

NIAAA SPECTRUM

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

FEATURE

WHAT IS EPIDEMIOLOGY ANYWAY, AND WHAT IS IT GOOD FOR?



How does the flu work its way through a population, sometimes reaching epidemic levels? Why do some members of a community or family succumb to certain diseases, whereas others do not? How does the environment affect a society's health? These are public health questions that epidemiologists try to answer every day.

Epidemiology is the study of how disease is distributed in populations and the factors that influence or determine this distribution. The underlying premise is that diseases and problems are not randomly distributed in the population. Rather, each of us has certain characteristics that predispose us to, or protect us from, a variety of different diseases and adverse outcomes. The origins of these risk and protective factors may be genetic or environmental and may also result from the interaction of genetic and environmental influences.

The objectives of epidemiology are to identify the cause of a disease or problem and the risk factors for it, determine its extent in a population,

study its progression and prognosis, evaluate existing and new prevention and treatment interventions, and inform public policy and regulatory decisions.

EPIDEMIOLOGY AND ALCOHOL

Epidemiologic research has been key to understanding the intersection of alcohol and human health and well-being. Using epidemiologic research, scientists have discovered the link between alcohol and birth defects, informed public policy regarding drinking and driving, and helped us learn about other important aspects of alcohol's effects.

FETAL ALCOHOL SPECTRUM DISORDERS

Alcohol use during pregnancy was not linked to the spectrum of problems now known as Fetal Alcohol Spectrum Disorders (FASD) until well into the 20th century. In the 1960s, a French pediatrician, Dr. Paul Lemoine, saw many newborns with serious anomalies. He was struck by the existence of an unknown syndrome among these children and began to look for answers to explain the severe growth retardation, behavioral problems, and specific facial dysmorphism with which these children were born.

Of his discovery of the link to alcohol, Dr. Lemoine later wrote: "... I was

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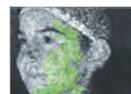


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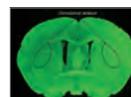
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FEATURE

GENE COMBINATIONS HELP PREDICT TREATMENT SUCCESS FOR ALCOHOLISM MEDICATION

Ondansetron, an experimental treatment for alcohol dependence, works better in individuals who possess specific combinations of genes that regulate the function and binding of serotonin, a brain chemical affected by the treatment, according to a study supported by NIAAA. A report of the finding by Johnson et al. appears online in the *American Journal of Psychiatry* (<http://ajp.psychiatryonline.org/Article.aspx?ArticleID=1722045>).

“This study is another important step toward personalized treatments for alcohol dependence,” said Kenneth R. Warren, Ph.D., acting director of NIAAA. “A personalized approach based on a person’s genetic makeup is increasingly being investigated for delivering optimum treatment to the ‘right’ patient.”

Ondansetron is a medication currently used to treat nausea and vomiting, often following chemotherapy. It works by blocking serotonin-3 receptors and has shown potential as a treatment for defined subpopulations with alcohol dependence.

In previous studies, Professor Bankole Johnson, D.Sc., Ph.D., M.D., and his team at the University of Virginia, Charlottesville, have shown that variations in genes which encode the serotonin transporter, a protein that regulates the concentration of serotonin between nerve cells, can significantly influence drinking intensity. They have also shown that the effectiveness of ondansetron therapy among people with alcohol dependence is influenced by variations of the serotonin transporter gene.

In the current study, Dr. Johnson and his colleagues extended their prior work by analyzing variants of serotonin receptor genes, collectively designated as HTR3, among nearly 300 alcohol-dependent individuals who were participating in a clinical trial of ondansetron. They found that three HTR3 variants were significantly associated with the effectiveness of ondansetron treatment for alcohol dependence.

“Taken together, these studies implicate a collective effect of serotonin receptor



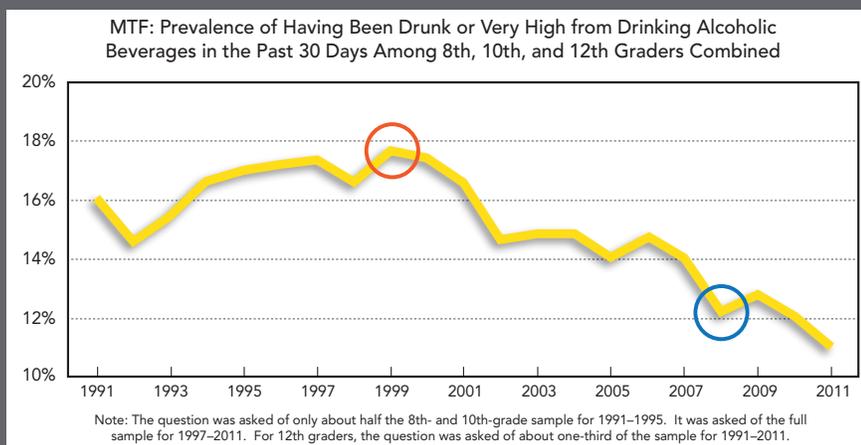
and transporter gene combinations, defined by a five-marker genotype panel, on the response to treatment with ondansetron for a genetically defined subpopulation of individuals with alcohol dependence,” said Professor Johnson. “Multi-site, larger studies are about to begin to progress this work.”

Reference:

Johnson, B.A.; Seneviratne, C.; Wang, X.-Q.; et al. Determination of genotype combinations that can predict the outcome of the treatment of alcohol dependence using the 5-HT₃ antagonist ondansetron. *American Journal of Psychiatry*, July 30, 2013 [Epub ahead of print]. PMID: 23897038.

BY THE NUMBERS

THE IMPORTANCE OF BEING TRENDY



Reprinted from *Surveillance Report No. 96: Trends in Underage Drinking in the United States, 1991–2011*. Chen, Chiung M.; Yi, Hsiao-ye; Faden, Vivian B. January 2013.

It’s back-to-school time, a reminder that in a few months we will be hearing about the results of the annual Monitoring the Future survey. MTF, as it’s affectionately known, produces one of the Nation’s most important reports on alcohol and other substance use by adolescents. MTF is extremely valuable for several reasons. For example, it reliably captures its target group—8th, 10th, and 12th graders—because it is conducted in schools.

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NEWS FROM THE FIELD

DISRUPTING DRINKING MEMORIES MAY HELP PREVENT RELAPSE

New research supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) suggests that a drug currently used to prevent the rejection of transplanted organs could someday help lessen the alcohol cravings that often lead to relapse among people with drinking problems. Alcohol-related memories, or cues—such as the smell of alcohol—can trigger cue-induced alcohol craving. Previous research has found that the mammalian target of rapamycin complex 1 (mTORC1), a group of proteins found in cells throughout the body, is involved in memory processes in the brain and also plays an important role in alcohol-seeking behavior by activating this complex in select brain regions.

In a study published online in *Nature Neuroscience*, researchers from the University of California,

San Francisco, examined whether inhibiting the activated mTORC1 could disrupt memories of alcohol cues—and thus diminish alcohol relapses in rats that had been trained to binge drink. After a period of alcohol abstinence, researchers exposed the rats to a small amount of alcohol to provide an odor and taste cue to the animals. The researchers then administered a dose of rapamycin, an mTORC1 inhibitor. Compared with a control group that did not receive rapamycin, rats which received the drug sought and consumed less alcohol for the duration of the experiment.

The researchers note memory disruption has shown success in humans who are addicted to heroin and suggest that it may prove helpful in developing new relapse-prevention strategies in alcoholics as well.



Source:

Barak, S.; Liu, F.; Hamida, S.B.; et al. Disruption of alcohol-related memories by mTORC1 inhibition prevents relapse. *Nature Neuroscience* 16(8):1111–1117, 2013. PMID: 23792945. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23792945>. PMID 23792945.

NEWS FROM THE FIELD

3-D IMAGE ANALYSIS PROMISES TO IMPROVE DETECTION OF CHILDREN AFFECTED BY PRENATAL ALCOHOL

Computerized image analysis can detect subtle changes in facial features that can occur when children are exposed to alcohol before birth, according to a study conducted through the NIAAA-funded Collaborative Initiative on Fetal Alcohol Spectrum

Disorders (CIFASD). The study suggests that three-dimensional (3-D) imaging could allow earlier identification of children at risk for cognitive deficits from heavy prenatal alcohol exposure, especially those who lack the



classic facial characteristics of Fetal Alcohol Syndrome (FAS).

Prenatal alcohol exposure causes a continuum of effects. Children with FAS, the most serious consequence of heavy drinking during pregnancy, have facial abnormalities including small eye width, smoothing of the ridges between the base of the nose and the upper lip, and a thin upper lip border. They may also have growth deficits and neurocognitive problems.

Collaborating with other CIFASD investigators and additional researchers in South Africa, lead investigator Peter Hammond, Ph.D., of the University College London, identified novel strategies for detecting the facial effects of prenatal alcohol exposure among children in Cape Town, South

Africa, where the incidence of heavy alcohol use during pregnancy and FAS are among the highest in the world.

Using 3-D photography and computerized image analysis, the researchers examined facial characteristics of children either not exposed or heavily exposed to alcohol and compared their observations with FASD categorizations. They found that 3-D facial image analyses enhanced the ability to detect a broad range of alcohol-induced facial changes. More testing of these techniques is planned in South Africa, the United States, and the Ukraine.

Source:

Suttie, M., et al. Facial dysmorphism across the fetal alcohol spectrum. *Pediatrics* 131:3 e779–e788, 2013. PMID: 23439907.

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comparing two of these children, looking for an answer, and while talking to the staff as I always did, one of them responsible for the two children indicated to me that both of their mothers were heavily alcohol dependent. And the spark hit! . . . I looked back at all my files and conducted in-depth inquiries: All the children marked by this syndrome had alcoholic mothers! I was rapidly convinced.”¹ Following up on Dr. Lemoine’s paper on 127 cases of this syndrome published in the *French Pediatric Archives*, Drs. David Smith and Ken Jones² published on eight cases in the United States, and Fetal Alcohol Syndrome (FAS) became widely known around the world.

Information about the role of alcohol in FAS and FASD resulted in the requirement of a Federal warning label on all alcoholic beverages in the United States.

Once heavy alcohol use during pregnancy was linked to FAS, research over the next several decades identified a range of neuropsychological and developmental problems that were associated with varying levels of alcohol consumption during pregnancy. This spectrum of problems is now referred to as FASD. Ultimately, information about the role of alcohol in FAS and FASD resulted in the requirement of a Federal warning label on all alcoholic beverages in the United States. After a number of iterations, a bill passed in November 1988, and which became effective one year later, settled on the following language: “According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects.” The law also required the health warning to appear in a “conspicuous

and prominent” place on all alcoholic products, and in February 1990, the Treasury Department ordered the warning label to include the heading “GOVERNMENT WARNING” in capital letters.

DRINKING AND DRIVING

Epidemiologic data from the National Highway Traffic Safety Administration (NHTSA) was used to establish that alcohol consumption increases a driver’s risk of being involved in a car crash and also enabled researchers to correlate increased risk with blood alcohol concentration (BAC). As a result, the labeling law for alcoholic beverages also required the following warning: “Consumption of alcoholic beverages impairs your ability to drive a car or operate machinery, and may cause health problems.” Federal and State regulations addressing drinking and driving, such as laws in all 50 States that make it illegal to operate a motor vehicle at or above .08 BAC, also were put into place as a result of this research. Analyses also showed that driving after consuming alcohol was even more dangerous for young drivers, which informed passage of zero-tolerance laws, essentially making it illegal for individuals under the age of 21 to drive after drinking.

ALCOHOL DEPENDENCE

Thanks to data from epidemiologic surveys, scientists and clinicians have a richer understanding of alcohol dependence. Epidemiologic information showed us that most people with alcoholism have one episode and recover after a period of a few years. Importantly, epidemiologic information and analysis have also helped us understand that there is more than one subtype of alcoholism. These subtypes vary by age; family history of alcoholism; age of onset of dependence; and comorbid conditions such as bipolar disorder,

anxiety, and other substance use. This characterization can inform intervention by helping us learn which treatments are most likely to be successful for which patients (see “Gene Combinations Help Predict Treatment Success for Alcoholism Medication” in this issue).

Epidemiologic information and analysis have also helped us understand that there is more than one subtype of alcoholism.

OTHER ISSUES

There are many more examples of epidemiology informing us of alcohol’s effects across the human lifespan, including the identification of the potential benefits of moderate drinking for cardiovascular health; the identification of high-risk groups, such as children of alcoholics, for targeted prevention of alcohol use disorders; and the relationship of alcohol consumption and interpersonal violence. Researchers are continuing to use epidemiologic methods to explore these and other alcohol-related issues to provide the public with the most accurate information to inform their decisions involving alcohol use.

¹ Lemoine, P.; Harousseau, H.; Borteyru, J.P.; and Menuet, J.C. Children of alcoholic parents: Observed anomalies: Discussion of 127 cases. *Therapeutic Drug Monitoring* 25(2): 131, 2003. Additional source material for this article was kindly provided by Dr. Lemoine and was published in the *Journal of Fetal Alcohol Syndrome International*. Lemoine, P. The history of alcoholic fetopathies, 1997. Available full text at www.motherisk.org/JFAS_documents/History_Alcoholic_Fetopathies.pdf. PMID: 12657907.

² Jones, K.L., and Smith, D.W. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 302(7836):999–1001, 1973. PMID: 4127281.

NEWS FROM THE FIELD

CHRONIC ALCOHOL USE SHIFTS BRAIN'S CONTROL OF BEHAVIOR

Chronic alcohol exposure leads to brain adaptations that shift behavioral control away from an area of the brain involved in complex decisionmaking and toward a region associated with habit formation, according to a new study conducted in mice by scientists at the National Institutes of Health.

The finding provides a biological mechanism that helps to explain compulsive alcohol use and the progression to alcohol dependence. A report appears online in the *Proceedings of the National Academy of Sciences (PNAS)*.

The brain's prefrontal cortex is involved in decisionmaking and controlling emotion, whereas the dorsal striatum is thought to play a key role in motivation and habit formation. Past studies have shown that alcohol-dependent individuals show problems with skills mediated by the prefrontal cortex, such as impulse control.

These same individuals often show an exaggerated neural response in the dorsal striatum to alcohol-related cues.

To investigate whether changes in the dorsal striatum might account for these observations, researchers, led by Andrew Holmes, Ph.D., in the Laboratory of Behavioral and Genomic Neuroscience at NIAAA, measured changes in the brains of mice that were chronically exposed to alcohol vapors.

Dr. Holmes and his colleagues found profound changes in the dorsal striatum of these mice, including the expansion of neuronal dendrites, the branching projections of the nerve cell that conduct signals. Such changes are also seen with chronic exposure to drugs such as amphetamine. These structural changes were associated with changes in synaptic plasticity, the brain's ability to change in response to experience, and reduced activity of endocannabinoid receptors, which are

part of a signaling system that may play a role in sensation, mood, and memory.

Such changes could contribute to the emergence of habitual and compulsive patterns of behavior in alcohol abuse, and suggest that treatments designed to normalize striatal function may be an important approach for alcohol treatment.



Source:

DePoy, L.; Daut, R.; Brigman, J.L.; et al. Chronic alcohol produces neuroadaptations to prime dorsal striatal learning. *Proceedings of the National Academy of Sciences*, August 20, 2013 [Epub ahead of print].

<http://www.pnas.org/content/early/2013/08/15/1308198110.abstract>

NEWS FROM THE FIELD

NEW INSIGHT ON HOW THE BRAIN FORMS HABITS



New data offer a glimpse into the neurobiological mechanisms underlying the formation of habitual actions, such as addiction to alcohol.

In a study conducted in mice and rats, and published in the July 2013 online edition of *Nature Neuroscience*, scientists in NIAAA's Laboratory for Integrative Neuroscience examined the cellular basis for learning and memory

in the dorsolateral striatum, a part of the brain involved in habit learning. A particular receptor in the dorsolateral striatum, the cannabinoid type 1 receptor (CB1), is critical for habit learning.

First author Brian Mathur, Ph.D., explained that direct and indirect pathways originating in the striatum are composed of medium-sized spiny neurons (MSNs) and have opposing effects on movement. The relative activation of the direct pathway over the indirect pathway, known as a "go signal," is believed to encode for reinforcement of an action. A change in a neural pathway associated with learning a behavior is called neuroplasticity.

The researchers examined the role of CB1 in a form of neuroplasticity known as long-term depression of synaptic transmission (LTD). LTD refers to the long-lasting decrease in

the strength of signal transmission at a synapse, where signals pass from one neuron to another.

Using a novel combination of techniques, the investigators determined the specific contribution of different inputs onto direct and indirect pathway MSNs to LTD. One offered a mechanism for go-signal generation.

"This is a big step forward in understanding the possible molecular and circuit dynamics underlying habit formation," said Dr. Mathur. The research team hopes their research will help uncover novel therapeutic strategies for the treatment of alcohol use disorders.

Source:

Mathur, B.N.; Tanahira, C.; Tamamaki, N.; and Lovinger, D.M. Voltage drives diverse endocannabinoid signals to mediate striatal microcircuit-specific plasticity. *Nature Neuroscience* 16(9):1275-1283, 2013. PMID: 23892554.

5 QUESTIONS WITH . . .

VIVIAN FADEN, PH.D.

Director of the NIAAA Office of Science Policy and Communications and Associate Director for Behavioral Research



1 You speak to audiences about the importance of understanding that not all data are created equal. What do you mean by that?

When I say that I am trying to help people understand that not all data they read about or hear about in the media are equally good. For example, a nationally representative survey provides a different kind of information than an informal convenience survey conducted in a mall. I also try to help people understand the difference between statistical and practical significance. Although a difference needs to be statistically significant to matter in the first place, after that you should think about whether the size of the difference has any practical significance. There are many other things I could say about data quality, but there are textbooks for that.

2 You also cite the importance of understanding “When is a trend a trend?” Can you explain?

This is another of my pet peeves. A year-over-year change may be the beginning of a trend or signal an important change in direction, but to really understand what is happening over time, we need multiple data points. For tracking changes in cancer incidence, traffic crashes, and underage drinking, among many, many other things, looking across multiple years of data is what really tells the story.

3 How has a reliance on solid data helped to shape NIAAA’s publications, such as *Helping Patients Who Drink Too Much: A Clinician’s Guide*, and the *Alcohol Screening and Brief Intervention for Youth: A Practitioner’s Guide*?

In these publications, analysis of data provided the foundation for critical pieces of information. For example, in the *Clinician’s Guide* we provide practitioners with information about the likelihood of patients with varying patterns of daily and weekly consumption having an alcohol use disorder. In the *Youth Guide*, the two screening questions are based on the analysis of data from an 8-year span of data from the National Survey on Drug Use and Health (NSDUH) and included information from more than 166,000 youth ages 12 to 18, and from multiple longitudinal surveys of young people as they grew up.

4 You have a background in child psychology. How has that integrated with your broader research at NIAAA?

My interests in child psychology have dovetailed beautifully with NIAAA’s relatively recent focus on underage and college drinking prevention. That and the fact that my oldest child entered college just as NIAAA began its college initiative in the late 1990s.

5 You’re a native New Yorker transplanted to the Washington, DC, area. What do you say about the claims that local bagels & pizza don’t taste as good as those from the Big Apple?

I say that just like it was for the cholera epidemic in 19th century London, which by the way was solved by epidemiology, it is ALL ABOUT THE WATER. And yes the bagels and pizza are better in New York City.



BY THE NUMBERS . . . Continued from page 2

Equally significant is the fact that the MTF results date back to 1991 for 8th and 10th graders—and all the way back to 1975 for 12th graders. This allows researchers to examine long-term *trends*, not just year-to-year fluctuations.

Why is that so important? From the graph, which illustrates the percentage of youth who reported being drunk in the past 30 days, it is easy to see some pretty steep year-to-year upticks (such as in 1999) and dips (such as in 2008).

Too much focus on these changes, however, can detract from the overall picture. A look at the data over time shows that since 1991 there has been a substantial decrease in the total number of students who reported having been drunk in the past 30 days—and that is actually pretty good news.

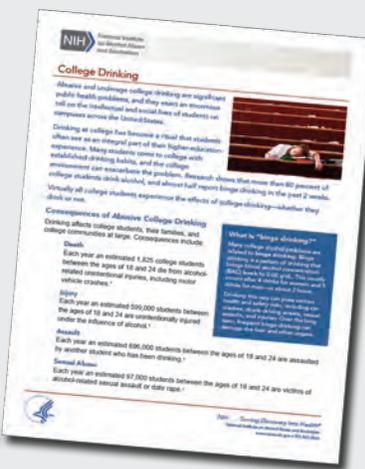
However, the MTF data also highlight that there is much work yet to be done, as unacceptably high percentages of students still report underage drinking and

getting drunk. When adolescents drink, they place themselves at greater risk for injuries, assaults, poor academic records, and other negative outcomes.

We still have work to do, but robust epidemiological data like those from MTF (and other national surveys) help build a reliable road map. We can both track progress and keep our eyes on the challenges ahead to better safeguard the health of young people.

Now Available—New Fact Sheets From NIAAA

Alcohol Overdose: The Dangers of Drinking Too Much provides information on the signs and symptoms of alcohol poisoning. It also provides guidelines on what to do if you suspect someone has alcohol poisoning. The fact sheet is available for download at <http://pubs.niaaa.nih.gov/publications/AlcoholOverdoseFactsheet/Overdosefact.htm>.



College Drinking describes the consequences of student drinking, from assault and academic problems to dependence and even death. It also includes information on strategies for preventing student alcohol use. The fact sheet is available

for download at <http://pubs.niaaa.nih.gov/publications/CollegeFactSheet/CollegeFact.htm>.

Visit www.niaaa.nih.gov or call 1-888-MY-NIAAA to download or order publications.

ABOUT US

NIAAA Spectrum is NIAAA's first-ever Webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences.

Each issue includes feature-length stories, new research findings from the field, image and data analyses, and an interview with an NIAAA staff member or alcohol researcher. *NIAAA Spectrum* is published three times a year.

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