebraska Medical Center and the Omaha VA Medical Center. “The study results indicate that consumption of alcohol may result in abnormal immune responses or that the control of the immune system is affected. This leads to questions about the significance of

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IS THERE A LINK BETWEEN ALCOHOL AND ALLERGIES?

the increased response to allergens by drinkers. If alcohol somehow affects the control of the immune response to these allergens, an exaggerated response would be expected.”

Jerrells speculated that alcohol, either directly or indirectly through metabolites, might non-specifically activate a very complicated function of the immune system to produce IgE. An alternative possibility is that alcohol, again directly or indirectly, might activate cells that carry preformed IgE to release the IgE. Jerrells added that cells in various tissues, especially the gut, have surface IgE such as mast cells.

Nonetheless, despite results suggesting that even low to moderate alcohol consumption may affect the immune system, study authors show caution in extending these findings beyond the specific results.

“It is important to realize that it cannot be concluded,” said González-Quintela, “that alcohol intake increases the likelihood of either developing allergic sensitization to aeroallergens such as dust mites, or developing more severe symptoms in patients already sensitized. Nor can it be concluded that alcohol intake should be avoided by allergic patients.”

González-Quintela said that ongoing, unpublished studies indicate that, rather, alcohol intake is likely associated with a variable rate of sensitization to distinct aeroallergens. In other words, the sensitization rate either increases or decreases depending on the allergen considered. Furthermore, allergic sensitization depends on multiple variables – including socioeconomic conditions – that cannot be always controlled for in observational or non-experimental studies.

“Not all atopic subjects develop allergic symptoms,” he said. “In addition to a genetic background, they will also need allergen exposure. Moreover, some environmental factors more than others favor allergic or IgE-mediated immune responses. We simply need more research to improve the understanding of allergic diseases and what role alcohol consumption may play.”



Article is based on the following published research:

Vidal, C.,
Armisen, M.,
Dominguez-
Santalla, M.J.,
Gude, F., Lojo S., &
Gonzalez-Quantela, A.
(January 2002).
Influence of alcohol
consumption on serum
immunoglobulin E
levels in atopic and
non-atopic adults.
*Alcoholism: Clinical
and Experimental
Research*,
26(1), 59-64.

How TO BUILD STRONG BONES: GET MILK, LOSE THE BOOZE

- *Alcohol consumption contributes to bone loss, and is a likely risk factor for osteoporosis.*
- *Alcohol-induced bone loss seems primarily due to reduced bone formation.*
- *An experimental drug treatment for osteoporosis called parathyroid hormone may reverse alcohol-induced bone loss in younger drinkers.*
- *Chronic adult drinkers remain at high risk of earlier and more severe osteoporosis.*

A popular bar and eatery in Austin, Texas sells t-shirts that say “Beer: It’s not just for breakfast anymore.” While the play-on-words may be initially amusing, osteoporosis is not. Alcohol consumption is known to be a significant contributing factor to bone loss, and is believed to be a risk factor for osteoporosis. Two rodent studies in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* examine alcohol’s effects on bone. Specifically, one study investigates if these effects are reversible; another explores what differences may exist between the effects of drinking during youth versus adulthood.

“The most common form of osteoporosis occurs in elderly women and is caused by estrogen deficiency,” said Russell T. Turner, professor of orthopedics at the Mayo Clinic and lead author of one of the studies. “Bone thinning occurs as a result of a large increase in bone resorption (a loss of substance). In contrast, alcohol-induced osteoporosis is caused by decreased bone formation and is frequently observed in middle-aged men.”

Alcoholics often have bones that are less dense than normal. Less bone density means less bone strength, which can increase an individual’s risk of bone fracture. In fact, alcoholics have a high rate of non-traumatic and trauma-induced bone fractures, especially in the femoral neck. Although good nutrition is essential for maintaining bone health – and alcoholics usually have poor nutritional habits – animal studies have shown that alcohol can slow bone growth even when nutrition is maintained. This indicates that alcohol is directly responsible for at least some detrimental effects on bone health.

“Drinking cessation does not result in a spontaneous reversal of alcohol-induced bone loss,” said Turner. “This may mean that alcohol has an irreversible toxic effect on bone cells or that alcohol interferes with the normal communication between bone cells which governs the delicate balance between how much bone is formed and how much bone is resorbed.” Turner and his colleagues tested the effects of parathyroid hormone (PTH), an experimental drug treatment for osteoporosis, on rats whose bone formation had been suppressed by alcohol. The animals were the human equivalent of young adults. “The fact that they responded so vigorously indicates that alcohol-induced bone loss can be reversed,” he said.

James R. West, professor and head of the Department of Anatomy and Neurobiology in the College of Medicine and interim vice-president for research at the Texas A&M University System Health Science Center, calls this finding very interesting.

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How TO BUILD STRONG BONES: GET MILK, LOSE THE BOOZE

However, he cautions, “PTH is also known to take calcium out of bone. So the fact that PTH can, under certain conditions, actually stimulate bone growth is a little bit unusual.” He called for longer-term studies.

Both Turner and H. Wayne Sampson, professor of human anatomy and neurobiology in the College of Medicine at the Texas A&M University System Health Science Center and lead author of the second study published in *ACER*, cautioned against adolescent drinking. “The issue of bone loss is especially critical for young people today since it is now reported that problem drinkers begin as preteens,” said Sampson. “Animal studies of an age comparable to human youth have repeatedly shown shorter bones, weaker bones and decreased bone density. Except for length, these qualities do not recover with age and, should osteoporosis occur, the bones would reach fracture threshold sooner.”

Sampson’s study is one of the first to demonstrate actual bone loss in animals that begin drinking as adults. This is an important distinction because if, as believed, alcohol has a direct effect upon osteoblasts (bone forming cells), then adults who drink heavily are causing potentially irreversible damage to their bones.

“In the younger animals tested,” said West, “you still had growth. The alcohol interferes with the growth and bone development, but when you stop the alcohol, growth resumes. Alcohol doesn’t prevent or stop the growth, it simply interrupts it. Of course, one of the dangers of growth resumption is that it gives the impression that alcohol exposure is really not a risk.” In adults, however, a grave risk of cumulative, alcohol-induced bone damage is that bone growth does not resume.

“After eight weeks,” said Sampson, “we saw nothing. But after 14 weeks, results were very dramatic. With time, alcohol had deleterious effects on adult bones. These findings indicate that if adults begin drinking chronically, they will weaken their bones and run the risk of earlier and more severe osteoporosis, should they develop the disease.”

“Demographics are changing,” said West, “and we’re seeing more osteoporosis. We need to ask ‘to what extent is alcohol abuse playing a role in this?’ People tend to think of someone who misuses or abuses alcohol as kind of a skid-row bum, but that’s not necessarily the case. There are some people out there who are drinking enough to cause organ damage and yet they’re going to work and keeping up a regular job. The cumulative, toxic effects of alcohol would surprise a lot of people.”



**Article is based
on the following
published research:**

Hogan, H.A.,
Argueta, F.,
Moe, L., Nguyen, L.P.,
& Sampson, H.W.
(May 2001).
Adult-onset alcohol
consumption induces
osteopenia in female rats.
*Alcoholism: Clinical
and Experimental
Research*,
25(5), 746-754.

A

LCOHOL, SODIUM SENSITIVITY AND BLOOD PRESSURE

- *Chronic heavy drinking is known to elevate blood pressure.*
- *Sodium sensitivity also tends to raise blood pressure.*
- *New research indicates that withdrawal from heavy drinking may derange sodium metabolism in such a way that a person's sodium sensitivity is increased, leading to higher blood pressure.*

Alcohol appears to have the potential for both beneficial and toxic effects on the heart. The “French Paradox,” for example, refers to the protective properties that red wine may have vis-à-vis heart disease. Chronic heavy drinking, on the other hand, is a leading cause of several cardiovascular illnesses, including high blood pressure. High blood pressure or hypertension, increases the risk for heart disease and stroke, both leading causes of death in the United States. A study in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that alcohol-induced sodium sensitivity may be one of the mechanisms underlying the association among heavy alcohol consumption, alcohol withdrawal and high blood pressure.

“We know that chronic exposure to heavy amounts of alcohol elevates blood pressure and contributes to hypertension among alcoholics,” said Cristiana Di Gennaro, a junior scientist at the University of Parma and corresponding author for the study. “We also know that sodium sensitivity is characterized by an increase of blood pressure, although not necessarily in the hypertensive range, when salt intake is elevated. In addition, sodium sensitivity has been shown to be an independent risk factor for cardiovascular disease. Our findings indicate that alcohol consumption may raise blood pressure through the induction of a sodium sensitive state.”

“There is some evidence that for heavy drinkers, even when they don’t drink, blood pressure is high,” said Maurizio Trevisan, professor and chairman of the department of social and preventive medicine at the School of Medicine, University of Buffalo. “The day after they drink, for example, their blood pressure may be higher than normal. If they drink chronically, they are in sort of a constant level of withdrawal. This can occur even in moderate drinkers, although the evidence is not as clear as it is for the heavy drinkers.” What happens during these “mini-withdrawals,” he said, is even more pronounced during extended or complete withdrawal.

Researchers examined 18 alcoholics (six females, 12 males) entering in-hospital detoxification at the University of Parma in Italy. Their blood pressure and sodium levels were assessed during their first eight days of stay. During this time, each patient was on a fixed hospital diet that provided 150 mM of sodium per day (considered normal). After one year of carefully monitored abstinence, study participants underwent a four-week phase of examination, which included measuring their blood pressure levels on three separate occasions. Then they were asked to adhere to a diet of 55 mM of sodium per day (considered low), which was later supplemented with 205 mM (for a total of 260 mM, considered high) of sodium per day.

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A LCOHOL, SODIUM SENSITIVITY AND BLOOD PRESSURE

During the first eight days of withdrawal, alcoholics on a 'normal' diet of sodium intake demonstrated high sodium levels, weight gain and increased blood pressure. A year later, and during exposure to the dietary sodium manipulations, the same group displayed much more significant changes in blood pressure and greater sodium sensitivity when compared to a group of teetotalers. In addition, changes in blood pressure during the early withdrawal period were related to sodium sensitivity during long-term abstinence. These findings suggest that salt sensitivity plays a key role in blood pressure regulation in early withdrawing alcoholics.

"Prior to this study," said Trevisan, "we knew about some of the conditions that increase sodium sensitivity. One of them is insulin resistance, another is being overweight. Now we have [yet] another factor that appears to increase someone's sodium sensitivity, that is, heavy alcohol consumption. It looks like heavy alcohol consumption for long periods of time appears to derange your sodium metabolism in a way that makes you more sodium sensitive."

"We do not know definitely whether sodium sensitivity is an acquired trait linked to alcohol abuse," added Di Gennaro, "or a genetic trait. We do know, however, that sodium sensitivity remains significant after at least one year of alcohol abstinence in heavy alcoholics. We believe that our demonstration of an important interaction among alcohol consumption, sodium metabolism, blood pressure regulation and cardiovascular diseases extends further our knowledge about the impact of dietary and lifestyle factors on one of the most important causes of morbidity and mortality in western countries. Our findings also suggest that a dietary reduction of both alcohol and salt is warranted."

Trevisan agrees. "Everybody should benefit from a low-sodium diet anyway," he said.



**Article is based
on the following
published research:**

Di Gennaro, C.,
Vescovi, P.P.,
Barilli, A.L.,
Giuffredi, C.,
Delsignore, R.,
Montanari, A.
(December 2002).
Sodium sensitivity as
a main determinant of
blood pressure changes
during early withdrawal
in heavy alcoholics.
*Alcoholism: Clinical
and Experimental
Research*,
26(12), 1810-1815.



A LCOHOL'S EFFECTS ON TESTOSTERONE

- *Most research has shown that alcohol inhibits testosterone secretion in male animals and humans.*
- *A new study has found that acute administration of alcohol can increase testosterone biosynthesis in some male rodents.*
- *These results provide evidence for individual differences in behavioral reactions to alcohol.*

Even though testosterone is often referred to as a “male sex hormone,” it is in actuality common to both genders of animals and humans. The overwhelming majority of research conducted in the past 25 years in both animals and humans has found that alcohol inhibits testosterone secretion. However, a new study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that acute administration of alcohol can induce a rapid increase in plasma and brain concentrations of testosterone in some rodents.

“We have demonstrated that there are very different results in the way two different groups of male rats form testosterone after acute administration of alcohol,” said Robert H. Purdy, senior staff scientist in the Department of Neuropharmacology at the Scripps Research Institute and senior author of the study. “These differences in animals may reflect similar individual differences in humans, and provide new insights for understanding individual differences in the behavioral and endocrine pathology associated with alcohol abuse.”

Researchers injected either alcohol or 1,1-dideuteroethanol (2 g alcohol/kg body weight) into the abdominal cavities of two groups of rats, 30 un-operated and 24 adrenalectomized and castrated (ADX/GDX) Wistar males. 1,1-dideuteroethanol is a nonradioactive form of alcohol in which two of the hydrogen atoms on carbon atom #1 of ethanol have been replaced by deuterium atoms, which can then be traced. Study authors used mass spectrometry, a very precise measure of the mass and structure of compounds derived from extracts of tissues and body fluids, to determine both the amount of neuroactive steroids present and the degree of deuterium incorporation into specific neuroactive steroids isolated from brain samples.

They found that concentrations of testosterone increased fourfold in the frontal cortex and threefold in the plasma of the un-operated rats 30 minutes after alcohol administration. ADX/GDX rats had testosterone concentrations that were only five percent of those found in the un-operated rats following alcohol administration. Tracing the effects of 1,1-dideuteroethanol demonstrated that alcohol oxidation is directly linked to testosterone biosynthesis.

“Our finding of a direct link between alcohol administration and the level of the neuroactive steroid testosterone in the brain of these experimental animals was unanticipated from prior studies with another species of rats,” Purdy said.

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LCOHOL'S EFFECTS ON TESTOSTERONE

“Although many other studies clearly demonstrate that chronic consumption of high dosages of alcohol appears to be consistently inhibitory and suppresses reproductive function,” said Dennis D. Rasmussen, research associate professor in the Department of Psychiatry at the University of Washington, “this study raises the possibility that episodes of alcohol consumption may also at least temporarily increase testosterone levels, with the direction of the response likely being dependent upon a variety of factors, including dosage and personal characteristics. This particular dosage produced blood alcohol levels and behavioral responses consistent with intoxication. So, alcohol consumption, under at least some conditions and by at least some individuals, may acutely stimulate testosterone levels in the plasma and brain of both males and females and thus could elicit some of the behavioral effects associated with increased testosterone levels, such as increased libido or aggression.”

Rasmussen added that these findings join those of two other studies in which alcohol administration increased plasma testosterone levels in a gender- and dose-dependent manner. “Together these studies are important,” he said, “because they illustrate that what has become a largely accepted principal – that alcohol consumption inhibits plasma testosterone levels and reproductive function – is not universally true.”

Rasmussen suggested that future research build upon and add to previous findings regarding alcohol's effects on testosterone. “It would be important to determine whether lower dosages of alcohol, which do not induce rapid pronounced intoxication and ataxia, would also produce the acute increase in testosterone, and whether this response to lower dosages would be consistent across different strains of rats. Also, does tolerance develop with repeated administrations? Does this increase in testosterone occur following elective self-administration of alcohol? Finally, and probably most interesting, what role might the demonstrated changes in testosterone play in behavioral responses to acute ethanol consumption? Are there gender differences in these responses? And, if the responses do occur in females, are they different during different stages of a woman's cycle?”



**Article is based
on the following
published research:**

Alomary, A.A.,
Vallee, M., O'Dell, L.E.,
Koob, G.F., Purdy, R.H.,
Fitzgerald, R.L.
(January 2003).
Acutely administered
ethanol participates
in testosterone synthesis
and increased
testosterone in rat brain.
*Alcoholism: Clinical
and Experimental
Research*,
27(1), 38-43.

M MODERATE ALCOHOL CONSUMPTION AFTER MEALS CAN DECREASE LEVELS OF INSULIN

- *Insulin is a hormone that allows blood glucose to provide energy to most of the body's cells.*
- *A lack of insulin can effectively cause some cells to "starve," leading to serious health consequences such as diabetes.*
- *New research shows that drinking a moderate amount of white wine on its own after a meal can cause levels of insulin to drop almost immediately.*

Insulin is a hormone that allows blood glucose to provide energy to most of the body's cells. New research published in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* shows that drinking a moderate amount of white wine on its own after a meal can cause levels of insulin to drop almost immediately.

"A small to moderate amount of alcohol is accepted and indeed often recommended as beneficial to one's cardiac health," said Anna Kokavec, a research psychologist affiliated with La Trobe University in Bundoora, Australia and first author of the study. "However, only a limited number of studies have assessed the effect of consuming readily available alcoholic products on major processes in the human body."

Eating foods high in carbohydrates will normally increase blood-glucose levels for several hours, which in turn, encourages insulin production by the pancreas. Insulin enables glucose, the body's chief source of energy, to gain entry into most of the body's cells located outside of the brain. A lack of insulin can effectively cause some cells to "starve," leading to serious health consequences such as diabetes.

"We know that drinking alcohol can affect the body's production of insulin," said Kokavec. "However, researchers in the past have obtained mixed results and it is only now becoming clear that the effect of alcohol on insulin may depend on the presence or absence of food. Given the discrepancy in the insulin data, the association between food and insulin production, and the important role of insulin in energy production and usage, we felt that the effect of drinking a popular alcoholic beverage such as white wine on insulin production under variable nutritional conditions warranted investigation."

Researchers examined eight non-diabetic males between the ages of 19 and 22 years. All were required to consume pizza and a soft drink for 45 minutes, and then slowly drink three standard units of white wine (10 grams of alcohol each; 30 grams total) during a 90-minute period following their meal. Plasma glucose and plasma insulin levels were assessed during and following the alcohol-consumption period.

"Our results showed that drinking a moderate amount of white wine on its own after a meal can cause the level of insulin to drop almost immediately," said Kokavec. "This was accompanied by a similar lowering of the blood-glucose level and, in some individuals, to a very dangerously low level. The level of insulin after little more than one glass of white wine was

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ODERATE ALCOHOL CONSUMPTION AFTER MEALS CAN DECREASE LEVELS OF INSULIN

similar to the level of insulin usually seen before a meal. When this is considered together with the blood-glucose finding, it suggests that drinking white wine on its own may promote a pseudo-diabetic condition, changing the way the body produces and uses glucose. This could have serious consequences because some of the cells in the body could be starved of energy, which could ultimately lead to disease.”

Kokavec added that these findings also support the previously published theory that alcohol may activate a new energy system that was thought, until recently, to exist only in plants and other organisms that do not require oxygen.

“The glyoxylate cycle is an energy system that can convert fat into carbohydrate,” she said. “The glyoxylate cycle does not require thiamin, utilizes acetate as an energy source and can be switched off by glucose. If alcohol does indeed activate the glyoxylate cycle in the human liver, then this could offer an explanation for alcohol-related fatty liver, thiamin deficiency, alteration in energy metabolism under fasting conditions and lack of appetite for carbohydrates [that are] found in alcoholics, the reasons for which have baffled researchers for years.”

Furthermore, said Kokavec, “present results highlight the need to strictly control for nutritional factors when designing alcohol research as nutritional status may be a confounding factor that is contributing to variability in the alcohol literature. In addition, given the possibility that alcohol may activate the glyoxylate cycle (an energy pathway that can be switched off by glucose) it may be important for scientists to specifically control for the presence of carbohydrates when investigating the effect of alcohol.”



**Article is based
on the following
published research:**

Kokavec, A.,
Crowe, S.F.
(November 2003).
Effect on plasma
insulin and plasma
glucose of consuming
white wine alone after
a meal.

*Alcoholism: Clinical
and Experimental
Research,*
27(11), 1718-1724.

CHRONIC ALCOHOL ABUSE DAMAGES REGULATING HORMONES

- *Chronic alcohol consumption is associated with higher rates of infections, cardiomyopathy, cardiac arrhythmias, bleeding complications and liver insufficiency.*
- *New research indicates that changes in hormones that regulate electrolyte and water balance in the body may not only account for some withdrawal symptoms, but persist over long periods of strictly controlled abstinence.*

Although it is well known that alcohol abuse causes a broad range of health complications, it remains unclear how much regeneration may occur during long-term abstinence. A new study carefully monitors major water and electrolyte regulating hormones – arginine vasopressin (AVP), atrial natriuretic peptide (ANP), aldosterone and angiotensin II – from early withdrawal up to 280 days of strict abstinence. The results, published in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)*, indicate that chronic alcohol abuse can cause severe alterations in hormones that regulate the body's electrolyte and water balance.

“Most available literature on regeneration from alcoholism is restricted to the first [few] days [and up to] three weeks of abstinence,” said Hannelore Ehrenreich, head of Clinical Neuroscience at the Max-Planck-Institute for Experimental Medicine and corresponding author for the study.

“Both chronic alcohol consumption and alcohol withdrawal can affect cell and homeostatic functions,” said Claudia Spies, medical associate director of the Department of Anesthesiology and Intensive Care Medicine at the University Hospital Charite Campus Mitte. “A chronic alcohol intake of at least 60g, or 1.5l beer, per day is associated with complications such as higher rates of infections, cardiomyopathy, cardiac arrhythmias, bleeding complications and liver insufficiency. During withdrawal, changes in electrolyte and water homeostasis occur.”

The consequences, however, are clear. “The hospital stay of alcoholics is prolonged compared with that of non-alcoholics,” said Spies. “A major complication is alcohol withdrawal syndrome (AWS), developed by approximately half of chronic alcoholics during their hospital stay. The majority of the patients who develop AWS have hallucinations or delirium. AWS can also be deadly. In one study, the mortality rate in patients with AWS was approximately 18 percent, whereas alcohol abusers without AWS had a mortality rate of four to six percent, and non-alcohol abusers had a mortality rate of zero percent.”

“Vasopressin, or AVP, is a hormone that is also part of the stress regulatory system,” said Ehrenreich. “In previous work, we showed that circulating levels of AVP are persistently suppressed in alcoholic patients over many weeks of abstinence. This is why we chose to further elucidate the recovery of vasopressin levels in alcoholics during long-term abstinence.”

Two groups of males participated: alcoholics (n=35), 30 to 61 years of age and controls (n=20), 25 to 50 years of age. The two groups were matched on cigarette use. “It is well known that

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CHRONIC ALCOHOL ABUSE DAMAGES REGULATING HORMONES

acute nicotine use increases the secretion of AVP,” explained Ehrenreich. “It has to be assumed that chronic cigarette consumption also alters AVP secretion or metabolism. Therefore, we used cigarette-matched controls to exclude the influence of such an interfering variable.”

Following an inpatient detoxification period of two to three weeks, 21 of the 35 alcoholics were successfully monitored for the full length of the study period, 280 days. Researchers collected data from all of the participants on their AVP, ANP, aldosterone and angiotensin II levels, as well as measures of kidney and liver function.

They found that basal AVP levels were suppressed during the entire study period. In contrast, ANP levels were elevated for the entire time. No persistent alterations were found for aldosterone or angiotensin II. “We learned that we are dealing with profound, long-lasting alterations of key hormones of water and electrolyte balance notwithstanding at least nine months of controlled abstinence,” said Ehrenreich. “These observations imply a number of causes and consequences: they may explain excessive thirst and fluid intake, what we call diabetes insipidus; may explain how alcohol-related cardiomyopathy develops; and may show that there is a subclinically impaired renal function in these patients which clearly underlines the concept of multi-organ involvement in alcoholism. Not only are the liver and brain affected, but basically all organs are.”

Both Ehrenreich and Spies believe these results can be used to develop new therapeutic options to support abstinence. “One possibility would be to substitute AVP,” said Ehrenreich, “which might not only contribute to recovery of water and electrolyte homeostasis but also benefit cognitive functions. The findings imply that some features of craving, such as drinking behavior and thirst, might be explained by biological alterations in the regulation of salt and water homeostasis. Therefore, approaches to normalize vasopressin regulation might result in a reduction of craving-induced relapses.”

Ehrenreich added that one of the most important findings is that “chronic alcoholism is associated with long-term persistent alterations of various organs and systems. There is no immediate recovery to be expected,” she stressed. “Both for psychological and medical reasons, we need to consider that we are dealing with individuals severely compromised over many months of controlled abstinence. Detoxification treatments are necessary to overcome life-threatening withdrawal symptoms.”

Article is based on the following published research:

Döring, W.K.H.,
Herzenstiel, M.N.,
Krampe, H., Jahn, H.,
Pralle, L., Sieg, S.,
Wegerle, S., Poser, W.,
Ehrenreich, H.
(May 2003).

Persistent alterations
of vasopressin and
n-terminal proatrial
natriuretic peptide
plasma levels in
long-term abstinent
alcoholics.

*Alcoholism: Clinical
and Experimental
Research*,
27(5), 849-862.





*P*regnancy,
Prenatal
Exposure &
Parenting



PREGNANCY, PRENATAL EXPOSURE & PARENTING

Articles in the *Pregnancy, Prenatal Exposure & Parenting* Category

1. Alcohol Consumption During Pregnancy Alters Thyroid Function
2. Alcohol, Women and Pregnancy
3. Pregnancy, Drugs and Alcohol, Emotional Instability:
What Nightmares Are Made Of
4. Exploring the Complexities of Prenatal Alcohol Exposure
5. Drinking During Pregnancy: Information May Not Be Enough
6. Drinking During Pregnancy: American Indians and African Americans
7. Genetic Protection Against Fetal Alcohol Syndrome?
8. Light to Moderate Drinking During Pregnancy Can Effect Adolescent Growth
9. Light to Moderate Drinking During Pregnancy May Lead to Learning and
Memory Deficits in Adolescents
10. The Power of the Mother-Child Bond
11. Parenting, Stress and Your Child's Risk for Alcoholism

ALCOHOL CONSUMPTION DURING PREGNANCY ALTERS THYROID FUNCTION

- *Normal fetal development requires both mother and fetus to supply appropriate levels of thyroid hormone at different times.*
- *Brain abnormalities found in children exposed to abnormally low concentrations of thyroid hormone during fetal development are similar to those found in children exposed to alcohol in utero.*
- *Researchers have found that alcohol consumption during pregnancy can alter thyroid function in both the mother and fetus.*

In order to assure normal fetal development, mother and fetus must both – at different times during gestation – contribute appropriate levels of thyroid hormone. If not, brain defects can result, some of which resemble those found in children suffering from fetal alcohol syndrome (FAS). Due to these commonalities, some researchers speculate that alcohol may mediate alcohol-related birth defects (ARBDs) by inducing hypothyroid conditions in utero. A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* investigates if alcohol consumption during the equivalent of the third trimester in sheep results in an alteration of fetal or maternal thyroid function.

“The thyroid hormone system plays important roles in growth, development and in the function of other hormone and organ systems,” explained Timothy A. Cudd, associate professor of physiology at Texas A&M University and lead author of the study. “Both mother and fetus must contribute thyroid hormone for normal fetal development. Early in development, before the fetus is capable of producing thyroid hormone, maternal thyroid hormone crosses the placenta to influence fetal development. Later in development, when higher concentrations are required for normal fetal development, a fetal contribution is required to create sufficient concentrations.”

Cudd and his co-authors knew that brain abnormalities found in children who were exposed to abnormally low concentrations of thyroid hormone during fetal development are similar to brain abnormalities found in children exposed to alcohol in utero. “From a behavioral standpoint,” said Cudd, “children born to hypothyroid mothers score less well on intelligence, attention, language, reading ability and school performance measures compared to children born to mothers with normal thyroid function. These deficiencies are similar to those in children with ARBDs. From an anatomical perspective, hypothyroidism and fetal alcohol exposure both affect the development of the hippocampus and the cerebellum.” Knowing these similarities, the study authors investigated if ARBDs are, in part, a result of alcohol-mediated thyroid hormone system dysfunction.

Researchers gave pregnant ewes alcohol doses of 0.75, 1.25, 1.5 or 1.75 g/kg or saline through catheters beginning on day 109 of gestation (a full term for sheep is 145 days). The ewes received alcohol or saline on three consecutive days, followed by four days without expo-

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LCOHOL CONSUMPTION DURING PREGNANCY ALTERS THYROID FUNCTION

sure, thereby mimicking a pattern of binge drinking. Fetal and maternal blood samples were collected on days 118 or 132.

“The administration of alcohol to sheep during the equivalent of the third trimester of pregnancy resulted in altered thyroid function in both the mother and fetus,” said Cudd. “This is an important study because even today so little is known regarding the mechanisms through which alcohol intake by pregnant mothers is bad for their fetuses,” said Catherine Rivier, a professor of neuroendocrinology/neurosciences at the Salk Institute. “In addition, the sheep is a good model for the human because the thyroid system of both species develops similarly during gestation. Prior to this study, we knew that, in general, fetal brain development requires thyroid hormones to grow normally and build all the right connections. These results show us that alcohol given to a pregnant mother lowers thyroid hormones in both the fetus and the mother. This finding gives investigators the rationale for doing additional experiments to see if these changes in thyroid hormones participate in defects due to alcohol.”

Cudd believes that the study’s findings do indeed support the hypothesis that alcohol might mediate ARBDs by altering thyroid function in the fetus and/or in the mother. “Nonetheless,” he said, “further studies are necessary to conclude that this is the case in humans. Clearly, abstaining from alcohol use during pregnancy is the safest course. However, if our findings are proven to hold in humans, then it may be possible to monitor thyroid function and even correct abnormal thyroid function in mothers to potentially mitigate the actions of alcohol on the fetal brain.”



Article is based on the following published research:

Cudd, T.A.,
Chen, W-J.A.,
& West, J.R.
(January 2002).
Fetal and maternal
thyroid hormone
responses to ethanol
exposure during the
third trimester
equivalent of gestation
in sheep.
*Alcoholism: Clinical
and Experimental
Research,*
26(1), 53-58.

A LCOHOL, WOMEN AND PREGNANCY

- *Pregnant women who drink moderate to heavy amounts place their offspring at risk for developmental deficits.*
- *Previous research suggests that alcohol exposure later in pregnancy may be particularly damaging.*
- *A new study has found that moderate alcohol exposure during early pregnancy may be just as damaging to neurobehavioral development as continuous or late exposure.*
- *Neurodevelopmental deficits caused by early exposure were more obvious than growth impairments.*

There is little question that women who drink heavily during pregnancy place their children at risk of developing fetal alcohol syndrome (FAS), characterized by growth retardation, cranio-facial anomalies and mental retardation. However, women who drink moderate amounts of alcohol may also place their children at risk of developing less severe deficits (once known as fetal alcohol effects but now called alcohol-related neurodevelopmental disorder), characterized by a lower IQ, attention deficits, learning deficits and reduced social competence. A study in the August issue of *Alcoholism: Clinical and Experimental Research (ACER)* has discovered that a crucial factor for the developing fetus may be *when* a woman drinks. Researchers found that moderate alcohol exposure during early pregnancy may be just as damaging to neurobehavioral development as continuous or late exposure.

“Previous research has found that alcohol exposure later in pregnancy is strongly associated with problems in growth and behavioral development,” said Mary L. Schneider, professor of occupational therapy and psychology at the University of Wisconsin-Madison and lead author of the study. “Yet women who report drinking late in pregnancy have usually consumed alcohol throughout and so it is hard to disentangle early drinking from late drinking. In addition, while animal studies have established that high doses cause numerous impairments, many questions remain regarding the issue of moderate fetal alcohol exposure. Since many women of childbearing age drink alcohol regularly, it is likely that some offspring are exposed to alcohol before pregnancy is detected. These are just some of the reasons for why I felt it was important to examine the effects of moderate drinking at different times during pregnancy.”

Study subjects were rhesus monkey infants whose mothers consumed a moderate dose of alcohol either continuously or during the human equivalent of the first or last two trimesters of pregnancy. (Moderate drinking in humans is defined as seven to 14 drinks per week or one to two drinks per day.) Schneider explained that not only do primate studies allow greater generalization to humans than rodent studies because of similarly complex social and cognitive abilities and brain development, but they are also less complex than “real life.” Among humans, she said, alcohol consumption can be confounded with cigarette smoking, less-than-adequate prenatal care, stress and other drug use,” all of which can have negative effects on fetal development. In addition, researchers can use adapted human tests such as the Brazelton Newborn Assessment Scale to assess early neurobehavior in monkeys.

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A LCOHOL, WOMEN AND PREGNANCY

“We found that early gestation alcohol exposure was related to noteworthy reductions in infant attention and motor maturity in rhesus monkeys,” said Schneider. “Yet there were no significant growth impairments. Thus, it appears that behavioral effects can be detected under circumstances in which growth was not affected. We also found that early exposure was as harmful as exposure throughout pregnancy in these monkeys. To the extent that these data generalize to humans, it suggests that subtle neurodevelopmental effects could be induced before pregnancy is detected.”

“There are at least four very important aspects to this research,” noted Joanne Weinberg, professor of anatomy at the University of British Columbia. “The primate model is very powerful in this case because it allows researchers to carry out sophisticated neurobehavioral tests, comparable to tests used in humans, to see what the effects of alcohol are. Another important aspect concerns the moderate levels of alcohol exposure. There are very few physical problems in these animals, you don’t see deficits in growth, and yet functionally they’re not normal. This finding probably has relevance for a more substantial percentage of the population. The third aspect is one of timing. I think it’s really critical to know *when* alcohol has its effects on fetal brain development because this gives us clues as to how and why these effects occur. Finally, the data from this study clearly separate early exposure from continuous exposure. This relates back to the advantages of animal research, where you can target drinking to specific times during pregnancy instead of asking people to self report on their drinking behavior.”

For Schneider, the study’s findings have a clear message. “Women of childbearing age should abstain from consuming alcohol if they are considering pregnancy,” she said.

Weinberg concurs. “We need to see more education for both the general public and physicians about the fact that alcohol can be harmful,” she said, “and that we really don’t know what a safe level of drinking during pregnancy would be. Although the public is now more aware of FAS, they know much less about the more subtle effects that alcohol can have on a developing fetus. Even some pediatricians and obstetricians are not very well informed about the effects of moderate levels of fetal alcohol exposure, although they may know about FAS. The bottom-line message is that, “if you’re pregnant or thinking of becoming pregnant, we don’t know what a safe level for drinking is and you’re better off not drinking at all.”



Article is based on the following published research:

Schneider, M.L.,
Moore, C.F.,
& Becker, E.F.
(August 2001).
Timing of moderate
alcohol exposure
during pregnancy
and neonatal outcome
in rhesus monkeys
(*Macaca Mulatta*).
*Alcoholism: Clinical
and Experimental
Research*,
25(8), 1238-1246.

PREGNANCY, DRUGS AND ALCOHOL, EMOTIONAL INSTABILITY: WHAT NIGHTMARES ARE MADE OF

- *Psychopathology is the study of emotional, behavioral and psychological problems.*
- *Pregnant women with co-occurring alcohol and drug dependencies have a unique psychopathology.*
- *They have more symptoms of depression, anxiety, impulsivity, aggression and suspiciousness.*
- *Drug-dependent women who are also alcohol dependent have special treatment needs.*

The majority of alcohol research to date has focused primarily on men, or on combined samples of men and women. Even fewer psychopathological studies – which examine emotional, behavioral and psychological problems – have focused exclusively on women with drug dependencies. Of those that have, the focus has been on single substances of abuse, such as cocaine. A study in the July issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the psychopathology of pregnant women with co-occurring alcohol and drug dependencies.

“Pregnant drug-dependent women present for treatment with a variety of medical, psychosocial and emotional problems,” said Donna R. Miles, postdoctoral fellow in the Department of Pharmacology and Toxicology at Virginia Commonwealth University and lead author of the study. “Rates of homelessness, poverty, unemployment and prostitution are high in this patient population. Many of these women have histories of emotional, physical and sexual abuse. Yet societal stigmatization typically prompts pregnant women to conceal substance use, which makes identification and intervention difficult. In fact, many alcohol- and drug abusing women avoid prenatal care altogether. Furthermore, in many states, delivery of a drug-positive infant results in legal sanctions that include termination of parental rights and criminal prosecution.”

“Pregnancy can have multiple effects on alcohol/drug-dependent women,” added Roy W. Pickens, associate vice president for research and professor of psychiatry at Virginia Commonwealth University. “On the one hand, concern about the effects of alcohol/drug use may cause a pregnant woman to be more willing to seek and complete treatment. On the other hand, pregnancy adds to the unfounded social stigma of being alcohol/drug dependent, which may keep a woman from entering treatment.”

In the study, the psychopathology of 170 pregnant women in treatment for drug dependency was measured using the Minnesota Multiphasic Personality Inventory-Revised (MMPI-2). The MMPI-2 uses 567 self-report items to measure different aspects of psychopathology, including depression, anxiety, impulsivity, aggression and suspiciousness. The majority of the women (79%) were drug dependent only; less than one quarter (21%) were both alcohol and drug dependent.

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PREGNANCY, DRUGS AND ALCOHOL, EMOTIONAL INSTABILITY: WHAT NIGHTMARES ARE MADE OF

“Our findings show that cocaine- and/or heroin-dependent pregnant women who also have problems with alcohol come into treatment with more psychological problems than those who don’t also have alcohol problems,” said Miles. “Specifically, they had more symptoms of depression and anxiety as well as problems controlling impulsivity and aggression. They were also more likely to misinterpret life experiences and react in atypical ways to their environment. These findings emphasize the need for universal screening for alcohol problems in drug-using pregnant women and, for those who screen positive, to make sure treatment is offered and tailored to meet their needs.”

“These findings illustrate that all drug-dependent individuals are not the same,” agreed Pickens. The study suggests that alcohol dependence, in particular, is a factor related to psychiatric/personality disorders in the drug dependent individual. This difference needs to be recognized by treatment providers, the individuals’ relatives and the general public.”

U.S. Department of Health and Human Services 1996 data reveal that 5.5 percent of women used illicit drugs during pregnancy, while 18.8 percent reported alcohol use during pregnancy. Pickens said a more recent study found that a similar proportion (5 to 6%) of women had used illicit drugs during pregnancy, while a greater proportion (25%) had used alcohol. Because research shows that alcohol use during pregnancy is the leading known cause of mental retardation, said Miles, its use should not be overlooked, even when women are using other drugs.

Prior to the creation of the Baltimore Center for Addiction and Pregnancy (CAP), where this research was conducted, less than five percent of pregnant drug abusing women followed through with an initial referral to standard drug treatment. (CAP uses what is considered an intensive approach: residential treatment followed by 6.5 hours per day of outpatient treatment for the duration of pregnancy.) Subsequent to CAP’s establishment, Miles estimated that approximately 50 percent of the pregnant, drug-dependent women referred to CAP actually followed through with the referral.

“The women seeking treatment at CAP have severe cocaine and/or opiate dependence as well as limited financial, family/social and medical resources,” said Miles. “They are also older women with several previous pregnancies.” Most of the women were also single (75%), African American (80%) and had a mean age of 29 years. “This kind of program is often so focused on illicit drug use,” Miles continued, “that alcohol problems often go undetected or receive less emphasis. Yet this study found that alcohol seems to be uniquely associated with greater psychopathology.”

Article is based on the following published research:

Miles, D.R.,
Svikis, D.S.,
Kulstad, J.L.,
& Haug, N.A.
(July 2001).

Psychopathology in
pregnant drug
dependent women
with and without
comorbid alcohol
dependence.

*Alcoholism: Clinical
and Experimental
Research,*
25(7), 1012-1017.



***F*EXPLORING THE COMPLEXITIES OF PRENATAL ALCOHOL EXPOSURE**

- *Children prenatally exposed to alcohol demonstrate distinct deficits in social and adaptive behavior.*
- *Researchers have found that children in psychiatric treatment who were not prenatally exposed to alcohol have the same deficits.*
- *As prenatally exposed children age, however, their social difficulties become more pronounced.*

Prenatal alcohol exposure is the leading cause of mental retardation of known origin in the industrialized world. Children prenatally exposed to alcohol are less likely to consider consequences to their actions, lack appropriate initiative, can be unresponsive to subtle social cues and often lack reciprocal friendships. They also have increased behavioral and learning difficulties during adolescence, and frequently exhibit hyperactivity, attention deficits and/or concentration difficulties. Similar deficits have been described in clinical samples of children who are in psychiatric treatment, but were not prenatally exposed to alcohol. A study in the July issue of *Alcoholism: Clinical and Experimental Research (ACER)* compares these two groups of children.

“Our study is the first to compare prenatally exposed children to clinically referred children with no prenatal exposure,” said Shannon E. Whaley, assistant research psychologist at the UCLA Neuropsychiatric Institute and lead author of the study. “Multiple studies have provided clear evidence that children prenatally exposed to alcohol show distinct social and adaptive behavior deficits as compared to normal children of the same age. If these deficits are unique to the prenatally exposed children, then they are important not only for the diagnosis of fetal alcohol syndrome (FAS) or the more common alcohol-related neurodevelopmental disorder (ARND), but also for the course of treatment. If, however, these behaviors are not unique to prenatally exposed children, they remain crucial for intervention but are less useful for specific diagnosis.”

The study found that the behavior deficits of the prenatally exposed children are not particularly different than those exhibited by children with other psychiatric difficulties. However, as prenatally exposed children become older, their difficulties with socialization skills in particular (making and keeping friends, understanding social cues, behaving appropriately in social situations) become more pronounced.

“It is vitally important to examine social and adaptive functioning among these children because any attempt to help them will be shaped by their problems,” said Marian Sigman, professor of psychiatry and psychology at UCLA School of Medicine. “If children exposed to alcohol prenatally are not getting along with others, adults need to find ways to help them with their social relationships. Adaptive functioning reflects a broader set of abilities, such as the capacity to take care of one’s basic needs and communication skills. The finding that the adaptive deficits were similar across both groups is important because it means that adap-

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EXPLORING THE COMPLEXITIES OF PRENATAL ALCOHOL EXPOSURE

tive deficits are not unique to children prenatally exposed to alcohol, but [instead] characterize children with a variety of problems. The fact that social deficits became more significant with age may mean that these children might have more serious social deficits when they are older. We need to understand what can be done to stop this developmental pattern.”

The study used the Vineland Adaptive Behavior Scales, a widely used measure of adaptive functioning, to test the children. Both groups demonstrated distinct difficulties across three domains of age-appropriate functioning: basic daily living skills, communication and socialization behavior. Daily living skills included tasks like helping to put things away, feeding and dressing one’s self completely without assistance, knowing the date, reading the clock and knowing the value of money. Communication skills included reading and writing, paying attention at school, articulating clearly and expressing ideas in more than one way. Socialization skills included making friends, following rules, initiating activity and carrying on socially appropriate play and conversation. Unlike previous studies, researchers found that none of the deficits in these three domains were attributable to deficits in intellectual functioning.

“In the early years,” summed up Whaley, “social deficits of prenatally exposed children are likely to look similar to those exhibited by other children referred for psychological/psychiatric treatment. In fact, the lack of differences in social and adaptive behavior exhibited by the two groups of children shows how easy it is for prenatally exposed children to ‘blend in’ to clinical settings.” Whaley said that during the critically important examination that doctors and clinicians make to determine potential contributors to social deficits, prenatal exposure is often missed and thus, not addressed.

“As prenatally exposed children become older,” she added, “their difficulties with social skills are likely to become more pronounced than those exhibited by clinically referred children who were not prenatally exposed. Thus, after about age six or seven, prenatally exposed children show more difficulty than clinically referred children with the social skills required of older children and early adolescents. This includes things like making and keeping friends, having a group of friends, responding appropriately to strangers, controlling hurt feelings when they don’t get what they want, initiating conversations, refraining from asking questions that might hurt or embarrass others and responding to hints or indirect cues in conversation. This is an interesting finding, and particularly important for intervention with these children.”



Article is based on the following published research:

Whaley, S. E.,
O’Connor, M.J.,
& Gunderson, B.
(July 2001).

Comparison of the
adaptive functioning
of children prenatally
exposed to alcohol to
a nonexposed clinical
sample.

*Alcoholism: Clinical
and Experimental
Research,*
25(7), 1018-1024.



DRINKING DURING PREGNANCY: INFORMATION MAY NOT BE ENOUGH

- *In most Western countries, the medical and official position on drinking during pregnancy has been to recommend abstinence.*
- *A Danish study shows that few pregnant women actually discuss drinking with their medical advisors.*
- *A majority of the women considered some alcohol during pregnancy to be acceptable.*

Numerous studies have clearly shown that heavy drinking during pregnancy is the largest preventable cause of birth defects and mental retardation in the United States. Among most Western countries, the medical and official position on drinking during pregnancy has been to recommend abstinence. However, research has shown that information about the potentially harmful effects of drinking alcohol during pregnancy does not necessarily lead to knowledge of the issue, nor do information and knowledge necessarily affect a pregnant woman's attitude toward drinking. A study in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines where a group of pregnant Danish women obtained their information about drinking during pregnancy, their knowledge of the subject and their attitudes toward it.

“Several studies have suggested that passive receipt of information may possibly – but not necessarily – influence awareness and knowledge, but not attitudes or behavior,” said Ulrik Kesmodel, associate professor of epidemiology and social medicine at the University of Aarhus and lead author of the study. “Yet it seems that many politicians and people working with public health believe that just more information will help people change their lifestyle. In reality, information is just one element in changing attitudes and behavior. Knowledge, previous experiences, social influences, current health habits and underlying possibilities of change are the key determinants of change in attitudes and motivation and, eventually, health habits. The current policy of informing each pregnant woman when she presents herself for prenatal care may affect her knowledge, at best, but none of the other elements are targeted.”

In Denmark, all pregnant women are offered and most take advantage of free prenatal care at centers run by midwives. For this 1998 study, researchers recruited and interviewed 439 pregnant, Danish-speaking women who were seeking prenatal care at 15 to 16 weeks of gestation. The women were asked about their sources and levels of information about drinking during pregnancy, their beliefs about and knowledge of drinking during pregnancy, as well as their attitudes toward drinking during pregnancy.

Only one third of the women had discussed drinking during pregnancy with their general practitioner (GP) or midwife. Most of their information was gleaned from the mass media (65%) and relatives (40%). A majority of the women (76%) considered some alcohol during pregnancy to be acceptable, mostly on a weekly level. However, 85 percent regarded binge drinking as harmful. The women's attitudes toward drinking during pregnancy appeared to exist independent of their knowledge of the subject.

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RINKING DURING PREGNANCY: INFORMATION MAY NOT BE ENOUGH

“It is true that only one third said they had discussed alcohol in pregnancy with their GP or a midwife,” said Kesmodel, “however, some pregnant women had probably forgotten discussing this, so the figures are likely higher. Still, this number is quite low, and seems to suggest two things: first, that GPs and midwives could probably do more to get the message across, and second, that health authorities should not rely on this method alone of getting the message across.”

“The mass media is a powerful medium for providing information to the general public,” said Kesmodel, “including the families of pregnant women. In addition, we know that pregnant women judge the information they receive from health personnel according to information available from the media, education, friends and family. Furthermore, by targeting the media and family as sources of information, health authorities may also affect social influences on pregnant women, a key determinant of change in attitude.”

“We see many studies of risk factors,” said Jørn Olsen, professor and head of the Danish Epidemiology Science Centre at the University of Aarhus, “and too few studies of how we could best handle health promotion. We need to track what kinds of effects different health information strategies have.”

“What is the evidence,” he asked, “that alcohol consumption of a few drinks per month or even per week, as opposed to daily intake, may be harmful in pregnancy? If there is no consistent data to suggest that an occasional drink is harmful, it is possible that a large proportion of pregnant women and health personnel will not be convinced by repeated statements that total abstinence is necessary during pregnancy. Many obstetricians in the U.S. do not appear to believe that a few drinks per week in pregnancy does harm to the fetus. If health professionals cannot reach a consensus on the issue, how can we expect pregnant women to follow an official recommendation?”

Kesmodel said that it’s important to ask some tough, albeit unpopular, questions. “There are many women who drink small amounts of alcohol [during] pregnancy, and many of them seem to be told by doctors and midwives that an occasional drink is all right. If the only official recommendation is to not drink, [then] these women are not told that there is a limit, nor approximately what the limit is. So we need to ask the question: Where is the limit? Reaching a consensus on this would allow us to standardize information for these women.”



Article is based on the following published research:

Kesmodel, U.,
Schioler Kesmodel, P.
(October 2002).
Drinking during
pregnancy: Attitudes
and knowledge among
pregnant Danish
women, 1998.
*Alcoholism: Clinical
and Experimental
Research*,
26(10), 1553-1560.



DRINKING DURING PREGNANCY: AMERICAN INDIANS AND AFRICAN AMERICANS

- *Most health campaigns recommend abstinence from alcohol during pregnancy.*
- *Some women nonetheless continue to drink at relatively high levels while pregnant.*
- *This study examines two groups considered most at-risk: American Indians and African Americans.*

Public health campaigns that recommend abstinence from alcohol during pregnancy have been, for the most part, successful. There are, however, some women for whom the “Just Say No” approach to drinking during pregnancy does not resonate. In an effort to better understand this anomaly, a study in the August issue of *Alcoholism: Clinical and Experimental Research (ACER)* closely examined the exposure and response to health warnings among two groups considered most at-risk for Fetal Alcohol Syndrome (FAS): American Indians and African Americans.

“We wanted to look at how some women interpret the messages they’re receiving,” said Lee Ann Kaskutas, a research scientist with the Alcohol Research Group at Berkeley and author of the study. “We wanted to discover what misconceptions women might have about the risk of drinking during pregnancy, what drinking habits they might have during pregnancy, and we also wanted to look very carefully at their drink size.”

As many people are aware, heavy drinking during pregnancy can cause FAS, which is the largest preventable cause of birth defects and mental retardation in the United States. Lighter drinking during pregnancy can lead to Fetal Alcohol Effects (FAE), such as low birthweight, slower postnatal growth and even spontaneous abortion. The Centers for Disease Control and Prevention (CDC) has found that about 15 percent of women consume alcohol during their pregnancies, and 2.1 percent consume alcohol frequently. The CDC also found that both alcohol use and frequent use of alcohol during pregnancy – after a decrease in the early 1990s – has lately increased.

Kaskutas said that some estimates have placed the cost of treating just some of the FAS disorders that occur at more than \$321 million per year. An alternative method of estimation is to look at the cost of taking care of mentally retarded people in one year (approximately \$11.7 billion), multiplying that by 11 percent (believed to be due to FAS), for an amount that exceeds one and one quarter billion dollars per year. Some ethnic groups seem to be more at risk than others, and Kaskutas’ study looked at the two groups with the highest rates of FAS: American Indians (2.97 per 1,000 births) and African Americans (0.6). Other rates are as follows: Whites (0.09 per 1,000 births), Hispanics (0.08) and Asians (0.03).

“Health campaigns that are directed at pregnant women have had a long reach,” observed Kaskutas, “and most women are abstaining just like the messages have said to do. Most of these women have seen the warning label on alcohol containers, most have seen an advertisement about drinking while pregnant, more than half have seen a sign at a liquor store or

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RINKING DURING PREGNANCY: AMERICAN INDIANS AND AFRICAN AMERICANS

restaurant, and the vast majority said they have had a conversation on the topic. Furthermore, all but 10 percent said that they understood and believed the messages.”

“Those women who continued to drink while pregnant,” explained Kaskutas, “were more likely to say that these messages made them feel negatively toward themselves. This can, in turn, contribute to a negative self-esteem spiral of drinking and lack of proper care.”

“Health campaigns may need to be part of a larger attempt to change social norms,” added Ernestine Vanderveen, director of the National Institute on Alcohol Abuse and Alcoholism’s Alcohol Research Centers Program, “such as consumption behavior that involves harmful substances like alcohol, nicotine and caffeine.” One of the obstacles that researchers and public health officials still face, she noted, is a basic lack of understanding of human behavior. “We still don’t fully know how one’s behavior relates to one’s state of health and well-being, nor do we really understand the difference between health-enhancing and health-compromising behaviors. “That’s why,” she continued, “we really don’t know a lot about women’s drinking.”

“This study has relevance because it attempts to get at information that is very difficult to extract,” Vanderveen said. “In general, we probably need more work in terms of finding out from real people what their behaviors are, and how those relate to their health and well-being.”

Kaskutas said, “When you consider the income of these women, then the higher rate for FAS that we see by ethnicity disappears. So some of this disease is about poverty.” Kaskutas said she chose to focus on urban women because most of the research on American Indians has been carried out on reservations, and the few studies on Black urban women have not included American Indian urban women.

“Fewer than one in five of these women realize that it helps to cut down any time during pregnancy; African Americans and heavier drinkers are the most likely to feel this way,” she continued. “We also found that some women think certain beverages are safer than others. ... In addition, the women who drank more often also tended to have larger drinks.”

Kaskutas continued, “Probably the two most important findings have to do with message content and determination of risk. We need to make it clear that it does help to cut down at any time during the pregnancy. We’ve also got to pay attention to drink size when we study drinking during pregnancy.”



Article is based on the following published research:

Kaskutas, L.A.
(August 2000).
Understanding
drinking during
pregnancy among
urban American Indians
and African Americans:
Health messages,
risk beliefs, and how we
measure consumption.
*Alcoholism: Clinical
and Experimental
Research*,
24(8), 1241-1250.

G ENETIC PROTECTION AGAINST FETAL ALCOHOL SYNDROME?

- *Fetal Alcohol Syndrome (FAS) may be influenced by genetic factors in both the mother and child.*
- *Allelic variations of the alcohol dehydrogenase (ADH2) gene influences alcohol metabolism.*
- *Researchers have found that the ADH2*2 allele is more common among the normal population than among FAS children and their mothers.*
- *The ADH2*2 allele may confer protection against and/or resistance to developing FAS.*

Fetal Alcohol Syndrome (FAS) is the most common cause of preventable mental retardation among children in the world today. Scientists believe that the development of FAS following excessive alcohol exposure is likely influenced by genetic factors in both the mother and child. Mixed-ancestry children in the Western Cape Province of South Africa have the highest frequency of FAS in the world. Knowing that allelic variation influences alcohol metabolising genes, researchers in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* examine what role polymorphisms of the alcohol dehydrogenase (ADH2) gene might have among this population.

“The socioeconomically deprived mixed-ancestry population of the Western Cape has a prevalence of FAS amongst school-entry children of 40-70 per thousand,” explained Denis Lowe Viljoen, head of the Department of Human Genetics at the National Health Laboratory Service and University of the Witwatersrand Faculty of Health Sciences. Viljoen, also the study’s lead author, uses “mixed-ancestry” to refer to descendents of the original Khoisan inhabitants and colonizing Europeans. Some farm laborers in these communities have received part of their wages in the form of alcohol for close to 300 years.

“This prevalence contrasts,” he continued, “with approximately 0.33 - 2.2 per thousand for the United States, eight per thousand amongst birth cohorts for North American Indians between 1970-1980, and 2.29 per thousand for selected inner-city African Americans.”

“The incidence of FAS in the Western Cape is frighteningly high, particularly if one considers two factors,” said Amanda Krause, researcher and associate professor at the National Health Laboratory Service and University of the Witwatersrand Faculty of Health Sciences. “One, these are minimum estimates, looking at children who reached school entry. Some FAS children may never reach school entry because of major birth defects. Two, FAS is the tip of the iceberg. Thus, the number of school children with fetal alcohol effects is likely exceedingly high.” The term fetal alcohol effects (FAE) is used to describe individuals known to be exposed to alcohol before birth who have discernible health anomalies, yet do not have the facial features characteristic of FAS.

“There is some good scientific evidence to suggest that FAS, like virtually all diseases, has some genetic and some environmental influences,” said Krause. “There is a small amount of data pointing to the obvious candidate genes, that is, genes involved in the body’s handling of

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G ENETIC PROTECTION AGAINST FETAL ALCOHOL SYNDROME?

alcohol.” ADH is one of two enzymes that act sequentially to metabolize alcohol in the liver. ADH converts alcohol to acetaldehyde. Aldehyde dehydrogenase (ALDH) subsequently converts acetaldehyde to acetate. Acetate is then metabolized by tissues outside of the liver.

“We evaluated all isozymes of the ADH2 gene following the findings of a previous study that demonstrated protection of the ADH2*3 allele against alcohol-related birth defects,” said Viljoen. “The latter allele was no different in the mothers and FAS children than in the ethnically similar control population in our study, nor was the ADH2*1 allele. However, there was a significant, protective difference between FAS children and the controls regarding the ADH2*2 allele.” Viljoen noted that the ADH2*2 allele, like the ADH2*3 allele, has a high “Vmax,” which results in a more rapid breakdown of alcohol to acetaldehyde than would occur with the ADH2*1 allele (which has a low Vmax).

“The inference is that the metabolism of alcohol by individuals from the control group would proceed more rapidly than in the mothers and FAS children, and result in lower blood alcohol levels than the latter subjects. Alternatively, the presence of such an allele may discourage the control persons from drinking as heavily as the latter subjects. However, this was not tested as the controls were anonymous participants.”

Krause calls the study’s findings “one piece in a large puzzle of undefined size, with many missing pieces. The exact factors or genes involved,” she said, “are still poorly understood. The individual role of each factor and how they interact with each other requires a great deal of future research.”

“This is the first study to find any connection between a gene and FAS,” said Viljoen. “Presumably, many genes are working in concert within each person to provide either susceptibility to or protection from the effects of alcohol. Should these ‘major’ genes be found, they would provide a means of screening at risk persons for having a child with FAS. Also, the pathogenesis of FAS could become clearer. This raises the real possibility of treating high-risk, alcohol abusing pregnant women, thereby reducing the risk of producing a baby with FAS.”



Article is based on the following published research:

Viljoen, D.L., Carr, L.G., Foroud, T.M., Brooke, L., Ramsay, M., & Li, T-K. (December 2001).

Alcohol dehydrogenase-2*2 allele is associated with decreased prevalence of fetal alcohol syndrome in the mixed-ancestry population of the Western Cape Province, South Africa. *Alcoholism: Clinical and Experimental Research*, 25(12), 1719-1722.



LIGHT TO MODERATE DRINKING DURING PREGNANCY CAN AFFECT ADOLESCENT GROWTH

- *Children with Fetal Alcohol Syndrome (FAS) commonly have growth deficits.*
- *Growth deficits also exist among children prenatally exposed to alcohol but without FAS.*
- *Researchers have found significant growth deficits among non-FAS children 14 years after birth.*
- *The deficits have a dose-response relation to gestational exposure, and are evident at consumption levels less than one drink per day.*

Growth deficits are common among children with Fetal Alcohol Syndrome (FAS), affecting their height, weight and head circumference. Growth deficits have also been found among offspring exposed to alcohol during gestation but who have not developed FAS. Studies have, however, differed in this finding. Furthermore, few studies have followed these offspring beyond their early and middle childhoods. A study in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the effects of alcohol exposure during gestation on the size of non-FAS offspring at 14 years of age.

“The Maternal Health Practices and Child Development (MHPCD) project began in 1982,” said Nancy L. Day, professor of psychiatry and epidemiology at the University of Pittsburgh School of Medicine and lead author of the study. “Its purpose has been to study the effects of prenatal exposure to alcohol, marijuana, tobacco and other illicit drugs on the growth and development of the offspring. At numerous intervals, we have measured demographic status; the psychological, social and household environment; maternal and paternal substance use and substance use of the male partner in the household. We have also assessed the children’s cognitive, behavioral, academic and physical status. Furthermore, at ages 10, 14 and 16, we have additional measures of the children’s pubertal maturity, neuropsychological status, cognitive and behavioral development, affect, academic performance, psychiatric status, delinquent behaviors, substance use and the substance use of their friends.”

For this study, part of the MHPCD project, women in their fourth month of pregnancy were recruited from an outpatient prenatal clinic between May 1983 and July 1985. The women were interviewed in their fourth month of pregnancy (n=1360), seventh month and at delivery (n=763). The MHPCD project evaluated the women (or current caregiver) and their children at eight and 18 months, three, six, 10 and 14 years of age. Data for this study were gathered when the children (n=565) were 14 years of age.

“This study population represents a light to moderately exposed group of children and is in contrast to most studies that have recruited only heavily exposed subjects,” said Day. “The former group, however, represents the most common pattern of alcohol and other substance use during pregnancy.”

Despite only light to moderate exposure, researchers identified significant growth deficits among the offspring. The adolescents were smaller in terms of their weight, height, head circum-

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LIGHT TO MODERATE DRINKING DURING PREGNANCY CAN AFFECT ADOLESCENT GROWTH

ference and skinfold thickness. Importantly, the growth deficits had a dose-response relation to gestational exposure and, furthermore, significant effects were found at consumption levels less than one drink per day. The researchers also evaluated the effects of pattern of use. They found that growth was affected by a continuous exposure to alcohol and not by concentrated or binge drinking. The frequency of heavy or binge drinking (drinking four or more drinks/occasion) did not predict growth.

“It is notable that growth effects of prenatal alcohol can be detected in children more than 14 years after exposure,” said Sandra W. Jacobson, professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University School of Medicine. “Moreover, the deficits were related to low-level alcohol exposure and a dichotomous measure of binge drinking during the first trimester, and were not found only among heavy drinkers or women who were alcoholic. The finding that growth effects can be related to first trimester drinking has very important implications for prevention and the need to identify women at risk earlier. Although the relatively small effects on head circumference and growth found at these low levels of exposure are unlikely to have any functional significance for the child, they suggest that there apparently was damage to the brain, particularly during sensitive fetal and early infant developmental periods. This damage may have serious implications for later cognitive and behavioral development.”

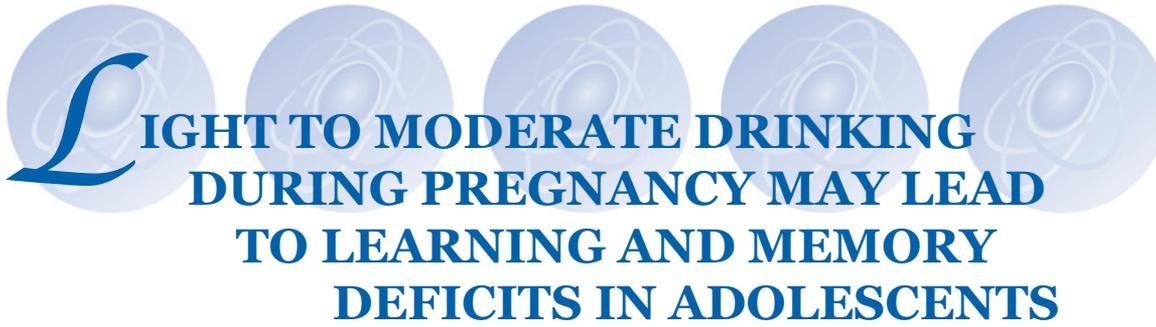
“In a dose-response relation, there is a direct association between the amount of exposure and the size of the effect. Those with a small exposure will have very small growth deficits; those with a large exposure will have much larger growth deficits. Exposure below the critical level will not have an effect, but exposure at or above that level will lead to the growth deficit. Our results have shown that the association between prenatal alcohol exposure and growth is one of dose-response. This is important for clinical and public health reasons because it means that even very small levels of alcohol exposure can affect the developing fetus. This means that there is no safe level for alcohol use during pregnancy. Women should abstain during these important months,” said Day.

Jacobson concurs. “However,” she said, “it is important to note that, although frequency of binge drinking was not statistically associated with reduced growth, the investigators reported that a dichotomous measure of bingeing was. Based on animal evidence, it is possible that these low level alcohol-related deficits may reflect maternal drinking on only a few days per week rather than drinking at very low levels every day.”

Article is based on the following published research:

Day, N.L., Leech, S.L.,
Richardson, G.A.,
Cornelius, M.D.,
Robles, N., Larkby, C.
(October 2002).
Prenatal alcohol
exposure predicts
continued deficits in
offspring size at 14 years
of age.
*Alcoholism: Clinical
and Experimental
Research*,
26(10), 1584-1591.





LIGHT TO MODERATE DRINKING DURING PREGNANCY MAY LEAD TO LEARNING AND MEMORY DEFICITS IN ADOLESCENTS

- *Heavy drinking during pregnancy can cause major impairments in the developing child.*
- *New research indicates that light to moderate drinking may also interfere with learning and memory as late as adolescence, particularly in the auditory/verbal domain.*
- *Most of the drinking in this study occurred during the first trimester.*

Many people know about the dangers of prenatal alcohol exposure, particularly the damaging effects that heavy drinking can cause to a child's cognitive development. A study published in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that even light to moderate drinking during pregnancy may interfere with learning and memory during adolescence.

“We have known for a long time that drinking heavily during pregnancy could lead to major impairments in growth, behavior and cognitive function in children,” said Jennifer Willford, assistant professor of psychiatry at the University of Pittsburgh School of Medicine and the study's first author. “This paper clearly shows that even small amounts of alcohol during pregnancy can have a significant impact on child development.”

“Learning and memory are cornerstones for success in school and in everyday life,” added Sarah Mattson, assistant professor in the Department of Psychology, and associate director of the Center for Behavioral Teratology at San Diego State University. “Disruption of the ability to learn and remember new information jeopardizes the job of children, that is, to go to school. The inability to learn new information in the verbal or nonverbal domain will interfere with a child's ability to achieve alongside his or her peers.”

The data examined in this study were collected as part of the Maternal Health Practices and Child Development Project (MHPCD), an ongoing longitudinal study of 580 children and their mothers. The MHPCD examines the effects of prenatal exposure to alcohol, marijuana, tobacco and other illicit drugs on the growth, behavioral and cognitive development of the offspring. Researchers measure demographic status, maternal psychosocial characteristics, household environment and substance use at numerous intervals. They also assess the children's growth, and behavioral, neuropsychological and academic status from birth onward.

For this study, mothers were assessed during each trimester of their pregnancies, and again with their children at regular intervals from birth to 16 years of age. Adolescent memory function was evaluated at 14 years of age (n=569) using the Children's Memory Scale, an assessment tool that measures learning and immediate and delayed memory function in the verbal and visual-spatial domains.

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LIGHT TO MODERATE DRINKING DURING PREGNANCY MAY LEAD TO LEARNING AND MEMORY DEFICITS IN ADOLESCENTS

“We chose measures that would help us understand the types of learning and memory difficulties experienced by adolescents who were prenatally exposed to alcohol,” explained Willford. “We assessed verbal/auditory and visual/spatial abilities because each of us learns through a combination of verbal and nonverbal abilities. We also examined learning and memory to determine whether subjects were having difficulty with initial learning, remembering information for a short time or after a long period of time.”

“During the first trimester,” said Willford, “45 percent of the women drank, on average, less than one drink per day.” Despite these relatively low levels of alcohol consumption, researchers found an association with subtle difficulties with learning and memory in the offspring at 14 years of age, specifically in the auditory/verbal domain. “This indicates that drinking during the first trimester of pregnancy ... has long-term effects on development. Many women do not realize they are pregnant and/or seek prenatal care during this critical time,” said Willford.

“These types of deficits have already been demonstrated in studies with much higher levels of exposure,” added Mattson, “and thus, these data extend the continuum of effect to include lower levels of exposure. Another important finding is that the effects of alcohol exposure on memory for verbal information were mediated by verbal learning, a finding that has also been documented following higher levels of exposure. This finding is relatively novel in the field and thus the replication in a lower exposed sample suggests that this effect is specific to alcohol exposure.”

Yet another finding concerns growth deficits among those children exposed to light to moderate drinking during gestation. “These findings parallel earlier reports of continued growth deficits among those children exposed to light to moderate drinking during their mothers’ pregnancy,” said Willford. “This shows us that prenatal alcohol exposure can lead to deficits in multiple domains.”

“There is no safe level of drinking during pregnancy and there is no safe time to drink during pregnancy,” said Willford. “Women need this information before pregnancy recognition and their first visit to an obstetrician so that they may make better choices about drinking if they are planning to become, or think that they may be, pregnant.”



Article is based on the following published research:

Willford, J.A.,
Richardson, G.A.,
Leech, S.L., & Day, N.L.
Verbal and visuo-spatial
learning and memory
function in children
with moderate prenatal
alcohol exposure.
(March 2004).
*Alcoholism: Clinical
and Experimental
Research*,
28(3), 497-507.

THE POWER OF THE MOTHER-CHILD BOND

- *An infant is extraordinarily sensitive to its mother's behavior.*
- *Baby rats nursed by their intoxicated mothers exhibit greater overall distress and aversion to alcohol.*
- *The infants' distress and aversion seem dependent on maternal reaction to alcohol.*
- *Alcohol's effects on maternal behavior may have long-lasting consequences for the infant.*

It's no secret that a baby's survival, under normal circumstances, is dependent on the mother's behavior. Nourishment, appropriate body temperature, protection from harm – these are the basics. Yet researchers are also beginning to determine, as shown in a study in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)*, that a mother's behavior, altered by alcohol, can have powerful and enduring effects on her infant's subsequent memories.

"Infants are exquisitely sensitive to maternal behavior," said Norman E. Spear, distinguished professor of psychology at Binghamton University and one of the study's lead authors. "If the mother's behavior deviates just a little bit from the norm, the infants notice and it's not a pleasant experience for them."

"Specific memories may be generated in relation to alcohol," added Juan Carlos Molina, co-author, professor of psychology at the University of Cordoba, and senior research scientist at the Instituto de Investigacion Medica Mercedes y Martín Ferreyra in Argentina.

In the study, baby rats were nursed by intoxicated mother rats. When compared with baby rats that nursed from alcohol-free mothers, the alcohol-exposed pups later demonstrated higher ultrasonic vocalizations (a traditional distress signal), greater motor activity during isolation (which is what rats do when they're disturbed), and aversion to a texture (sandpaper) that had been matched through smell with alcohol. Spear believes that the mother's alcohol-altered behavior, rather than the pup's reaction to the alcohol itself, is what caused their distress and related behavior.

"The effects of the alcohol on the mother's behavior are very subtle," he explained, "but enough to make the experience aversive for the rat pup. There are some aspects of maternal behavior that are poorer in mother rats that have had alcohol. For example, retrieval behavior – when a mother retrieves a baby rat that has wandered away from the nest – is inhibited by alcohol. Another effect of alcohol on the mother is a decrease in body temperature; it may be a drop of only one and a half degrees centigrade, but the pups may detect the difference in warmth."

"The animal model and the human literature are telling a similar story," said Julie A. Mennella, biopsychologist at Monell Chemical Senses Center. "Memories are not only formed as a result of early sensory experiences with alcohol in the context of the mother, but they're also retained for a considerable time span. This study is telling us that the presence of alcohol odor is capable of supporting some type of conditioning, such as aversion, when it's paired with a new stimulus, such as sandpaper."

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THE POWER OF THE MOTHER-CHILD BOND

Mennella said that Spear and Molina's study is part of a growing body of research that speaks to the relevance of early learning. "Other research has shown that elementary-school-aged children of alcoholics were more likely to report more negative experiences about alcohol than children from non-alcoholic homes," she said. "Some of the early learning about alcohol appears to be based on sensory experience and the context in which alcohol is experienced." Indeed, Mennella believes this study speaks to the power of odor associations.

"Odors are often thought to provide us with the best memory cues," she said. "Some of our oldest and most emotionally laden memories are associated with odors." Mennella described a study conducted at her institution in which children were asked to complete a difficult task in a room that was scented with a particular odor. None of the children completed the difficult task. Shortly afterwards, the children were divided into three groups, all were given the same simple task to complete, but each were placed in three different rooms with different odors.

The group of children located in the room scented with the same odor as the room of the preceding difficult task performed worse than the other two groups. Mennella said that exposing rat pups to a sandpaper texture and children to a difficult task could both be classified as "arousing, emotionally salient" situations. The emotional context in which children or infants experience an odor can influence their subsequent behaviors, likes, dislikes and conditioning to alcohol.

A related area of study is what Mennella calls the "folklore" of alcohol consumption by lactating women. This refers to beliefs, brought to America by various immigrant groups, that alcohol consumption might increase milk production, facilitate milk release, relax the mother, increase the infant's milk intake and/or help the baby sleep. Yet apart from possibly helping the mother relax, said Mennella, "there's no scientific evidence that supports the folklore, in fact, it's the opposite."

"Some doctors today still recommend drinking before nursing," observed Spear, "but there is still so much that is unknown. In addition, there are a lot more days during a human infant's nursing period (up to two or three years) than a baby rat's (21 days). Perhaps there is a cumulative effect."

"The most important contribution about our study," he said, "is simply to indicate that breastfeeding potentially represents a source of generating alcohol-related memories." He nonetheless noted that cumulative studies "emphasize the need to avoid alcohol exposure during prenatal, neonatal and early postnatal periods of development."

Article is based on the following published research:

Molina, J.C.,
Pepino, M.Y.,
Johnson, J.,
& Spear, N.E.
(April 2000).

The infant rat learns about alcohol through interaction with an intoxicated mother. *Alcoholism: Clinical and Experimental Research*, 24(4), 428-437.



PARENTING, STRESS AND YOUR CHILD'S RISK FOR ALCOHOLISM

- *A recent study has found that the absence of a parent as role model can be stressful for infants.*
- *Concentrations of cortisol, a principal stress hormone, can indicate levels of stress.*
- *Cortisol may serve as an early biological marker of future alcohol consumption.*
- *Adult absence during infancy has long-term psychobiological consequences.*

A study in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found a link among the rearing environment (how a child is raised), sensitivity to stress and subsequent alcohol consumption. "It's pretty clear that parents are the crucial role models and crucial shapers of their offspring's behavior," said J. Dee Higley, research psychologist at the National Institute of Child Health and Human Development and lab director of the experiment. "Adults are very good at helping youngsters to understand that 'this is dangerous, this is not dangerous.' In the absence of that kind of adult influence, children don't have any kind of certainty about what to fear or enjoy, what is good or bad. Adults are also very good at cueing into whether their offspring are aroused or anxious, and then helping them to calm themselves down."

Higley's study looked at rhesus monkeys, which share between 90 to 95 percent of their genetic material with humans. These monkeys also have a similar adrenal system which, for the purposes of this study, means that they respond to stress like humans do. In addition, primates have very complex societies; they create social groups, they have rules about social behavior and they are (under normal circumstances) trained from youth to learn and use appropriate social skills. The monkeys used in this study were part of an ongoing longitudinal study investigating genetic and environmental influences on neurobiology, behavior and alcohol consumption.

The monkeys were divided into two groups for the first six months of their lives. The first group was "peer-reared," meaning that group members were raised without the presence of their mothers or other adults, but surrounded by same-aged peers. Members of the second group were raised normally, in the presence of their mothers. At six months of age, all of the monkeys were separated from their groups for portions of a four-week period. Stress levels were assessed during this time by examining concentrations of cortisol, a principal stress hormone. At 50 months of age (roughly equivalent to young adulthood), the monkeys were allowed access to alcohol for five to seven weeks.

"This study very clearly showed that early life experiences can have a dramatic effect on subsequent development of alcohol consumption," noted Larissa A. Pohorecky, professor of neuropharmacology at the Center of Alcohol Studies at Rutgers University. "It helps elucidate the mechanisms involved in stress/alcohol interaction." She added that most of the other alcohol research, including her own, has focused on rodents. "So these are particularly important findings because these primates are the closest animal species to humans," she said.

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PARENTING, STRESS AND YOUR CHILD'S RISK FOR ALCOHOLISM

The study found that infant monkeys from both groups, peer-reared and mother-reared, were stressed by their separation from the group (as evidenced by cortisol concentrations), although the peer-reared monkeys more so. In addition, those infant monkeys (from both groups) who were highly stressed as a result of their group separation, later consumed more alcohol (as young adults) than their less-stressed peers did.

"We may have found a biological marker," he said, "which can be obtained very early in life and may predict future alcohol consumption. This is probably the strongest marker we've found so far in the non-human primate that predicts alcohol consumption." He added that, "to the extent that this can be generalized to humans, we may have identified a biological predictor of future alcohol problems." Higley said another implication is that "early-rearing experiences that increase anxiety – as measured by cortisol output – also increase subsequent alcohol consumption."

In this experiment, separation from the group was what induced stress, but the monkeys' peer-rearing environment may have 'set them up' for experiencing a greater level of stress. "The peer-reared monkeys had all the opportunities to socialize that mother-reared monkeys did – they could play with other-aged mates, form strong friendships, they could even fight, they could do all sorts of socially appropriate and inappropriate things – but what was lacking in their environment was an adult," explained Higley. "These monkeys showed emotional instability, they were more fearful, they were much more reactive to the stimuli around them, and they did not have an adult around to calm them down. So what you have is a monkey who is chronically anxious and chronically fearful."

Adult absence during infancy appears to have had other long-term psychobiological consequences, noted Higley. "As young teenagers, the peer-reared monkeys still showed infant-like fearfulness and anxiety that was absent in the mother-reared monkeys." Indeed, other studies have found that prolonged stress in infancy (and a peer-rearing environment among monkeys is regarded as a stressor) may permanently alter the hormonal stress response and subsequent reactions to new stressors.

"These findings speak to the importance of how society handles children who have problems, families with parenting problems, general parenting issues and orphans to name a few," she said. "We may not be paying enough attention to the importance of parenting roles and how they can affect children's lives," said Pohorecky.

Article is based on the following published research:

Fahlke, C., Lorenz, J.G., Long, J., Champoux, M., Suomi, S.J., & Higley, J.D. (May 2000).

Rearing experiences and stress-induced plasma cortisol as early risk factors for excessive alcohol consumption in nonhuman primates. *Alcoholism: Clinical and Experimental Research*, 24(5), 644-650.



*P*revention,
Intervention
& Treatment



PREVENTION, INTERVENTION & TREATMENT

Articles in the *Prevention, Intervention & Treatment* Category

1. Alcohol and Drug Treatment Among HMO Patients
2. Examining the Effects of Managed Care on Alcohol and Other Drug Treatment
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6. Brief Mail- and Computer-Generated Interventions Work Best for Problem Drinking Among Young People
7. Educational Attainment May Predict Drinking Outcomes Following Alcohol Treatment
8. Alcohol and Smoking: Why They Go Together
9. Nicotine Patch Treatment Works for Smokers with Long-Term Sobriety
10. Alcohol, Friends and Courtship

A LCOHOL AND DRUG TREATMENT AMONG HMO PATIENTS

- *Many alcohol and drug treatment programs have merged since the early 1990s.*
- *Yet a study has found that alcohol-only and alcohol-and-other-drug dependent clients appear to have different treatment needs and risk factors for developing problems.*
- *Those with an alcohol-and-other-drug dependency were more likely to be younger, male, less educated, African American and have greater psychiatric and family/social problems.*
- *Those with an alcohol-only dependency were much more likely to be older, female, Caucasian and college educated than those individuals with a combined dependency.*

Until approximately a decade ago, alcohol and drug treatment programs in the United States were separate. Each type of program had its own patients, policies and methods of treatment. Yet many individuals who were dependent on alcohol also used, and were often dependent on, other drugs. This might explain why numerous alcohol and drug treatment programs were merged in the early 1990s. The effectiveness of these combined treatment programs, however, remains unclear. A study in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* is one of the first to attempt to understand how the needs and problems of alcohol and drug patients may differ even though they are now usually treated in the same program.

Researchers interviewed more than 700 people seeking treatment in a program operated by their health maintenance organization (HMO). Clients were divided into two samples: those who were dependent only on alcohol (491 or 69%) and those who were dependent on both alcohol and other drugs (217 or 31%). The objectives were to identify treatment needs as well as risk factors for developing substance abuse-related problems among the two client types.

“The two groups of clients in this HMO treatment population can be distinguished by demographic characteristics,” explained Tammy Tam, a scientist with the Alcohol Research Group and lead author of the study. “Those with combined alcohol-and-drug dependence were more likely to be younger, male, less educated and African American.” Conversely, said Keith Humphreys, assistant professor of psychiatry at Stanford University School of Medicine, those who had problems with alcohol only “were much more likely to be older, to be women, to be Caucasian and to be college educated than were those individuals who had problems with both alcohol and drugs.”

“In terms of substance use and initiation of use,” said Tam, “those with a combined dependence were more likely to initiate use of a substance at an earlier age, start with multiple substance use, and initiate heavy drinking before the age of 18. They also tended to have more severe psychiatric and family/social problems and fewer social resources.”

A major finding of this study,” she added, “is that many of the differences between the two groups of clients were related to the younger age of the combined dependence group. It suggests that there may be generational differences in treatment needs for different age cohorts

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LCOHOL AND DRUG TREATMENT AMONG HMO PATIENTS

that the merged alcohol-and-drug treatment programs fail to address.” It also suggests that, as this generation ages, treatment programs will have an increasing number of clients with multiple alcohol and drug dependencies.

Further commenting on the study, Humphreys noted that its findings also speak to the cliché of who a drug user may be. “This study shows that contrary to the stereotype of who the typical middle-class substance abuser is,” he said, “... it is not just poor people who get into serious trouble with substances like cocaine and heroin. Even among middle-class people who have HMO coverage, just like the average American, many people with alcohol problems are using ‘hard’ drugs like cocaine and heroin, and these people have different needs for treatment than do people who are ‘just’ alcoholics.”

Tam pointed out that most of the research on treatment populations has been conducted on “public populations” (those without private insurance), and populations where substances other than alcohol were the focus. “This is a managed care population,” she said, “most of whom are insured through their own or a family member’s employer. It gives us the opportunity to see how, even in such a population, treatment needs and the development of problems can differ among those there to be treated. However, the homogeneity of the population and the managed care setting of the study ... does mean that the results cannot necessarily be generalized to different kinds of treatment populations.”

“Another important finding,” said Humphreys, “is that race really seems to shape the substances that people use. We have known for a long time that when Caucasians get into trouble with substances, it is usually alcohol, and when African Americans get into trouble with substances, it is usually drugs. This pattern is usually attributed to social class differences. This study shows that this explanation is probably not true because almost everyone in the sample was a middle-class person. So, a substance abuser’s race seems to change their substance of choice beyond what can be explained by social class.”

“Yet another important finding,” added Humphreys, “is that men are more likely than women to have problems with both alcohol and drugs. This may explain why women, on average, have better treatment outcomes, because they are often only struggling with one kind of substance instead of multiple kinds.”

Humphreys hopes that people who operate HMOs read this study because it will give them some important guidance on what services should be covered in their benefit packages.

Article is based on the following published research:

Tam, T.W., Weisner, C.,
& Mertens, J.
(December 2000).
Demographic
characteristics, life
context, and patterns
of substance use
among alcohol-
dependent treatment
clients in an HMO.
*Alcoholism: Clinical
and Experimental
Research*,
24(12), 1803-1810.



EXAMINING THE EFFECTS OF MANAGED CARE ON ALCOHOL AND OTHER DRUG TREATMENT

- *Different types of managed care organizations as well as contracting arrangements will affect accessing alcohol and other drug (AOD) treatment.*
- *AOD treatment seeking, entry and completion are three successive but distinct stages of success.*
- *Introducing managed care to the Massachusetts Medicaid population reduced AOD treatment costs without arbitrarily cutting services or restricting access for disadvantaged groups.*
- *The American Society of Addiction Medicine's Patient Placement Criteria appears to successfully match alcoholism patients to their appropriate level of care.*

The term “managed care” continues to evoke strong opinions from patients, health-care providers, employers and insurers. Many managed care organizations (MCOs) tend to provide some degree of mental health and alcohol and other drug (AOD) treatment as part of behavioral health services. Rigorous research on AOD treatment under managed care, however, is lacking. A manuscript in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* gathers four different study perspectives on managed care influences on AOD treatment.

“Managed care companies seem to be more accepting of mental health treatment than of AOD treatment,” noted Stephen Magura, deputy executive director of National Development and Research Institutes (NDRI) and lead author of the manuscript. “This is largely because of the continuing development of effective medications for mental disorders that can be prescribed through the regular medical care system. AOD treatment, however, is not at this time primarily based on medications, with the rare exception such as methadone treatment for opiate addiction. AOD treatment has a greater burden of proof because it is more difficult to demonstrate the effectiveness of the more multifaceted behavioral therapies upon which the field continues to depend.”

“For many clients,” added Alexandre Laudet, a principal investigator at NDRI, “substance abuse disorders are chronic, relapsing conditions that cannot be ‘resolved’ by a short-term treatment episode. In order to address this, service providers and researchers are increasingly seeking to identify effective – and cost effective – modalities for substance abuse problems. As a result, it can be said that the advent of managed care has contributed greatly to emphasizing evidence-based clinical practices.”

Indemnity insurance coverage was the prevalent form of health care in the United States 25 years ago. Today more than half of all Americans with health insurance are enrolled in some kind of managed care plan. The predominant forms of MCOs are health maintenance organizations (HMOs), point-of-service (POS) plans and preferred provider organizations (PPOs). HMOs are the oldest form of MCOs; members are offered a range of health benefits for a set monthly fee, and primary-care doctors act as care coordinators. Some HMOs offer a POS plan,

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EXAMINING THE EFFECTS OF MANAGED CARE ON ALCOHOL AND OTHER DRUG TREATMENT

which is an indemnity-type option that allows members to refer themselves outside of the plan for a negotiated fee. A PPO is a form of MCO that is closest in nature to indemnity coverage; members have more flexibility for self-referral but also tend to have more copayments for doctors and/or prescriptions.

One of the studies (Horgan, et al.) in the Magura manuscript found that, outside of inpatient and residential care, PPOs were less likely than HMOs and POS plans to require prior authorization for AOD treatment. “This finding implies that requirements for prior authorization can set up a barrier to receiving timely treatment,” said Magura. “In addition, when patients and providers do not exactly follow the sometimes involved prior-authorization procedures, reimbursement may be denied. In my opinion, if MCOs establish clear and specific guidelines for covered services, prior authorization for the great majority of AOD patients and treatments should not be necessary.”

A second study (Mertens, et al.) found that analysis of AOD treatment access and utilization needs to distinguish among treatment seeking, entry and completion as there are both similarities and differences among the three steps.

“Distinguishing among these three successive stages is important because many treatment seekers do not return to the agency after intake and admission,” said Laudet, “and many clients who begin treatment, drop out before completing the planned duration of services. As stated by the authors in their study, one in four clients did not return for services; that is, they sought services but never entered treatment. In addition, retention/completion rates vary across treatment modalities, ranging from as low as 35 percent to more than 60 percent. Yet research evidence from AOD treatment populations across modalities indicates that longer retention in treatment is associated with significantly more positive outcomes as measured by subsequent substance use as well as measures of social functioning such as psychological functioning, employment and involvement in criminal activities. Therefore, when assessing penetration and effectiveness, it is important to distinguish among these three concepts.”

“It may be necessary for ‘the system’ to reach out more to people with AOD problems,” said Magura, “and for employers especially to ‘legitimate’ and encourage treatment seeking, partly by making it clear treatment seekers won’t lose their jobs. Treatment programs should also be held accountable not only for the number of patients they admit, but also for the number that stay long enough to get some real therapeutic benefit.”

Article is based on the following published research:

Magura, S.,
Horgan, C.M.,
Mertens, J.R.,
& Shepard, D.S.
(March 2002).
Effects of managed
care on alcohol and
other drug (AOD)
treatment.
*Alcoholism: Clinical
and Experimental
Research*,
26(3), 416-422.

DOCTOR, COUNSELOR, COST-CUTTER

- *Primary-care doctors do not typically talk to their patients about problem drinking.*
- *A new study tests the effectiveness of doctor-initiated advice generated by a routine visit.*
- *Advised patients show a significant decrease in alcohol use, accidents and health-care utilization.*
- *Benefit-cost analysis estimates a \$43,000 reduction in future health-care costs for every \$10,000 invested in early intervention.*

People who drink above what could be considered a healthy level – that is, more than two to three drinks per day – are at risk for a number of health and safety problems. Excessive alcohol use has been implicated as a cause of liver disease, stroke, cancer, infant neurodevelopmental disorders and hospital admissions in older adults. A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* takes a method also used for smoking cessation – physician intervention – and applies it to problem drinking.

“I was interested in finding out if what I did as a physician made a difference with my patients,” said Michael F. Fleming, director of the Family Medicine Research Program at the University of Wisconsin-Madison and lead author of the study. “What happens when I talk to my patients for a few minutes about their drinking? Do they decrease their alcohol use? Do they have fewer health problems? Are they hospitalized less often? Do they get into fewer accidents?”

During a routine visit to the doctor, Wisconsin patients (ages 18 - 65) were given a questionnaire to establish at-risk alcohol behaviors. Of the 774 who screened positive, 382 were assigned to a control group and 392 received an intervention program called Project TrEAT (Trial for Early Alcohol Treatment), a protocol originally developed in England that was modified by Fleming and his co-authors. Project TrEAT consists of two 15-minute face-to-face physician conversations, followed by two five-minute nurse phone calls. Project components include a review of ‘acceptable’ drinking, patient-specific alcohol effects, a worksheet on drinking cues, cards to record drinking habits and a drinking agreement. Forty-eight months later, researchers examined the success and performed a benefit-cost analysis of the project.

“If physicians spend five to 10 minutes talking to their patients about alcohol use,” said Fleming, “15 to 20 percent of their patients will significantly decrease their alcohol use, health care utilization, risk of accidents and overall health care costs. Physicians who spend a few minutes talking to their patients about their alcohol problems can make a difference. I would like to see physicians regularly ask all of their patients with mental health, medical and family problems how much they drink; especially if they are going to prescribe medication because many medications interact directly with alcohol.”

“Research on the impact of physician advice about alcohol use,” said Jeffrey H. Samet, associate professor of medicine and public health at Boston University, “has built upon the knowledge base that problem drinking is common among patients going to see their regu-

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DOCTOR, COUNSELOR, COST-CUTTER

lar physician, that identification of these drinkers can be accomplished by a few key brief questions, and that physicians do not as yet regularly incorporate national recommendations for screening and brief intervention for alcohol problems.”

Samet added that most physicians likely ask new patients about alcohol use but, even so, only a minority of physicians use the best tools available to carry out this task. “Formal screening tests generally require less than one minute to administer,” he said. Furthermore, he added, offering advice to problem drinkers is not routinely provided.

“Reasons as to why these medical activities have not as yet been fully embraced,” said Samet, “include physicians’ lack of confidence in alcohol history taking, lack of familiarity with expert guidelines, concern that patients will object and the typical lack of reimbursement for this physician activity. Changing physician behavior is not an easy task, but not an impossible one either. The time has come for health systems to prioritize implementation of screening for alcohol problems in the primary care setting and delivering brief interventions to those that can benefit. This will require broad training of physicians, particularly those in primary care specialties, in order to ask about and address patients’ alcohol problems. This training should occur in medical schools, residency-training programs and in clinical practice. Finally, physician reimbursement for this work must occur.”

Costs of physician reimbursement could be offset by projected savings in future systemic costs. The study estimates a \$43,000 reduction in future health-care costs for every \$10,000 invested in early intervention. “These benefits could still be appreciated four years after the intervention,” noted Samet. “This is an impressive cost savings from a societal perspective. Furthermore, this kind of cost savings for a medical intervention is very uncommon in medicine.”

“We know there are 30 to 40 million Americans who drink too much,” added Fleming, “with 100,000 of these Americans dying each year because of their drinking. There is also the effect these persons have on their families, their co-workers and on innocent persons killed on our streets and highways. If physicians would conduct brief intervention with these individuals, we could expect a significant reduction in alcohol-related harm in the United States.”



Article is based on the following published research:

Fleming, M.F.,
Mundt, M.P.,
French, M.T.,
Manwell, L.B.,
Stauffacher, E.A.,
& Barry, K.L.
(January 2002).
Brief physician advice
for problem drinkers:
Long-term efficacy and
benefit-cost analysis.
*Alcoholism: Clinical
and Experimental
Research*,
26(1), 36-43.

FINDING SOBRIETY AND SAVING MONEY THROUGH SPIRITUALITY

- *Skepticism abounds regarding the role of “faith-based” groups in achieving and maintaining sobriety.*
- *Yet treatment programs – both spiritual and cognitive-behavioral in approach – have the same inpatient costs and clinical outcomes.*
- *One study found that spiritually-oriented programs have lower post-discharge costs and a higher rate of abstinence.*
- *Fellowship provided by faith-based groups may be the key.*

Addiction treatment, like many other aspects of health care, does not entail a standard, paint-by-numbers approach. There exists a wide spectrum of treatment options. On one end lies the medical approach, such as cognitive-behavioral treatment. On the opposite end are “faith-based” initiatives such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA). A study in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* evaluates the post-discharge health-care utilization and associated costs of these two very different types of approaches.

Inpatient treatment costs and clinical outcomes are approximately the same notwithstanding which of the two approaches is chosen, said Keith Humphreys, assistant professor of psychiatry at Stanford University School of Medicine and the study’s lead author. “We found that the staffing levels, three-to-four week lengths of stay and costs were fairly similar regardless of the specific nature of the two types of treatment we examined,” he said. Clinical outcomes – defined as whether or not the patients stopped using drugs and alcohol, stopped having addiction-related problems such as conflicts at work and/or with their families, and/or enjoyed good mental health (such as the absence of depression, worries, nervousness, emotional upset) – were likewise comparable.

The focus of Humphreys’ study, however, was on the care provided in the year after discharge from inpatient treatment, when costs are very different. “Patients with serious drug and alcohol problems who are treated in programs based on the approaches of spiritually-oriented self-help organizations like AA,” he said, “are more likely to abstain from drugs and alcohol after treatment and also have much lower health-care costs than do patients treated in programs that do not emphasize AA-style principles.” The study showed that the faith-based approach lowers post-treatment costs by about two-thirds, or about \$5,000 per year per patient.

AA, founded in 1935 by Bill W. (AA members use first names only), requires its members to follow 12 steps of behavior that are based on 12 spiritual principles. Twelve-step oriented treatment programs strongly encourage patients to attend self-help groups after treatment is completed. As a result, these individuals tend to rely on their AA and NA groups for support and much less on professional counseling services after they leave the hospital. Cognitive-behavioral treatment, on the other hand, uses more professional and scientific

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FINDING SOBRIETY AND SAVING MONEY THROUGH SPIRITUALITY

activities such as cognitive skills training and cognitive-behavioral psychotherapy to teach people how to contend with situations that may tempt them to drink, cope with negative moods that may lead to drinking, etc. Once treatment is completed, these patients tend to rely more on professional services for support.

“There has always been debate about AA,” noted Lee Ann Kaskutas, a research scientist with the Alcohol Research Group at Berkeley. “Medical people have been suspicious more often than not, because they feel AA is unproven, and also because AA has a ‘god component’ that doesn’t make it seem very scientific. Members of AA, people who have become sober there, are at the other end of the spectrum. They are total believers, and they can be heard saying ‘there is no easier, softer way’ than AA.”

Yet despite skepticism by the medical establishment, said Kaskutas, studies such as this one show that treatment methods that emphasize AA methods do not result in high rates of hospitalization or psychiatric visits after treatment. In fact, she said, another of the study’s key findings is that patients in programs with a 12-step orientation had a higher rate of abstinence, in addition to much lower health-care costs, following treatment completion.

“You might not think it would have that effect,” she said, “because of the non-medical and non-psychiatric flavor of 12-step methods. Dr. Humphreys suggests one thing that may contribute to this effect: during treatment people make connections with each other and get advice from one another. So later, if they feel sick or worried and talk to someone they met in treatment about this, they will likely send that person back to the same type of program where they met. When people who were in cognitive treatment need help, they immediately think of going to the doctor. People [who were] in 12-step treatment immediately think of going to a meeting. Whether or not he is right about [the effects of fellowship] is an area for future research. His study has set up a lot of important questions to pursue next.”

“We as a society are fortunate to have a developed system of self-help organizations that do not cost the taxpayer or the health-care system a dime,” said Humphreys. “Organizations like AA not only reduce human misery, they also take a big burden off of our increasingly resource-strapped health-care system. Hence, it is important for health care professionals to learn about these organizations and develop connections with them.”



Article is based on the following published research:

Humphreys, K.,
& Moos, R.
(May 2001).

Can encouraging
substance abuse
patients to participate
in self-help groups
reduce demand for
health care? A
quasi-experimental
study.

*Alcoholism: Clinical
and Experimental
Research,*
25(5), 711-716.

C OMPARING SCREENING INSTRUMENTS FOR ALCOHOL DEPENDENCE AND ABUSE

- *The usefulness of many screening instruments for alcohol use disorders may be limited to certain populations.*
- *New research compares the performance of two short screening instruments, RAPS4 and CAGE, against established criteria for alcohol dependence and abuse.*
- *RAPS4 outperformed CAGE among the population examined.*
- *When quantity-frequency (QF) questions were added, the RAPS4-QF performed even better for alcohol abuse.*

Despite the challenges of living in an excessively busy world, clinicians do not have the luxury of “cutting corners” where their patients are concerned. If they do, their patients’ health may be compromised. An overt illness may be treated while underlying alcohol problems avoid diagnosis. The distinctions between alcohol abuse and alcohol dependence may be overlooked. Without intervention, problem drinking may develop into dependence. In an effort to identify for clinicians an effective and short screening instrument for alcohol use disorders, a study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* compares the performance of two short screening instruments.

The Rapid Alcohol Problems Screen (RAPS) is a five-item instrument, derived from other screens, that is designed to maximize sensitivity while maintaining good specificity. The RAPS4, a further refinement of the RAPS, asks if an individual felt guilt after their drinking (**R**emorse), could not remember things said or done after drinking (**A**mnnesia), failed to do what was normally expected after drinking (**P**erform), or had a morning drink (**S**tarter). The CAGE questionnaire is a short screening instrument commonly used in the clinical setting that asks if an individual has thought about **C**utting down on their drinking, become **A**nnoyed by criticism of their drinking, felt **G**uilty about their drinking, or had a morning drink as an ‘**E**ye opener.’ The study compares performance of the RAPS4 and CAGE against the *World Health Organization’s (WHO) International Classification of Disease (ICD-10)* and the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV)* criteria.

“Numerous screening instruments exist for alcohol use disorders,” explained Cheryl J. Cherpitel, a senior scientist with the Alcohol Research Group and author of the study. “Their usefulness may be limited to certain populations, however, and for identifying alcohol dependence rather than harmful drinking. Most brief screening instruments, for example, have been developed and tested in White male populations. Conversely, little research has been done on how well these instruments work for women or among ethnic minorities in the U.S. Since the RAPS4 was developed from a number of instruments tested in hospital emergency rooms, and performed better in that population – for the total population and by gender and ethnicity – than any of the instruments from which it was developed, it seemed important to test its performance in clinical populations as well as in the general population. The RAPS4 was compared to CAGE in this study because CAGE is the shortest and most widely used brief screening instrument by clinicians.”

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C O M P A R I N G S C R E E N I N G I N S T R U M E N T S F O R A L C O H O L D E P E N D E N C E A N D A B U S E

Researchers analyzed data from the Alcohol Research Group's 2000 National Alcohol Survey, which were gathered from 7,612 interviews with individuals from the U.S. general population, aged 18 years and older in 50 states and the District of Columbia.

In general, the RAPS4 outperformed CAGE among the population examined. When two quantity-frequency (QF) questions (drinking five or more drinks on an occasion and drinking as often as once a month) were added to the RAPS4, the RAPS4-QF performed significantly better for alcohol abuse, and outperformed CAGE across all gender, ethnic and service-utilization groups. The RAPS4-QF also appeared to be most sensitive for alcohol abuse among both males and females reporting emergency-room (ER) use. Both Cherpitel and Robert Woolard, chair of Brown Medical School's Section of Emergency Medicine, noted the importance of distinguishing between "alcohol dependence" and "alcohol abuse."

"Given the findings reported in this article," said Cherpitel, "and previous findings from ER studies, I think the RAPS4 and RAPS4-QF hold a great deal of promise for use in brief screening for alcohol dependence and harmful drinking, respectively, for both men and women and across ethnic groups in both clinical populations – ERs, primary care clinics, other clinical settings – and in the general or non-clinical population. For the average [person, this] means that a few questions can help the doctor or nurse determine who may have a drinking problem which could be helped."

"Busy clinicians need reliable and short screening tests," concurred Woolard. "[But] the greatest utility of Dr. Cherpitel's work will be the more universal adoption of alcohol screening by clinicians using questionnaires such as RAPS4-QF. Hopefully universal screening in general health surveys, primary care offices and emergency departments will become the norm." Woolard added that he hoped to see future testing of RAPS4-QF by clinicians, and a progression from screening to treatment. "Although it seems obvious and trivial," he said, "demonstrating the impact of the clinical introduction of RAPS4-QF when used by working clinicians would help translate Dr. Cherpitel's valuable research findings into practice."

Cherpitel will in fact be analyzing the performance of the RAPS4 and RAPS4-QF in ER samples obtained from 12 countries associated with the WHO Multi-Site Collaborative Study of Alcohol and Injury. She calls this "a wonderful opportunity to test the sensitivity and specificity of the instrument from a cross-cultural perspective, [with] implications for its use in other cultures and other countries where resources have not been available for such instrument development."

Article is based on the following published research:

Cherpitel, C.J.
(November 2002).
Screening for alcohol
problems in the U.S.
general population:
Comparison of the
CAGE, RAPS4 and
RAPS4-QF by gender,
ethnicity, and services
utilization.

*Alcoholism: Clinical
and Experimental
Research,*
26(11), 1686-1691.





BRIEF MAIL- AND COMPUTER- GENERATED INTERVENTIONS WORK BEST FOR PROBLEM DRINKING AMONG YOUNG PEOPLE

- *Brief mail- and computer-generated interventions work best for problem drinking among young people.*
- *In-person brief interventions are best directed toward those who engage in hazardous drinking and/or abuse of alcohol rather than those who are alcohol dependent.*
- *A five-minute in-person intervention has proven to be as effective as longer interventions.*

Health professionals who are concerned about hazardous drinking among young people can take heart: research indicates that brief intervention methods relying on mail or computers are both appealing and effective among this hard-to-reach population. Findings were presented during a symposium given at the joint 2002 Research Society on Alcoholism/International Society for Biomedical Research on Alcoholism meeting in San Francisco. Symposium proceedings are published in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)*.

“The purpose of this research is first and foremost to determine whether brief intervention is effective in reducing hazardous drinking among young people, and secondly, to figure out the specific conditions which make it effective: setting, duration and method of presentation,” said Kypros Kypri, research fellow at the University of Otago in New Zealand and corresponding author for the symposium proceedings. “In contrast with brief intervention research in older populations, which has been going on for about 20 years, there have been relatively few studies of brief intervention with young people, those aged 15 to 24 years.”

Symposium presentations addressed what is known about the efficacy of brief interventions in the general population, a review of college student drinking in four countries, a review and commentary on brief motivational interventions with college students and the preliminary results of a large trial of a brief intervention for college students. Some of the key points were:

- In-person brief interventions are best directed toward those who engage in hazardous drinking and/or abuse of alcohol rather than those who are alcohol dependent.

“The vast majority of hazardous drinkers do not develop chronic alcohol dependence,” explained Kypri, “but instead experience transient or intermittent periods of problem drinking. Studies show that the majority of hazardous drinkers ... can benefit from a brief intervention designed to reduce hazardous drinking. Individuals with clear signs of alcohol dependence, on the other hand, may warrant interventions of greater duration, sometimes including pharmacotherapy. Nonetheless, brief interventions ... are a way of identifying individuals who are possibly alcohol dependent, and referring them for treatment.”

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BRIEF MAIL- AND-GENERATED INTERVENTIONS WORK BEST FOR PROBLEM DRINKING AMONG YOUNG PEOPLE

- A five-minute in-person intervention has proven to be as effective as longer interventions.

“It is generally impracticable for a health practitioner to deliver a one-hour intervention to a young person whose drinking is risky,” said Kypri. “Ten to 15 minutes of assessment and advice in the waiting room, however, may be quite deliverable to a large proportion of individuals with hazardous-drinking habits.”

- Among college students, hazardous drinkers respond well to electronic assessment and feedback about their alcohol consumption, as opposed to a discussion about their drinking with a doctor or other health professional.

“Our research suggests that young people who are not seeking treatment for an alcohol problem would be disinclined to discuss their drinking with a health practitioner through fear of being judged,” said Kypri. “Young people are nonetheless curious about how risky their drinking is and how it compares with that of their peers. Computerized approaches capitalize on this curiosity while reducing the potential that young people will be put off by the prospect of having to discuss their drinking and its consequences with a health practitioner.”

Kypri added that Web-based approaches can also address what he called the “tyranny of distance” experienced by people in remote areas. “If designed well, Web-based intervention can mimic some aspects of the clinical interview, in particular, the assessment, presentation of feedback and encouragement to make healthier choices,” he noted. “This is an area where more research is needed, but it shows great promise.”

- The use of “motivational feedback” among college students is most effective when private – for example, mailed to the individual – and could reach even more students if disseminated through electronic means.

“ Motivational feedback is information which draws the individual’s attention to their risk status in a non-threatening and non-judgmental fashion,” explained Kypri.

In addition, added Kypri, although much of the presented research focused on college students, there is a need to develop and evaluate interventions for non-students.



Article is based on the following published research:

Saunders, J.B.,
Kypri, K., Walters, S.T.,
Laforge, R.G.,
& Larimer, M.E.
(February 2004).
Approaches to brief
intervention for
hazardous drinking
in young people.
*Alcoholism: Clinical
and Experimental
Research*,
28(2), 322-329.



EDUCATIONAL ATTAINMENT MAY PREDICT DRINKING OUTCOMES FOLLOWING ALCOHOL TREATMENT

- *Previous literature has shown that alcohol use may hinder educational achievements.*
- *Conversely, education may serve as a protective factor against the development of alcohol use disorders.*
- *New findings indicate that educational attainment can predict drinking outcomes following alcohol treatment.*

The relationship between educational attainment and alcohol use is bidirectional. For example, alcohol use may hinder educational attainment; whereas education may serve as a protective factor against the development of alcohol use disorders. A study in the August issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that educational attainment may also be able to predict drinking outcomes following alcohol treatment.

“People have been interested in the association between educational attainment and alcohol disorders because education is a modifiable factor,” said Shelly F. Greenfield, assistant professor of psychiatry at Harvard Medical School and medical director of the alcohol and drug abuse ambulatory treatment program at McLean Hospital. “Education is something you might have influence over. Although previous studies have looked at this association, none to our knowledge, have looked at the influence of educational attainment on the outcome of inpatient alcohol treatment.”

For this study, researchers consecutively recruited 101 individuals (60 males, 41 females) who were hospitalized for alcohol dependence between 1993 and 1996, and monitored their progress for one year following discharge. Each study participant was interviewed during their hospital stay, and at monthly intervals following discharge. Study authors examined the relationship between the inpatients’ educational attainment prior to treatment and their post-discharge drinking outcomes, including time to relapse.

Results indicate that an individual’s years of education are able to significantly predict alcohol-treatment outcomes. “Lower levels of educational attainment among patients in alcohol treatment before they entered treatment predicted a poorer outcome in the year following discharge from treatment,” said Greenfield. “In particular, lower educational attainment predicted a shorter time until they took their first drink following discharge from inpatient alcohol treatment; it also predicted a shorter time to relapse. Specifically, if someone had high school or less, and they entered this treatment program and received the same treatment as the others, upon discharge they would likely have their first drink and relapse almost three times more quickly than the others. Significantly, this finding was the same for men and women.”

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EDUCATIONAL ATTAINMENT MAY PREDICT DRINKING OUTCOMES FOLLOWING ALCOHOL TREATMENT

Greenfield added that one of the more important components of this study was the “robust” nature of the association found between educational attainment and treatment outcomes. “We controlled for a lot of other variables, characteristics that we thought might have made a difference in our findings: gender, marital status, income levels, other psychiatric illnesses they might have had, severity of the drinking problem, age of onset of the drinking problem, family history and parental income levels. However, despite searching for factors that might affect our results, educational attainment still stood out.”

Greenfield said the results raise the question of why this may be. “Part of it might be the type of treatment that people receive for alcohol dependence,” she said. “Our study used what is fairly typical of alcohol treatment in the United States, which consists mainly of talking therapies, group therapies and some individual treatment,” she said. “It is possible that this particular form of treatment may be less successful in people who have lower levels of education, which may in turn reflect different styles of learning. The verbal form of therapy that is most often used in treatment may too closely resemble a school-like format that may be less successful for these individuals.”

Greenfield suggested that future research address issues related to better “matching” patients to various kinds of treatment. “Our results should make people question how individuals with different levels of educational attainment mesh with the treatment program that they’re in. The bottom line is trying to make treatment optimal for people who are trying to help themselves with an alcohol problem.”



Article is based on the following published research:

Greenfield, S.F.,
Sugarman, D.E.,
Muenz, L.R.,
Patterson, M.D.,
He, D.Y., Weiss, R.D.
(August 2003).
The relationship
between educational
attainment and relapse
among alcohol-
dependent men and
women: A prospective
study.
*Alcoholism: Clinical
and Experimental
Research*,
27(8), 1278-1286.

A LCOHOL AND SMOKING: WHY THEY GO TOGETHER

- *Alcoholics, the heaviest of drinkers, are also the heaviest of smokers.*
- *A recent study found that nicotine is especially rewarding for smokers in recovery from alcoholism compared to smokers with no history of alcoholism.*
- *Smokers who are former alcoholics probably require special help to deal with nicotine addiction when they try to stop smoking.*

It's no secret that "smokers drink and drinkers smoke." In fact, the heaviest drinkers are also the heaviest smokers. According to information provided by the National Institute on Alcohol Abuse and Alcoholism, between 80 and 95 percent of alcoholics smoke cigarettes – a rate that is three times higher than among the population as a whole. Approximately 70 percent of alcoholics are heavy smokers (meaning they smoke more than one pack a day), compared with just 10 percent of the general population. A study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* closely examines this association to see if smokers with a past history of alcoholism are more nicotine dependent than smokers with no such history.

"There are many theories of why smoking and alcoholism go together," said John R. Hughes, professor of psychiatry at the University of Vermont/Fletcher Allen Healthcare and lead author of the study. "Some studies suggest that the same genes that predispose people to alcoholism also predispose them to smoking. Some have thought there is an 'addictive personality' that becomes addicted to many things, but research suggests this is not so. Another idea is that since smoking stimulates and alcohol relaxes, smokers use alcohol to prevent over-stimulation from smoking and alcoholics use cigarettes to prevent sedation. Yet another idea is that those who become alcoholics are people who use substances for the drugs within them, for example, to get high or to cope with life. This theory would predict that alcoholic smokers use tobacco mostly for the nicotine in it."

Hughes' study examined if smokers with a past history of alcoholism would report more positive effects from nicotine alone (using nicotine gum) and would self-administer nicotine more often and in greater amounts than smokers without this history. What they found was that smokers with a history of alcoholism did not report more positive effects from nicotine itself, but these smokers did more often choose to use pure nicotine, and ingested greater levels of nicotine than smokers without this history. This means that smokers with a history of alcoholism didn't necessarily like nicotine more, but they did seem to find nicotine more rewarding.

"It may seem unusual," explained Hughes, "that we found a difference between the self-administration or rewarding effects of nicotine and the subjective effects or the liking of nicotine. Usually these two go hand in hand, but not always. In fact, many smokers state they can't understand their use of cigarettes because they feel they really don't get much out of it. Sometimes we can like something but not be able to express what it is we like about it. It's like husbands. If you went by their words, many husbands would seem not to be much in love with their wives. But if you went by what they do, they would seem very much in love."

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LCOHOL AND SMOKING: WHY THEY GO TOGETHER

Despite the strong association between smoking and alcoholism, and numerous theories concerning that association, relatively few studies have examined the two together. Furthermore, alcoholism treatment professionals have generally not addressed the issue of smoking cessation, largely because of the belief that the added stress of quitting smoking might jeopardize an alcoholic's recovery.

"Research attention has been minor until recently," acknowledged Kenneth A. Perkins, professor of psychiatry at the University of Pittsburgh Medical Center. "Many in the alcohol field did not feel smoking was an important problem for alcoholics, that maintaining sobriety was the critical factor. Most studies in the smoking field would exclude those with current or past alcohol dependence. Furthermore, funding has typically come from different agencies – one for alcohol, another for smoking/nicotine – which allowed studies of alcohol and smoking to fall through the cracks."

Yet, noted Hughes, recent data indicates that smoking actually kills more alcoholics than alcohol does. Indeed, according to the American Cancer Society, smoking is the most preventable cause of death in American society. Nearly one in five deaths in the U.S. results from the use of tobacco; more than 400,000 die from smoking in the U.S. each year.

"What this means," said Hughes, "is that we need to get alcoholics to stop smoking either while stopping their alcohol or soon after. Our study suggests these smokers especially need to use medications that fight nicotine dependence, like the patch, gum, an inhaler or Zyban." (Zyban is the trade name for an antidepressant that is used by some to quit smoking.)

Perkins concurs. "This study shows us that chronic use of alcohol can induce long-term changes in the brain's response to nicotine, making nicotine more rewarding and thus more difficult to quit," he said. "Medications to block these effects or counseling to totally avoid nicotine exposure, may be suggested by these results. Although someone might think that use of nicotine replacement therapy (NRT) would pose a problem for those with past history of alcohol, this is not a reasonable concern. NRT is safe and effective, and someone with alcohol problems should not be concerned about using NRT to quit smoking. In fact," he added, "alcoholics are at least as likely to die from smoking as from alcohol. Treatment for smoking in that population is critical."



Article is based on the following published research:

Hughes, J.R.,
Rose, G.L.,
& Callas, P.W.
(November 2000).
Nicotine is more
reinforcing in smokers
with a past history
of alcoholism than in
smokers without this
history.
*Alcoholism: Clinical
and Experimental
Research*,
24(10), 1633-1638.



NICOTINE PATCH TREATMENT WORKS FOR SMOKERS WITH LONG-TERM SOBRIETY

- *At least 80 percent of alcoholics smoke.*
- *Smokers with past alcoholism are more nicotine dependent than smokers without a history of alcoholism.*
- *New research has found that nicotine patch treatment works as well for smokers with long-term sobriety as it does for smokers without a history of alcoholism.*
- *Optimal treatment options for smokers with current alcoholism or recent sobriety remain unclear.*

A clear majority of alcoholics smoke. According to the National Institute on Alcohol Abuse and Alcoholism, between 80 and 95 percent of alcoholics smoke cigarettes, which is more than three times higher than among the population as a whole. Research has also shown that smokers with a history of alcoholism are more nicotine dependent than smokers with no such history, and suggests smoking cessation may prompt a relapse to drinking among a small number of smokers with a history of alcoholism. However, findings published in the June issue of *Alcoholism: Clinical and Experimental Research (ACER)* indicate that nicotine replacement therapy (NRT) works as well for smokers with long-term sobriety as it does for smokers without a history of alcoholism.

“This study refutes the common perception that smokers with a history of alcoholism have more difficulty quitting smoking and are likely to relapse back to alcoholism,” said John R. Hughes, professor of psychiatry at the University of Vermont and lead author of the study. “Our results suggest smokers with this history need to be encouraged to attempt to stop smoking.”

Hughes also said that “for 85 percent of smokers with past alcoholism, quitting smoking is not a problem. Furthermore, as our findings indicate, we found smokers with past but not current alcoholism were able to quit as well and benefited from nicotine patch treatment to the same degree as smokers without this history.”

This study was designed to duplicate and build upon a previous study that examined heavy smokers with no history of alcoholism. Researchers examined 115 heavy smokers with a past history of alcoholism (78 males, 37 females); most had been abstinent from alcohol for more than five years. Study participants were recruited through media advertisements, and from outpatient alcohol treatment sites and Alcoholics Anonymous meetings. Past and present alcohol and drug dependence was assessed using *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV)* criteria. Participants were randomly assigned to either a 21 mg. nicotine patch (n=61) or a placebo (n=54). Abstinance from smoking, alcohol and other drugs was verified by breath and urine tests.

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NICOTINE PATCH TREATMENT WORKS FOR SMOKERS WITH LONG-TERM SOBRIETY

“These findings are consistent with other studies of smokers with long-term sobriety,” said David Kalman, assistant professor of psychiatry at Boston University School of Medicine. “First, quit rates of smokers with and without a history of alcohol dependence are similar. Second, NRT is neither more nor less effective for smokers with or without a history of alcohol dependence. Note that ‘long-term sobriety’ is not precisely defined, but most smokers in these studies have at least a year of sobriety and the median length of sobriety is typically around five years. By contrast, other studies have found that smokers with less than a year of alcohol abstinence have greater difficulty quitting.”

Kalman added that a practical implication of the study is that “people in long-term recovery who use the nicotine patch in combination with counseling can and do quit smoking, and they are no less successful than smokers without such a history. Future research should focus on identifying effective treatment approaches with smokers in early recovery,” he said. “We should also continue to examine the effect, if any, of trying to quit smoking on sobriety, particularly for people in early sobriety. However, consistent with the preponderance of data, I believe that we should be encouraging all smokers in alcohol recovery – including those with less than a year of sobriety – to consider quitting smoking and that we should certainly not be discouraging them to try to quit on the assumption that it will jeopardize their sobriety.”



**Article is based
on the following
published research:**

Hughes, J.R.,
Novy, P.,
Hatsukami, D.K,
Jensen, J.,
& Callas, P.W.
(June 2003).
Efficacy of nicotine
patch in smokers with
a history of alcoholism.
*Alcoholism: Clinical
and Experimental
Research*,
27(6), 946-955.

A LCOHOL, FRIENDS AND COURTSHIP

- *Drinking among adults has traditionally been linked to individual characteristics.*
- *The influence of friends on adult drinking habits may have been underestimated.*
- *The year before marriage is considered a key transitional time of adulthood and drinking behaviors.*
- *The individual's friends as well as the spouse's friends significantly influence drinking during courtship.*

Research on drinking among adolescents usually focuses on two major influences on drinking behavior: peer drinking and alcohol expectancies. Research on drinking among adults has likewise focused on the influence of alcohol expectancies, but tends to assume the predominance of individual characteristics over peer influence. A study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* questions the underlying assumption that adults are less influenced by their peers than adolescents when it concerns their drinking behavior.

“Although we legally define adulthood as 18,” said Kenneth E. Leonard, senior research scientist at the Research Institute on Addictions, research professor of psychiatry at the State University of New York at Buffalo and lead author of the study, “marriage is often viewed by individuals, friends and family as a turning point, an event that marks the change from adolescence to adulthood. At this point, many aspects of your life begin to change, including how you think about yourself, how friends and family interact with you and how you interact with them. In the midst of all these changes, people often change their drinking behaviors, and it is important to understand who doesn’t change and why.”

“The year before marriage presents an interesting and important opportunity to test theory,” said John S. Baer, research associate professor of psychology at the University of Washington. “We are quite certain that drinking can be influenced by a host of factors, some more biological, some more psychological and some more social. What we are just beginning to work out is how these factors might combine, or not, at different points in time during life to increase or decrease the likelihood of alcohol-related problems.”

Research on drinking among adults usually focuses on individual characteristics that may result in excessive drinking, such as whether the person is the child of an alcoholic or has certain personality tendencies. Prior research has rarely considered the possibility that one’s friends may be an important influence on drinking, even though this is a well-known, important influence among adolescents. Studies of drinking during courtship have focused largely on alcohol’s potential impact on unwanted sexual advances or “date rape.” No studies have focused directly on alcohol use and peer influence during the transition to marriage. In an effort to fill this gap, researchers recruited couples at the time of license application for their first marriage. Couples were asked to later complete self-administered questionnaires at home, separately.

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A LCOHOL, FRIENDS AND COURTSHIP

“The influence of friends and companions on adult drinking just hasn’t received nearly as much attention as that same kind of influence on adolescent drinking,” noted Richard W. Wilsnack, a professor in the department of neuroscience at the University of North Dakota School of Medicine and Health Sciences. “This is important to recognize because there may be an exaggerated assumption that adult drinkers are independent individuals whose drinking habits come from inside them rather than outside of them. There may also be an exaggerated assumption that adolescents are extremely vulnerable to peer pressure in ways that adults – particularly married and employed adults – are not. So in the end, you have a situation where we may underestimate the importance of personal characteristics for adolescent alcohol use, and may underestimate the important of peer influences on adult alcohol use.”

The study’s key finding, according to Leonard, was that drinking was related to both individual characteristics and friends’ drinking. The most influential individual characteristic involved was the extent to which the participant believed that alcohol had a positive social effect [on their behavior]. The surprising part of the findings, however, was not only the drinking influence of the individual’s friends but also the influence of the spouse’s friends.

“When partners get married,” said Wilsnack, “his friends and her friends become friends of the couple. As with other things in marriage, his and hers become ours. This is one more demonstration of the importance of looking at drinking behavior – at least chronic drinking patterns – as social processes that are affected by characteristics of the individual drinker but cannot be described or understood by looking only at information about individual drinkers. You have got to know with whom they’re drinking and where they’re drinking. You cannot do much to reduce the risks of problem drinking unless you pay attention to the audience or the co-participants.”

Wilsnack added that a large number of “average drinkers” will nonetheless become ill, have accidents, and/or contribute to damaging personal conflicts because of how they’ve consumed alcohol on particular occasions, in particular settings.

“Statistically,” he said, “most of the alcohol-related behaviors that occur in this country, such as ‘driving under the influence,’ occur among people who have not developed pathological drinking habits. They’re just ordinary or moderate drinkers who happen to have drunk inappropriately which has led to problems. It’s not an internally compulsive pattern with these people, at least not yet. However, before it becomes a problem, it’s very important to look at the social circumstances that led them to drink inappropriately in the first place.”

Article is based on the following published research:

Leonard, K.E., & Mudar, P. (November 2000). Alcohol use in the year before marriage: alcohol expectancies and peer drinking as proximal influences on husband and wife alcohol involvement. *Alcoholism: Clinical and Experimental Research*, 24(10), 1666-1679.





*V*iolence
& Injury



VIOLENCE & INJURY

Articles in the *Violence & Injury* Category

1. Alcohol, Drugs and Violence Between Intimate Partners
2. Alcohol, Interpersonal Violence and Mexican American Women
3. Alcohol Consumption and Intimate Partner Violence
4. Marriage, Alcohol and Violence
5. Alcohol's Double Threat: A Greater Chance of Crashing and More Severe Injuries
6. Alcoholics May Be More Injury Prone Than Illicit Drug Users
7. Drinking and Drugging Can Be Painful



ALCOHOL, DRUGS AND VIOLENCE BETWEEN INTIMATE PARTNERS

- *Intimate partner violence (IPV) refers to verbal, psychological and/or physical violence between two members of an intimately involved couple.*
- *A study has found that female and male alcohol-related problems, as well as female drug use, are associated with an increased risk of moderate and severe male IPV (where the man is the perpetrator).*
- *Living in high unemployment neighborhoods also increases risk for severe male IPV.*

As a disturbing sign of the times, perhaps, or because of a search for clarity, the term “domestic violence” no longer means – as it was first coined 30 years ago – husband-to-wife violence. The term now encompasses all types of violence in the home, including spousal violence, elder abuse and parent-to-child violence. Intimate Partner Violence (IPV) has become the subset of domestic violence that refers specifically to the verbal, psychological and physical violence between two members of an intimately involved couple, married or unmarried.

While research indicates that female IPV (where the woman is the perpetrator) occurs as often or even more often than male IPV (where the man is the perpetrator), women are more likely than men to sustain injuries and need medical care as a result of IPV. A study in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines associations among male and female alcohol problems, drug use and risk of IPV in a general household population sample.

“Our key findings were that female and male alcohol-related problems and female drug use, were associated with an increased risk of moderate and severe male IPV,” said Carol B. Cunradi, epidemiologist, associate research scientist at the Pacific Institute for Research and Evaluation and lead author of the study. “In addition, couples living in high unemployment neighborhoods are at increased risk for severe IPV compared to couples living in low unemployment neighborhoods, even after statistical adjustment for other factors.”

“Not surprisingly,” added Roland S. Moore, a research anthropologist at the Pacific Institute for Research and Evaluation, “men and women who had been victims of childhood violence were more likely to be involved in severe male-to-female partner violence. In contrast, and similar to those couples who lived in neighborhoods with low unemployment, White and Hispanic couples were also less likely to engage in male-to-female IPV.”

Researchers examined a multiethnic sample of 1,615 married or cohabiting couples from the 1995 National Study of Couples, a cross-sectional study of alcohol and IPV that was part of the ninth National Alcohol Survey. The sample included 555 White couples, 527 Hispanic couples, 358 Black couples and 173 couples of “mixed” ethnicity. Participants were asked about sociodemographic and psychosocial variables, as well as alcohol problems, drug use and IPV during the 12 months prior to the interview. In addition, neighborhood unemployment data were collected for each couple from the 1990 census.

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LCOHOL, DRUGS AND VIOLENCE BETWEEN INTIMATE PARTNERS

Alcohol-related problems and, to a lesser degree, drug use were associated with an increased risk of male IPV. This does not necessarily mean that high levels of alcohol consumption will cause more IPV, however. In fact, alcohol-related problems (such as withdrawal or negative social consequences) rather than heavy alcohol use might prove more relevant.

“Alcohol-related problems indicate a loss of control over drinking that mirrors loss of control in other aspects of life,” said Moore. “Such loss of control in relationships can lead to more unstable situations in which intimate partner violence is more likely.” In other words, lack of restraint regarding alcohol may be part of a larger problem that includes aggressive or violent interpersonal exchanges, which can collectively lead to discord and/or fighting.

“The neighborhood unemployment association,” said Cunradi, “is part of a growing body of literature examining the association between neighborhood factors or characteristics and various health outcomes or behaviors. We don’t know why characteristics of the neighborhood are associated with greater risk for severe male IPV. One can certainly speculate on the emotional/psychological sequelae of residing in a high unemployment neighborhood. Given that men are still expected to be the household breadwinners, living in such a neighborhood may be associated with feelings of depression, powerlessness and stress. These factors may provide a toxic atmosphere for the resolution of conflict between the couple.”

Both Cunradi and Moore said that although this study finds an association between IPV and substance use or abuse, it does not clarify which comes first. “A person engaging in heavy drinking or other forms of intoxication certainly increases their odds of being victimized,” said Moore. “And ‘self-medication’ through heavy alcohol or drug use may be a response to the traumatic experience of being victimized. The direction of causality in some of the associations discussed in this paper could be better established with longitudinal studies.”

Cunradi said this was next. “Although the National Study of Couples was originally conceived as a cross-sectional study, additional funds were obtained to re-interview the participating couples during the year 2000. The data obtained from those interviews are currently being analyzed and may provide insight into which factors may be causally related to IPV.”

“IPV is a difficult topic to study because it usually takes place behind closed doors,” said Moore. “The association between alcohol and other drug use and IPV is common knowledge, but there are relatively few studies examining the links between them in a sophisticated way. Detailed analyses of intimate partner violence and substance use are relatively rare.”

Article is based on the following published research:

Cunradi, C.B.,
Caetano, R., Schafer, J.
(April 2002).

Alcohol-related
problems, drug use, and
male intimate partner
violence severity among
U.S. couples.

*Alcoholism: Clinical
and Experimental
Research,*
26(4), 493.





ALCOHOL, INTERPERSONAL VIOLENCE AND MEXICAN AMERICAN WOMEN

- *The development and consequences of alcohol abuse or dependence (ADA) differ for men and women.*
- *Women who report sexual abuse or assault during their childhood or life history are particularly vulnerable to later ADA.*
- *Elements of ADA may also differ by culture.*
- *Mexican American women who report assault by someone other than a partner are more likely than those not assaulted to develop ADA.*

A study in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* is the first to examine alcohol abuse or dependence (ADA) among Mexican American women who report physical or sexual assault. “In this study, women reporting interpersonal violence are much more likely to meet the criteria for ADA than women reporting no violence,” said E. Anne Lown, a post-doctoral fellow and associate research scientist at the Alcohol Research Group, as well as the lead author of the study. “Abuse by a partner was not associated with ADA when we controlled for pertinent factors. Abuse by someone other than a partner, however, was strongly linked to ADA in Mexican American women.” This latter category might have included childhood sexual or physical assault, ex-partner battering, stranger mugging or date rape.

“What is especially interesting about this study,” said Tom Greenfield, center director at the Alcohol Research Group, “is the strong relationship between alcohol abuse disorders and physical or sexual assault ‘ever’ in the person’s life, which has not been reported previously among Mexican American women. This relationship was strong enough that it remained even after controlling for other factors influencing both ADA and assault, such as parental drinking problems. This study suggests that for many Mexican American women, victimization in the past may be part of the clinical picture in the present. It also leaves open the possibility that alcohol abuse disorders may make such assaults more likely.”

Research on ADA and violence against women has examined three groups: women who report child abuse, a lifetime history of sexual assault, and/or intimate partner violence (also known as domestic violence). Numerous studies have shown that sexual abuse during childhood is linked to the later development of ADA. Two factors in particular, the earlier the age of sexual abuse and abuse severity (if it involved intercourse), are strongly associated with the later development of ADA. Physical abuse during childhood, however, has not generally been found to be associated with alcoholism. Three community studies of ADA and sexual assault ‘reported ever’ during a woman’s life all showed that assault preceded the alcoholism. Furthermore, one study showed that women with ADA had a 2.77 greater chance of reporting a later sexual or physical assault, which means that alcoholism may also place a woman at increased risk of assault.

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LCOHOL, INTERPERSONAL VIOLENCE AND MEXICAN AMERICAN WOMEN

“An outstanding weakness in previous epidemiological and biomedical research has been the use of unrepresentative samples that do not reflect today’s population composition,” said William A. Vega, professor of psychiatry at Robert Wood Johnson Medical School, co-author of the paper and principal investigator. “Although medical and mental health research has been done on Hispanics as a whole, groups of Hispanics differ greatly from one another. Mexican Americans constitute two-thirds of all U.S. Hispanics. They are, therefore, a substantial fraction of the largest ethnic minority group in the United States. Mexican Americans are generally infrequent users of health and mental health services and Mexican American men are often occasional heavy drinkers.”

Both Lown and Greenfield noted that assimilation into U.S. society tends to increase the frequency of alcohol consumption among both men and women in this ethnic group. Prevalence rates of ADA also increase in later generations, added Greenfield, after “the immigrant generation,” which has higher levels of abstention than subsequent generations.

“We critically need to understand more about how sexual and physical abuse increase the risk of alcohol problems, or are themselves made more likely if the woman abuses alcohol. This is important both for treatment and prevention of alcohol as well as other mental health problems. In addition, there is some evidence that a number of these findings are not unique to Mexican American women. Some of the results may be relevant to all cultural groups where there are numerous risk factors such as poverty, environmental stresses, discrimination, treatment barriers and other health disparities,” said Greenfield.

Greenfield noted, however, that questions remain about the temporal sequence of alcohol and violence. “Causal sequencing still needs to be teased out,” he said. “This will not be easy since prospective studies going back to childhood are rare and difficult to accomplish both for ethical and practical reasons, but we will need to begin with retrospective studies that document the sequence of events so histories can be reconstructed.”

These findings highlight the importance of screening for physical and sexual assault in settings that treat alcohol disorders, said Lown, as well as screening for alcohol disorders among women seeking services for previous or current violence. She continued, “The assaulted Mexican American women in this study, who are more likely than not to have alcohol disorders, would likely be barred from shelter, putting them and their children at risk for further battering or less safe housing alternatives.”

Article is based on the following published research:

Lown, E.A.,
& Vega, W.A.
(October 2001).
Alcohol abuse or
dependence among
Mexican American
women who report
violence.
*Alcoholism: Clinical
and Experimental
Research*,
25(10), 1479-1486.



A LCOHOL CONSUMPTION AND INTIMATE PARTNER VIOLENCE

- *Members of a couple perceive and remember domestic disputes in different ways.*
- *Days of heavy drinking by male partners have an increased probability of physical aggression.*
- *Black and Hispanic couples are at a higher risk for intimate partner violence (IPV) than White couples.*
- *Male-perpetrated violence decreases significantly following individual treatment.*

These findings, presented at a symposium during the joint June 2002 Research Society on Alcoholism/International Society for Biomedical Research on Alcoholism meeting in San Francisco, can be found in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)*.

“The association between domestic violence and drinking has been recognized for quite some time,” said Raul Caetano, professor of epidemiology and assistant dean at the University of Texas School of Public Health and corresponding author for the *ACER* manuscript. “Many of those who are involved in IPV are drinking during the event or have been diagnosed as alcoholic. However, there is still discussion about the nature of the link between alcohol and violence. Some think, for example, it is due to the disinhibiting effect of alcohol, which triggers a disinhibition of aggressive tendencies, leading then to aggression and domestic violence. Some think that the link between alcohol and violence is due to their association with a third factor such as a personality disorder.”

Understanding the association or link between alcohol and IPV, said Caetano, is fundamental to providing effective prevention and treatment interventions. The symposium also focused on improving research methods and exploring treatment options. Some of the key findings were:

- Alcohol researchers have thus far neglected to focus on agreement between couples who report partner violence and alcohol-related partner violence. New evidence shows that this agreement is low, due to differences in both memory and perception of the dispute. In order to obtain valid data, researchers must develop precise and standardized methods of data collection.
- For couples in which male partners have a fairly recent history of perpetrating partner violence, drinking – particularly heavy drinking – by male partners is a highly significant risk factor for the recurrence of physical aggression. There is an eight times higher probability of domestic violence occurring on days of heavy drinking compared to days when drinking was not heavy.
- Analysis of national data shows that prevalence, incidence and stability of IPV are higher among African Americans and Hispanics than Whites. “We need to recognize that IPV is another example of health disparities between whites and ethnic minorities,” said Caetano.

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LCOHOL CONSUMPTION AND INTIMATE PARTNER VIOLENCE

- Male-perpetrated IPV appears to decrease following individually-based alcoholism treatment. One study found that the proportion of individuals in an alcoholic sample reporting domestic violence was 56 percent in the year before treatment, four times that of the comparison sample (14%). In the year following treatment, that proportion decreased significantly to 25 percent, but still remained higher than the comparison sample.

“The symposium proceedings have multiple applications,” said Caetano. “Investigators need to be careful about data collection in this area and make sure that they have information from both members of the couple. We can see that techniques for treatment do exist that are effective in reducing domestic violence in alcoholics and perhaps also for other individuals. It is also important to note that this type of violence seems, unfortunately, to affect minorities more than whites, and resources from prevention and treatment should be distributed in accordance with this higher risk.”



**Article is based
on the following
published research:**

Caetano, R.,
Schafer, J.,
Fals-Stewart, W.,
O’Farrell, T.,
Miller, B.
(February 2003).
Intimate partner
violence and drinking:
New research on
methodological issues,
stability and change,
and treatment.
*Alcoholism: Clinical
and Experimental
Research*,
27(2), 292-300.

MARRIAGE, ALCOHOL AND VIOLENCE

- *The exact relationship between alcohol use and marital aggression has been unclear.*
- *A recent study has found that alcohol can contribute to marital violence under certain circumstances.*
- *Alcohol seems to exacerbate marital problems when conflict already exists.*
- *Different drinking patterns by the husband and wife may be an additional source of conflict.*

As part of an ongoing examination of drinking and marital violence among newlywed couples, recent findings from the Buffalo Newlywed Study confirm that excessive alcohol use may indeed be involved in marital aggression. However, as the study notes in the July issue of *Alcoholism: Clinical and Experimental Research (ACER)*, alcohol does not simply lead to marital violence, but alcohol may contribute to marital violence within a certain context, for particular people, in particular kinds of relationships.

“It is not unusual to find that violence that occurs early in marriage is predictive of violence occurring later on in marriage,” said Brian Quigley, research associate at the Research Institute on Addictions at the State University of New York at Buffalo. “What this study has found is that certain patterns of alcohol use by couples during the first year of marriage, plus marital conflict, are predictive of violence later in marriage. More specifically, when husbands tend to be heavy drinkers and wives tend to be light drinkers during the first year of marriage, these couples seem more likely to experience husband-to-wife violence in the second and third years of marriage.”

According to the National Coalition Against Domestic Violence, 33 percent of American women experience domestic violence. (The term “domestic” is used to refer to a relationship composed of partners, whereas “marital” refers to a husband-and-wife couple.) Domestic violence can be physical, sexual and/or psychological in nature. In all cultures, the perpetrators are most commonly the men of the family; women are most commonly the victims of violence. Rural and urban women of all religious, ethnic, economic and educational backgrounds, of varying ages, physical abilities and lifestyles can be affected by domestic violence.

Debate continues regarding the exact relationship between alcohol use and domestic violence. Some people believe that alcohol causes domestic violence; others believe that alcohol use may be a reaction to, or a form of coping with, discord or violence that already exists in the relationship. Quigley’s study supports the view that alcohol can lead to marital violence, albeit not simply across the board, but under particular circumstances.

“Alcohol is not simply used as a way of coping with violence that already exists,” Quigley noted. “Alcohol use does play some role in the development of marital violence, but patterns of alcohol use are an important part of that role. In addition, although alcohol use is definitely a risk

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MARRIAGE, ALCOHOL AND VIOLENCE

factor for marital violence, we need to keep in mind that not all marital violence that occurs involves alcohol; maybe 50 percent of it is sober violence.”

“There is a common public perception,” concurred Julie Schumacher, a doctoral candidate in clinical psychology at the State University of New York at Stony Brook, “that alcohol is a direct cause of marital violence. Eliminating domestic violence isn’t as simple as getting rid of alcohol, which the common public myth about alcohol and violence might lead you to believe. This study shows that marital violence is related to alcohol use in conjunction with other factors such as personality, certain demographics and conflict in the relationship.”

The major finding of Quigley’s study was that alcohol seems to exacerbate problems when conflict already exists, and different patterns of drinking by the husband and wife may be an additional source of conflict. Quigley is not entirely sure why the most marital violence occurred when the husband was a heavy drinker and the wife was a light drinker, but he suspects that “discrepant drinking patterns may lead to disagreements about the drinking itself, about things associated with drinking like hangovers and legal difficulties, or perhaps the different drinking styles are indicative of two different types of personalities. He added, “other studies by co-author Kenneth Leonard have found that when husbands and wives have similar drinking patterns, there is higher intimacy and marital satisfaction than when they have discrepant drinking patterns.”

Schumacher agreed with Quigley’s assertion that different factors may predict violence at different times in a couple’s relationship. “When you’re trying to initially predict whether or not a couple may become aggressive,” she explained, “it’s really important to look at the characteristics of the people involved, including personality factors like hostility and demographics like employment status. But later, once a couple has become aggressive, it becomes more important to look at their relationship and the conflict that’s going on, because that will predict the continuation of the aggression more than personality or demographics.”

The study also found that verbal aggression that occurred during the first year of marriage seemed to develop into physically aggressive behavior during later years. Quigley said both findings can be useful for professionals who work with couples.

“Couples who have not experienced violence,” he said, “but are in marriages in which there are discrepant drinking patterns and high levels of verbal conflict have the potential to experience violence in later years. Counseling professionals need to be attuned to this potential for violence and be ready to intervene.”



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Quigley, B.M.,
& Leonard, K.E.
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Alcohol and the
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marital aggression.
*Alcoholism: Clinical
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24(7), 1003-1010.



ALCOHOL'S DOUBLE THREAT: A GREATER CHANCE OF CRASHING AND MORE SEVERE INJURIES

- *Alcohol is known to be a causal factor in motor vehicle crashes (MVCs).*
- *New research has found that alcohol can also affect outcome after an MVC injury occurs.*
- *Alcohol's potentiating effect on injury occurs at both low and high levels of crash severity as well as both low and high levels of alcohol.*

Alcohol clearly impairs judgment and performance during the operation of a motor vehicle, as evidenced by the number of injured patients treated in emergency departments (EDs). A study in the April issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that the relationship between alcohol and motor vehicle crash (MVC) injury is even more insidious – alcohol can actually exacerbate injury.

“We wanted to know, ‘what is the impact of alcohol on injury severity if a crash occurs?’” said Ronald F. Maio, director of the Injury Research Center at the University of Michigan and one of the primary authors of the study. “It concerned us that many physicians and researchers – while acknowledging the effects of alcohol on the chance of an MVC occurring – were nonetheless uninformed or misinformed, about the effects of alcohol on injury severity once the crash has occurred. In fact, many clinicians have said that alcohol has a ‘protective effect,’ which may lead lay people to mistakenly think that there is a ‘good side’ to drinking and driving.”

“Both acute and chronic alcohol abuse have a number of adverse effects on the body that could conceivably increase the severity of an MVC injury,” said Carl A. Soderstrom, associate director of the Medical Advisory Board and Driver Safety Research at the Maryland Motor Vehicle Administration. “These include, but are not limited to, effects on the body’s blood clotting system that could result in an increased potential for bleeding; a decreased tolerance for low blood pressure or shock, which in the case of injury, is usually from bleeding; an increase in dangerous heart beats and rhythms from impacts to the chest, such as striking the steering column or impacts from air bags; and an increase in the amount of injury to particular organs, such as the brain or spinal cord.”

Soderstrom added that this study further distinguished itself from previous research by taking into account the severity of each victim’s crash. “This was ascertained by factoring in the amount of vehicle deformation in each crash,” he said. “It is not only important to know that a car crashed into a tree, but how hard that car crashed into a tree.”

In this study, researchers collected data for 1,362 motor-vehicle-crash victims, 18 years of age or older, who were treated and released, admitted to a hospital or died following the accident. All of the victims were transported from the crash scene to one of two EDs within six hours of the crash. Data were collected for 29 months at the university hospital, and for 15 months at the community hospital.

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A ALCOHOL'S DOUBLE THREAT: A GREATER CHANCE OF CRASHING AND MORE SEVERE INJURIES

Using regression analysis, study authors found that the best predictors of injury severity were vehicle crush, safety belt use, interaction between vehicle crush and safety belt use and age. Alcohol use further predicted injury, increasing the victims' score on the Injury Severity Scale by about 30 percent, all else being equal. In short, alcohol increases injury, although the effects of various alcohol levels are less clear.

"Clinical implications pertain to triage, patient evaluation and intervention," said Maio. "Because patients who have been drinking are at greater risk for injury from a given set of injury mechanism conditions than patients who have not been drinking, triage decisions and evaluation may need to be modified based on the presence or absence of alcohol." In other words, previous consumption could very well have an effect on appropriate treatment and, possibly, recovery.

"Implications for injury prevention are substantial," said Maio. "All motor vehicle occupants who have been drinking are at increased risk for injury. Alcohol's potentiating effect on injury occurs at low levels of crash severity as well as high, and at low levels of alcohol as well as high, suggesting that these findings may be relevant to other injury mechanisms, such as falls or assaults, which usually involve lower levels of kinetic energy. The findings further underscore the importance of clinicians taking an active role in preventing alcohol use where there is risk of injury. In addition, because excess injury from alcohol occurs even at alcohol levels below a blood alcohol concentration of 0.10 percent, previous analyses of alcohol-related injury costs may have underestimated the true cost of alcohol in MVCs."

Maio said there are two "take-home messages" from this study. "Having a designated driver is not completely adequate in protecting you from the harm that alcohol can do if you are involved in a crash," he said. "Furthermore, even if your alcohol level is well below the legal limit and you are driving, you are still increasing your chances of a serious injury if you are involved in a crash."



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Waller, P.F., Hill, E.M.,
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motor vehicle crash
injury.

*Alcoholism: Clinical
and Experimental
Research,*
27(4), 695-704



ALCOHOLICS MAY BE MORE INJURY PRONE THAN ILLICIT DRUG USERS

- *Considerable research has linked alcohol and drug use to both major and minor trauma.*
- *Most studies have used emergency department admissions data to establish this relationship.*
- *A new study looks at patients entering detoxification for alcohol and other drug dependence.*
- *People with alcohol problems seem more injury prone than people who use illicit drugs.*

Numerous publications have documented the association between alcohol and drug use – particularly alcohol use – and motor vehicle crashes, pedestrian and bicycle injuries, falls, burns, drownings, suicides, assaults, domestic violence and even murder. Most studies have examined the association between alcohol consumption and injury using hospital emergency department admissions data. A study in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)* reconsiders the issue in a different clinical setting, among patients entering detoxification for alcohol and other drug dependence. The findings indicate that injury is a serious problem for a substantial proportion of patients undergoing detoxification, particularly those with alcohol dependence.

“Our hypothesis was simply that when it comes to substance abuse, the consequences vary for each substance and for the group of users,” explained Jeffrey H. Samet, associate professor of medicine and public health at Boston University and the study’s senior author. “What the substance is may be an important factor in the outcomes of the user. In particular, in the case of injury, we hypothesized that alcohol use is more of a risk factor for injury than illicit drug use. Furthermore, we hypothesized that this was the case amongst the most severely affected substance abusers, those receiving care in a detoxification unit.”

The authors recruited 470 patients (360 males, 110 females) from a Boston detoxification unit. Study participants were divided into three groups: those considered alcohol dependent; those considered alcohol and drug dependent and those considered drug dependent. Reported drug choices were cocaine, heroin or other (mainly sedatives and marijuana). Participants were interviewed at baseline (during detoxification), and then at six months, 12 months, 18 months and 24 months following detoxification. Self-reported episodes of injury were defined as: a gunshot wound, a stab wound, accidents or falls requiring medical attention, fractures or dislocation of bones or joints, an injury from a road traffic accident such as a car or motorcycle, or a head injury.

“One key finding is that among the health-related complications of alcohol and drug abuse,” noted Samet, “serious injury is common. We found that 24 percent of the 470 subjects reported at least one instance of injury during the six-month period prior to detoxification. The other key finding is that problems with alcohol, more so than illicit drugs, are associated with injury.”

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Samet added that researchers had originally thought that a significant proportion of those entering detoxification were doing so because recent serious injury had helped them realize they might have a substance abuse problem. “And this is probably true,” he said. “But then we found that at the follow-up interviews during the next two years, the prevalence of injury in the previous six months was still nearly one out of five.”

“It is very interesting that this increased risk for serious injury persisted for two years after detoxification,” said Gail D’Onofrio, associate professor in the Section of Emergency Medicine at Yale University School of Medicine, “even when patients were not drinking. The fact that even in recovery, alcohol-dependent patients still continue to be at risk for injury, may be a result – as the authors hypothesize – of chronic nerve and muscle damage that occurs with dependence creating unsteady gaits, problems with coordination and poor sensation. The idea that they are ‘risk takers’ with impulsive behavior, or may have depressive symptoms which may influence injury, needs to be further investigated.”

Samet said that the continuing high incidence of injury did not necessarily mean that the alcoholics had relapsed and were once again drinking alcohol. In fact, he said, “the follow-up high prevalence of injury came as a bit of a surprise. Our hypothesis that injury at follow up would be significantly associated with ongoing alcohol consumption was not shown to be a strong association. We conjectured that perhaps a personality trait of the alcohol dependent person accounted for the injury prevalence to an extent even greater than consumption itself. Although this issue will require further study, another issue has become abundantly clear. These individuals comprise a prime opportunity to focus on injury prevention within the confines of, or directly linked to, substance abuse treatment programs.”

“The identification of the detoxification center as place to offer prevention is a unique contribution to the field,” said D’Onofrio. “This may include educating patients about the risks of injury as well as including assessments of their living conditions to prevent falls and subsequent fractures and dislocations. Identifying patients with depressive symptoms and impulsive behaviors may also be beneficial, so that additional counseling sessions be provided. Future studies should look at different prevention strategies offered in detoxification programs for their ability to decrease injury rates.”



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detoxification
patients: Alcohol
users’ greater risk.
*Alcoholism: Clinical
and Experimental
Research*,
26(2), 212-217.



DRINKING AND DRUGGING CAN BE PAINFUL

- *People are more likely to sustain injuries if they use alcohol and/or other drugs.*
- *People clinically identified as substance abusers have an elevated risk of injury.*
- *People who abuse both alcohol and other drugs have the highest risk of injury.*
- *Substance abusing women over the age of 50 have an especially elevated risk for injury.*

The association among alcohol and other drug use and injury is well documented. Alcohol alone is known to be a factor in 60 to 70 percent of homicides, 40 percent of suicides, 40 to 50 percent of fatal motor vehicle crashes, 60 percent of fatal burn injuries, 60 percent of drownings and 40 percent of fatal falls. Additional studies have also confirmed an association between alcohol and nonfatal injuries. Yet only recently has research – such as a study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* – examined the injury risk among individuals clinically diagnosed with substance abuse problems.

“We know that people often have alcohol on board when they get injured,” explained Ted R. Miller, a principal research scientist at Pacific Institute for Research and Evaluation and lead author of the study. “Very little is known about the injury risk associated with drug abuse, or whether alcohol and drug abusers have higher injury risks than those who abuse only drugs. If substance abusers have excess injury risks, physicians need to know that so they can reduce this health threat.”

Miller and his co-authors examined medical claims data from a database for 1.5 million people with health care coverage provided by 70 large corporations. Specifically, they analyzed the injury-claims histories during a three-year period of people who were treated for an alcohol- or drug-related diagnosis.

“We included all medically treated non-work injuries except alcohol and drug poisonings,” said Miller. “This included falls, car crash injuries, assaults, suicide attempts, near-drownings, suffocations, poisonings that were not substance abuse related, injury deaths in the hospital, among many others. We excluded medical misadventures that resulted in injury. We also excluded injuries treated at the same time that someone was admitted to the hospital primarily for substance abuse treatment because some of those injuries might not have been treated without the substance abuse treatment. This latter decision considerably lowered our injury counts for substance abusers, making them conservative.”

Despite the conservatism of their injury findings, the researchers found a notable difference in the risk of injury between those who abused alcohol and other drugs and those who did not. Those individuals clinically identified as substance abusers had an elevated risk of injury. Alcohol-and-drug abusers had the highest risk of injury (58%), followed by drug-only abusers (49%), alcohol-only abusers (46%), and those who did not abuse any drugs (38%). Compared to those without a diagnosed substance abuse problem, said Miller, alcohol abusers were twice as likely,

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RINKING AND DRUGGING CAN BE PAINFUL

drug abusers were three times as likely, and alcohol-and-drug abusers were almost four times as likely to be hospitalized for an injury during the three years examined.

“This study provides important evidence regarding the extent of substance abuse disorders and injuries in a population of people who are employed and receive insurance coverage through their employers,” said Linda C. Degutis, assistant professor of surgery and public health at Yale University. Each year, she added, substance abuse costs businesses at least \$10 billion in absenteeism, injuries, medical liability and health care costs.

“Investment in treatment is an effective strategy to reduce these costs,” said Degutis. “Research shows that following substance abuse treatment absenteeism, disability days and disciplinary actions all decrease by more than 50 percent. ... However, in order for treatment to occur, the problems must first be identified.”

Both Miller and Degutis noted that health care practitioners – particularly family physicians and trauma personnel – have an invaluable role in detecting, intervening on the behalf of, and referring substance abusing patients to the appropriate care. Miller said that family physicians have an especially important role in helping older, female substance abusers.

“Among working-age adults who are not substance abusers,” said Miller, “women are much less likely to be injured than men. Among substance abusers, that’s not true. Indeed, by age 50, we found that substance abusers are significantly more likely to get injured if they are women. This finding is alarming, because substance abusing women are not typically targeted for intervention. Usually it’s the men who get attention for substance abuse problems and are pushed into treatment. More physicians, especially family physicians, need to identify female abusers, assess their treatment needs, and see that those needs are met.”

Degutis added that, in the context of discussing substance abuse disorders, a more fundamental issue must first be addressed. “Addiction is a brain disease,” she said. “Too often, addiction is treated as a moral issue, or a ‘defect’ in someone’s personality or behavior or judgement. There are many things that can place someone at risk for developing an addiction, and we now know that it can have a genetic basis. It is a chronic disease, just like heart disease, diabetes and other diseases. Unfortunately, there is still a great deal of stigma related to addiction and substance abuse. ... We should not be reluctant to discuss these issues, and should bring them out into the open, just as we have done with diseases such as breast cancer, prostate cancer and heart disease.”

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Key Word
Index

INDEX

- Abstinence 36, 37-38, 45, 47, 54, 66, 67, 75, 96,
 103-104, 105, 152, 157-158, 163-164, 176, 177,
 197-198, 207-208
 Academic achievement 33-34
 Acetaldehyde 95, 99-100, 147-148, 149-150, 180
 Acetate 95, 147, 149, 162, 180
 ADH2*2 allele 179-180
 Adolescents 18, 21, 22, 25-26, 27-28, 29-30, 31,
 33-34, 96, 114, 166, 174, 181, 183-184, 209-210
 African American 29, 64, 69-70, 71, 95-96, 97, 166,
 172, 177-178, 179, 191-192, 217
 Aggression 18, 27-28, 81, 83, 123, 160, 171-172, 217,
 219, 221
 Agoraphobia 110, 115-116
 Alcohol dehydrogenase (ADH) 95, 147, 149
 Alcohol dependent 113, 171, 201, 223-224
 Alcohol sensitivity 80, 93-94, 103
 Alcohol withdrawal syndrome (AWS) 129-130, 163
 Alcohol-related birth defects 167, 180
 Alcoholics Anonymous (AA) 197, 207
 Aldehyde dehydrogenase (ALDH) 95, 149, 180
 Aldehyde dehydrogenase-2 (ALDH2) gene 149
 Aldehydes 99, 147-148
 Allergies 144, 153-154
 American Indian(s) 64, 75-76, 77, 166, 177-178, 179
 Amnesia 49, 51, 199
 Anger 39
 Anglo-Saxon 135
 Anorexic 49, 52
 Anti-nicotine drug 128, 139-140
 Anticonvulsants 129-130
 Antipsychotics 142
 Antisocial 27-28, 47, 78, 83-84, 110, 113-114,
 121-122
 Antisocial personality 121
 Antisocial personality disorder 110, 113, 122
 Anxiety 21, 39, 53, 57, 59, 81, 83-84, 85-86, 87, 110,
 117-118
 Anxiety sensitivity 117-118
 Asian 29, 95, 148, 149-150
 Asian American 29
 At risk 29-30, 38, 41, 49, 62, 65, 70, 76, 85-86, 87,
 89, 94, 96, 105-106, 108, 133, 151, 169, 177, 180,
 182, 195, 216, 224, 226
 Ataxia 93, 160
 Attention Deficit Hyperactivity Disorder (ADHD)
 39, 47-48, 110, 121-122, 123
 Automobiles 18, 29-30
 Behavioral sensitization 36, 61-62, 63
 Behavioral therapies 128, 137, 193
 Benzodiazepines 129-130
 Beta-endorphin 87, 89
 Binge drinking 18, 19-20, 21, 36, 41, 43-44, 47, 145,
 168, 175, 182
 Biochemical marker(s) 80, 87, 136
 Biological marker(s) 187-188
 Biology 36, 40, 90, 96, 98
 Biomarker(s) 87-88, 89
 Black 64, 71-72, 178, 213, 217
 Blood alcohol concentration 29, 31, 99-100,
 123-124, 222
 Blood pressure 53, 65, 104, 111, 139, 144, 157-158,
 221
 Bone loss 155-156
 Brain 21-22, 27-28, 36, 37-38, 39, 41-42, 43-44,
 45-46, 47, 49-50, 51, 53, 55, 57-58, 59-60, 61,
 64, 67-68, 69, 80, 82, 83, 85-86, 87-88, 89-90,
 91-92, 94, 95, 98, 99-100, 101-102, 103-104,
 108, 112, 113, 119, 123, 126, 129, 131-132, 133,
 135, 137-138, 139, 159-160, 161, 164, 167-168,
 169-170, 182, 206, 221, 226
 Brain chemistry 27-28
 Brain damage 41, 43-44, 45, 49-50, 64, 67-68, 91,
 104
 Brain derived neurotrophic factor (BDNF) 39
 Brain gene analysis 80
 Brain gene expression 91-92
 Brain injury 41-42
 Breastfeed 186
 Brief intervention 196, 201
 Burn injuries 225

 CAGE questionnaire 199-200
 Cancer 144, 147-148, 149-150, 151-152, 195, 206,
 226
 Carbohydrate 161-162
 Carcinogens 147
 Cardiac arrhythmia 163
 Cardiomyopathy 65-66, 163-164
 Cardiovascular 64, 65-66, 67, 99, 111, 129, 157-158
 Caucasian 150, 191-192
 Cell death 21-22, 40, 45
 Central nervous system 42, 91, 101
 Cerebellum 37-38, 44, 45-46, 93-94, 167

INDEX

- Child/Children 28, 30, 62, 80, 83-84, 85-86,
 87-88, 90, 95, 108, 110, 114, 115, 117, 122, 138,
 166, 167, 169-170, 173, 175, 179-180, 181-182,
 183-184, 185-186, 187-188, 209, 213, 215-216
 Childhood trauma 116, 117
 Children of alcoholics 80, 83, 85-86, 87, 90, 108,
 186
 Children's Memory Scale 183
 Cigarette(s) 56, 100, 139, 147, 163-164, 169, 205,
 207
 Cirrhosis 64, 71-72
 Co-existing 85, 114, 121-122, 128, 141-142
 Cocaine 61, 99, 132, 171-172, 192, 223
 Cognitive function 36, 55-56, 57, 67-68, 124, 164,
 183
 Cognitive functioning 46, 55, 110, 123-124, 125
 Cognitive-behavioral 78, 197-198
 College students 18, 19-20, 21, 23-24, 25, 201-202
 Comorbid/Comorbidity 75, 115-116, 117, 119, 123,
 141-142, 143, 173
 Compulsive 39, 210
 Conduct disorder 27-28, 86, 114
 Coping skills 137-138
 Cortisol 27-28, 36, 53-54, 55, 103-104, 111-112,
 187-188, 189
 Costs 193, 195-196, 197-198, 222, 226
 Counselor 137, 190, 195-196
 Crash 29, 31, 212, 221-222, 223, 225
 Cue exposure 137-138
 Culture 20, 63, 64, 76, 200, 215, 219
 Cytokines 69
- D1 dopamine 77-78
 Ddel polymorphism 77-78
 Death 21-22, 29, 31, 40, 43-44, 45, 71, 119, 151, 157,
 206, 225
 Delta opioid receptor 36, 59, 60
 Dementia 49, 51
 Deoxyribonucleic acid (DNA) 91, 147
 Depression 26, 70, 81-82, 83-84, 97, 101, 103,
 115-116, 119, 121, 141-142, 171-172, 197, 214
 Detoxification 36, 46, 55-56, 57, 66, 128, 129-130,
 157, 164, 223-224, 225
 Diagnostic and Statistical Manual 25, 75, 77, 98,
 199, 207
 Disinhibition 47, 81, 83, 85, 217
 Divalproex sodium 129-130, 131
 Doctor 71, 121-122, 190, 195, 198, 200, 202
 Domestic violence 213, 215, 217, 218, 219-220, 223
- Dopamine 39, 60, 77-78, 79, 131, 133, 135, 138, 139
 DRD1 gene 78
 Driving 18, 29-30, 31-32, 33, 38, 71, 73-74, 124,
 210, 221-222
 Driving under the influence (DUI) 64, 73-74, 75
 Drowning 223, 225
- Education 31-32, 71, 137-138, 170, 176, 190,
 203-204, 205, 219
 Elderly 155
 Electroencephalogram 85-86
 Electrolyte 163-164
 Emergency department/ER 199-200, 221, 223
 Emotional instability 166, 171-172, 188
 Emotional reactivity 110, 113-114
 Endogenous 59, 60, 61, 87-88, 131, 134, 135, 148
 Endogenous opioid system 59-60, 87-88
 Endorphin 87
 Environmental conditions 47, 94
 Environmental factors 77, 87, 101, 107, 115, 153-154
 Ethanol 23, 40, 45, 51, 53, 59, 61, 63, 95, 126,
 147-148, 150, 159-160, 169
 Ethnic 20, 29, 31, 64, 70, 73, 75, 95-96, 177,
 199-200, 216, 217, 219
 Ethnicity 63, 64, 69, 71-72, 178, 199, 201, 213
 Euphoria 87, 90, 103, 129, 131, 133, 139
 Excitotoxicity 39, 41
 Executive cognitive functioning 110, 123, 125
 Executive function 42, 55
 Exogenous 131, 134, 135
 Eye 51, 80, 89-90, 91, 114, 199
 Eye movements 51, 89
- Faith-based 197
 Familial history 40, 89
 Family members 87, 98, 105
 Female 19, 37, 65, 67, 97, 101, 116, 125, 151, 156, 191,
 213, 226
 Fenfluramine 27, 103-104, 121
 Fetal alcohol effects (FAE) 169, 177, 179
 Fetal alcohol syndrome (FAS) 166, 167, 169-170,
 173, 177-178, 179-180, 181
 Fetal development 167, 169
 Food 52, 58, 60, 103, 107, 130, 133, 149, 151, 161
 Frontal cortex 41, 42, 44, 91-92, 93, 112, 123, 159
 Frontal lobes 37-38, 45-46, 55-56
 Functional magnetic resonance imaging (fMRI)
 37, 47, 67

INDEX

- Gender 41, 64, 70, 76, 116, 120, 140, 141-142, 160, 199, 201
 Gene 40, 62, 77-78, 79, 80, 83-84, 91-92, 93-94, 95-96, 120, 121, 149, 179-180
 Gene array technology 91-92
 Gene expression 62, 91-92, 93
 Genetic 19-20, 40, 41, 64, 77-78, 80, 81-82, 83-84, 87-88, 89-90, 93-94, 95-96, 97-98, 101-102, 106, 107-108, 120, 121-122, 132, 147, 153-154, 158, 166, 179, 187, 226
 Genetic predisposition 40, 95-96, 107, 122, 153
 Genetic risk 80, 87-88, 89-90, 97-98, 107-108, 122
 Genotyping 19, 121
 Glucocorticoid 53
- Health care 53, 64, 71, 72, 73, 74, 193, 195, 197, 199, 225, 226
 Health maintenance organization (HMO) 190, 191, 192, 193, 194
 Heroin 60, 131, 132, 134, 135, 172, 192, 223
 Hispanic 71-72, 74, 96, 213, 217
 Homicides 225
 Hormone 27, 39, 53, 69, 80, 87, 103-104, 105, 111, 144, 152, 155, 159, 161, 163-164, 167-168, 169, 187
 Hospital 25, 138, 157, 163, 195, 197-198, 199, 203, 221, 223, 225, 226
 Human immunodeficiency virus (HIV) 69, 144, 145-146
 Hyperactivity 22, 48, 62, 110, 121-122, 123, 173
 Hypertension 65-66, 67, 157
 Hypothyroid 167
- Illicit drug 172, 181, 183, 212, 223-224
 Immigrant 71, 186, 216
 Immune system 69-70, 104, 146, 151, 153-154
 Immunoglobulin E 153-154
 Impulsive 27, 39, 81-82, 83, 224
 Impulsiveness 18, 27, 48, 77, 106, 121
 Impulsivity 27-28, 29, 47, 77, 171-172
 Infants 169, 185-186, 187
 Infection 144, 145-146, 147, 152
 Infectious disease 69, 151
 Inherited 86, 87, 90, 95, 97-98, 150
 Inhibitor 81, 83, 141, 148, 160
 Injury 29, 41-42, 45, 200, 211, 212, 221-222, 223-224, 225-226
 Injury Severity Scale 222
 Inpatient treatment 142, 197
- Insulin 144, 158, 161-162
 Insurance 73-74, 192, 193, 226
 Interleukin 69, 71
 Interpersonal violence 212, 215
 Intervention 26, 28, 31, 32, 34, 72, 76, 98, 136, 138, 171, 173, 174, 189, 190, 195-196, 199, 201-202, 203, 217, 222, 226
 Intimate partner violence 212, 213-214, 215, 217-218
 Intoxication 36, 40, 43-44, 53-54, 55, 89, 91, 93, 99, 123-124, 129, 133, 145, 160, 214
- Jewish 18, 19-20, 21
- Kindling 129
 Korsakoff's syndrome 49-50, 51
- Label 24, 177
 Latino 25, 29-30
 Learning 21, 46, 51, 103, 113, 125, 138, 166, 169, 173, 183-184, 185-186, 204
 Liver 44, 52, 64, 69, 71, 72, 95, 99-100, 126, 133, 134, 147-148, 149, 151, 162, 163, 164, 180, 195
- Magnetic resonance imaging (MRI) 45, 67
 Male 19, 27, 37, 43, 54, 55, 58, 65-66, 77-78, 97, 101, 113, 120, 130, 140, 145, 159, 181, 191, 199, 213-214, 217-218
 Managed care 190, 192, 193-194
 Marital violence 219-220
 Markers 80, 87-88, 89, 105-106, 136
 Marriage 209-210, 211, 212, 219-220
 Maternal 116, 167-168, 169, 181-182, 183, 185
 Mecamylamine 139-140, 141
 Medication 40, 55, 131-132, 133-134, 137, 195
 Mediterranean drinking pattern 128, 135
 Memory 21, 24, 49, 51, 53, 57, 67-68, 103, 110, 113, 125-126, 127, 166, 183-184, 185-186, 217
 Men 46, 55, 64, 65-66, 67, 70, 74, 76, 77-78, 79, 105, 116, 119-120, 126, 136, 140, 142, 155, 171, 192, 200, 203, 205, 213-214, 215-216, 219, 226
 Mental 25, 39, 48, 49, 51, 67, 75, 77, 98, 110, 111, 113, 115-116, 123, 126, 141-142, 169, 172, 173, 175, 177, 179, 193, 195, 197, 199, 207, 216
 Mental health 110, 115, 126, 141, 193, 195, 197, 216
 Mental retardation 169, 172, 173, 175, 177, 179
 Metabolism 19, 28, 41, 95, 99-100, 102, 131, 147-148, 152, 157-158, 162, 164, 179-180

INDEX

- Methadone 193
 Mexican American 73, 212, 215-216
 MK-801 61-62, 63
 Mother 119, 166, 167-168, 169-179, 180, 183-184, 185-186, 187-188
 Motivation 58, 80, 97, 98, 99, 175, 201-202
 Motor vehicle crash 31, 221, 223, 225
- N-methyl-d-aspartate 39, 61
 Naltrexone 58, 60, 108, 128, 131-132, 133-134, 135-136, 137-138, 139
 Narcotics Anonymous (NA) 197
 Neurobiology/Neurobiological 28, 35, 36, 57, 81-82, 99, 155-156, 187
 Neurochemical 60, 61, 81, 93
 Neurodegeneration 43
 Neurogenetic 80, 81-82
 Neuropeptide Y (NPY) 57-58
 Neuroscience 36, 47, 48, 51, 57, 60, 101, 104, 163, 168, 182, 210
 Neurotoxic/Neurotoxicity 21, 41, 43, 82, 91
 Neurotransmitter 27, 36, 39, 57, 81-82, 83, 93, 103, 131, 133, 135, 137-138, 139
 Nicotine 56, 61, 65, 80, 99-100, 101-102, 103, 121, 128, 132, 139-140, 164, 178, 190, 205-206, 207-208, 209
 Nicotine patch 190, 207-208
 Nicotine replacement therapy 206, 207
 Nicotinic acetylcholine (NACH) receptor system 139
 NMDA receptors 21-22, 40, 61
 Nutrition 46, 49-50, 52, 70, 155, 161-162
- Olfactory bulb 43
 Opiate antagonists 60
 Opiates 60, 61, 131, 135
 Opioid antagonist 88, 108, 131-132, 134, 135, 138
 Opioid receptors 59-60, 132
 Osteoporosis 155-156
- Parathyroid hormone 155
 Parenting 165, 166, 188
 Paternal 78, 105-106, 107-108, 181
 Paternal history 105-106, 107-108
 Peptides 57, 59
 Pharmacology 37, 39-40, 41, 57, 92, 93-94, 101, 128, 147, 171
 Pharmacotherapy/Pharmacotherapies 128, 136, 137-138, 140, 201
- Physical 19, 26, 29, 61, 67, 91, 103-104, 105, 111, 113, 115-116, 144, 170, 171, 181, 213, 215-216, 217, 219
 Physical aggression 217
 Physical assault 215
 Physical violence 213
 Physician 131, 136, 138, 170, 195-196, 197, 221, 225-226
 Physiological response 111-112
 Polymorphism 77-78, 79, 85, 121-122, 179
 Positron emission tomography 28, 132
 Post traumatic stress disorder (PTSD) 65, 110, 115-116
 Poverty 70, 171, 178, 216
 Pregnancy 95, 166, 167-168, 169-170, 171-172, 175, 177-178, 179, 181-182, 183-184
 Pregnant 167-168, 169-170, 171-172, 173, 175-176, 177-178, 180, 184
 Prenatal 165, 166, 169, 171, 173-174, 175, 181-182, 183-184, 185-186
 Prevention 28, 29-30, 31-32, 33, 40, 62, 72, 75-76, 88, 94, 118, 126, 150, 151, 177, 182, 190, 216, 217-218, 222, 224
 Prolactin 27-28, 121
 Protective factor 85, 203
 Protective gene 80, 95-96
 Psychiatric 26, 54, 75, 77, 81-82, 84, 97, 105-106, 113-114, 115-116, 117, 119-120, 121-122, 128, 130, 141-142, 143, 172, 173-174, 181, 191, 198, 204
 Psychological 19, 29, 67, 97, 103, 110, 111, 164, 171-172, 174, 181, 194, 209, 213-214, 219
 Psychological stressors 110, 111
- Rapid Alcohol Problems Screen 199
 Recovery 38, 41-42, 131, 141, 163-164, 205-206, 208, 222, 224
 Relapse 46, 58, 60, 62, 82, 126, 131-132, 133, 136-137, 138, 203, 205, 207
 Religion 20, 96
 Religious 19-20, 75, 96, 219
 Reproduction 53, 58, 103
 Residential treatment 54, 172
 Resistant 93, 137
 Retention 42, 125, 194
 Reverse tolerance 61
 Ribonucleic acid (RNA) 91
 Risk factor 34, 41, 72, 85-86, 96, 114, 115, 119, 122, 153, 155, 157, 176, 191, 216, 217, 219, 223
 Rural 219

INDEX

- Saccades 89-90
 Scandinavian 135
 Screening 88, 116, 150, 172, 180, 190, 196, 199, 201, 216
 Seizure 55, 129
 Self-help group 197, 199
 Senior citizen 49, 52
 Sensation seeking 64, 77-78, 79
 Sensitization 36, 39, 52, 61-62, 63, 154
 Serotonin 27-28, 29, 39, 81-82, 83, 85, 103-104, 121, 123, 141
 Sexual abuse 115-116, 171, 215
 Sexual assault 216
 Six-beta-naltrexol 131, 133-134
 Sleep 53-54, 70, 103, 186
 Smell 43, 185
 Smoke 99, 102, 150, 205, 207
 Smokers 99-100, 101-102, 139, 190, 205-206, 207-208, 209
 Smoking 32, 39, 56, 100, 101, 139, 147, 169, 190, 195, 205-206, 207, 208
 Sobriety 46, 124, 138, 190, 197-198, 206, 207-208
 Social anxiety 97-98, 141
 Social phobia 110, 115-116
 Sodium sensitivity 144, 157-158
 Spirituality 190, 197-198
 Stress 53, 59, 65, 67, 70, 76, 80, 81-82, 96, 103-104, 105, 110, 111-112, 113, 115-116, 118, 163, 166, 169, 187-188, 189, 206, 214
 Stress hormone 53, 80, 103, 105, 111, 187
 Stroke 65, 111, 157, 195
 Suicidal 110, 119-120, 122
 Suicide 116, 119-120, 121-122, 141, 225
 Sweet tooth 80, 107-108
 Sweets 60, 107-108, 109

 Taste 80, 105-106, 107
 Teen/Teenager 18, 21-22, 30, 31, 33, 67, 188
 Testosterone 144, 159-160
 Thiamin 36, 41-42, 49, 50, 51-52, 53, 162
 Thyroid 166, 167-168, 169
 Toxicity 43, 99, 135-136
 Trauma 87, 115-116, 117, 155, 223, 226
 Treatment 26, 27-28, 32, 33-34, 41-42, 45-46, 49-50, 51, 54, 55-56, 57, 60, 61, 65, 71-72, 73-74, 78, 82, 94, 117, 128, 129-130, 131-132, 133-134, 136, 137-138, 139, 141-142, 143, 155, 189, 190, 191-192, 193-194, 195, 203-204, 207-208, 216, 217, 219, 222, 224, 225-226

 Tumor 151-152
 Twelve step 198
 Type I 77
 Type I alcoholism 27, 78
 Type II alcoholism 27

 Underage drinking 29, 31
 Unemployment 96, 171, 213-214
 Urban 75, 178, 179, 219

 Vasopressin (AVP) 163-164
 Violence 212, 213-214, 215-216, 217-218, 219-220, 223
 Vitamin B1 49, 51

 Wernicke-Korsakoff Syndrome 50, 51
 Wernicke's Encephalopathy 49, 51
 White(s) 19-20, 21, 25, 71-72, 73-74, 75, 177, 199, 213, 217-218
 Withdrawal 21, 25, 36, 39-40, 43, 46, 53-54, 55-56, 65, 77, 129-130, 131, 135, 157-158, 163-164, 214
 Women 46, 49, 64, 65-66, 67-68, 69-70, 76, 77, 95, 116, 119-120, 126, 136, 140, 142, 151, 155, 166, 169, 170, 171-172, 173, 175-176, 177-178, 180, 181-182, 184, 186, 191-192, 199-200, 203, 205, 212, 213, 215, 217, 219, 225-226

 Youth 18, 28, 29-30, 31-32, 33-34, 67, 155-156, 187

 Zero-tolerance 30, 31