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FEATURE

CLOSING THE TREATMENT GAP FOR ALCOHOL-ASSOCIATED LIVER DISEASE

Drinking too much—whether on a single occasion or over many years—can take a serious toll on an individual's health. Clinicians across the health care spectrum can play important roles in preventing and treating the harmful effects of alcohol. This role is particularly important among providers who manage patients with liver diseases.

Alcohol-associated liver disease (ALD) represents a spectrum of liver conditions, including steatosis, alcohol-associated hepatitis (AH), and cirrhosis. Alcohol misuse accounts for nearly half of liver disease deaths each year, and ALD is the most common alcohol-related cause of death. ALD-related deaths increased 22.4% between 2019 and 2020, and research suggests that mortality rates are increasing faster among women and among young adults ages 25–34 than in other groups.

"We've known for a long time that the liver is one of the principal sites of alcohol-related harm and disease," said National Institute on Alcohol Abuse and Alcoholism (NIAAA) Director George F. Koob, Ph.D. "Recent findings highlight the need for a paradigm shift in caring for patients with ALD."

A growing body of evidence indicates that integrating treatment of ALD with treatment of alcohol use disorder (AUD) can improve patient outcomes. For example, a 2020 study examined the rate of hospital readmission among patients with AH who either received outpatient or residential addiction treatment or participated in a

IN THIS ISSUE

mutual-support group shortly after hospital discharge. The researchers found the rate of 30-day hospital readmission was two to three times lower than among those who did not receive such treatment. These early treatments had even greater effects on the rates of alcohol relapse in the 30 days after hospital discharge and were associated with an 80% lower risk of long-term mortality.

In a recent commentary in *JAMA Network Open*, Lorenzo Leggio, M.D., Ph.D., of NIAAA and the National Institute on Drug Abuse and M. Katherine Jung, Ph.D., of NIAAA summarized the state of the science supporting a paradigm shift toward integrated treatment of AUD and ALD:

- Treating AUD with medications reduces the chances of ALD and the progression of existing ALD.
- However, most patients with ALD do not receive any form of AUD therapy.
- Work is needed to develop and study health care models that integrate ALD treatment with treatment for AUD.

Need for Clinical Trials

Although research shows promise for improving patient outcomes, integrated AUD and ALD treatment has not been tested extensively through clinical trials. To address this gap, NIAAA is working with specialists in liver disease, AUD, clinical trial design, and statistics, as well as with the U.S. Food and Drug Administration (FDA) and industry, to lay the groundwork for clinical trials in this area. In July 2022, NIAAA sponsored a workshop, Clinical Trial Design for Integrated Care for Patients with AUD and ALD, to explore the design of the next generation of clinical trials to evaluate the impact of active treatment of alcohol misuse on outcomes for patients with ALD.

"We know from observational studies in patients with ALD that treatment of the underlying AUD improves clinical outcomes among this patient population both in term of severity and mortality," said Svetlana Radaeva, Ph.D., of NIAAA, who organized the recent workshop. "Now we need to find the best ways to accomplish that goal."

Ongoing Research Programs

Clinical trials for integrating ALD and AUD treatment will complement NIAAA's established and ongoing research programs to close the ALD treatment gap:

- **Alcohol-associated Hepatitis Network (AlcHepNet)**: A network of translational and clinical studies testing potential therapies, and identifying risk factors, for the onset and progression of severe AH. Research conducted through AlcHepNet is helping to pave the way for integrated treatment of ALD and AUD.
- **Liver Cirrhosis Network**: An initiative established by the National Institute of Diabetes and Digestive and Kidney Diseases and co-funded by NIAAA and the National Cancer Institute to better understand the natural history of liver cirrhosis and evaluate the use of statins in cirrhosis treatment.
- **Medications Development Programs**: Cooperative Agreement and Small Business Innovation Research (SBIR) initiatives to advance promising compounds through the drug development pipeline for the treatment of alcohol-associated organ damage and AUD.

Early Liver Transplant for Alcohol-Associated Liver Disease?

ALD is now the most common indication for liver transplantation in the United States. Many U.S. transplant centers, however, require six months of alcohol abstinence before an individual with ALD can receive a liver transplant. The rationale for this waiting period is based in part on the belief that a significant period of abstinence might allow a person's ALD to stabilize, thereby obviating the need for transplantation. Stigma against people with alcohol-related problems may also play a role. This waiting period presents a particular challenge for patients with severe AH—a condition with a very high mortality rate in the first three to six months after diagnosis.

An emerging body of evidence suggests that patients who receive a liver transplant without the six-month waiting period (called early liver transplantation) have similar survival outcomes and alcohol relapse rates as patients who receive a transplant after the six-month waiting period. To stimulate research in this area, NIAAA has issued a request for applications (RFA) titled "Early Liver Transplantation Cohort Study for Alcohol-associated Liver Diseases." The RFA encourages collaborative, multidisciplinary research on the factors that influence the selection, management, and long-term outcomes of patients who receive early liver transplantation.

References:

Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ. 2018 Jul 18;362:k2817. PubMed PMID: 30021785

White AM, Castle IP, Powell PA, Hingson RW, Koob GF. Alcohol-related deaths during the COVID-19 pandemic. JAMA. 2022 May 3;327(17):1704–6. PubMed PMID: 35302593

Peeraphatdit TB, Kamath PS, Karpyak VM, Davis B, Desai V, Liangpunsakul S, Sanyal A, Chalasani N, Shah VH, Simonetto DA. Alcohol rehabilitation within 30 days of hospital discharge is associated with reduced readmission, relapse, and death in patients with alcoholic hepatitis. Clin Gastroenterol Hepatol. 2020 Feb;18(2):477–85.e5. PubMed PMID: 31042580

Leggio L, Jung MK. The need for integrating addiction medicine and hepatology. JAMA Netw Open. 2022 May 2;5(5):e2213022. PubMed PMID: 35594051

Vannier AGL, Shay JES, Fomin V, Patel SJ, Schaefer E, Goodman RP, Luther J. Incidence and progression of alcohol-associated liver disease after medical therapy for alcohol use disorder. JAMA Netw Open. 2022 May 2;5(5):e2213014. PubMed PMID: 35594048

Winder GS, Fernandez AC, Mellinger JL. Integrated care of alcohol-related liver disease. J Clin Exp Hepatol. 2022 Jul–Aug;12(4):1069–82. PubMed PMID: 35814517

NIAAA. Clinical trial design for integrated care for patients with alcohol use disorder (AUD) and alcohol-associated liver disease (ALD). [cited 2022 Oct 24]. Available from: https://www.niaaa.nih.gov/news-events/meetings-events-exhibits/clinical-trial-design-integrated-care-patients-alcohol-use-disorder-aud-and-alcohol-associated-liver

Herrick-Reynolds KM, Punchhi G, Greenberg RS, Strauss AT, Boyarsky BJ, Weeks-Groh SR, Krach MR, Anders RA, Gurakar A, Chen PH, Segev DL, King EA, Philosophe B, Ottman SE, Wesson RN, Garonzik-Wang JM, Cameron AM. Evaluation of early vs standard liver transplant for alcohol-associated liver disease. JAMA Surg. 2021 Nov 1;156(11):1026–34. PubMed PMID: 34379106

NIAAA. Early liver transplantation cohort study for alcohol-associated liver diseases. [cited 2022 Oct 24]. Available from: https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-22-003.html

NEWS FROM THE FIELD

NEW RESEARCH CHARACTERIZES ALCOHOL USE DISORDER PROFILES TO PREDICT TREATMENT OUTCOMES

Alcohol use disorder (AUD) is a heterogeneous disorder, meaning individuals with AUD differ in their clinical symptoms and in the biological and psychological factors that contribute to their disorder. A better understanding of individual differences in AUD could inform the development of tailored treatment approaches to increase treatment effectiveness. New research from the University of New Mexico, the University of Washington, and Syracuse University published in *Psychology of Addictive Behaviors* shows that assessing patients based on biological and psychological domains of addiction could be a good way to predict treatment outcomes.

Addiction to alcohol and other substances can be framed as a repeating cycle of three stages that link to and feed on each other. The binge/intoxication stage is characterized by seeking the positive feelings of reward associated with alcohol. This stage also leads to the development of incentive salience, in which an object or event associated with alcohol consumption can itself trigger powerful urges to drink. The negative affect stage is marked by seeking alcohol for relief from the negative emotional and physical pain as well as other unpleasant feelings brought on by withdrawal when a person stops drinking. The preoccupation/anticipation stage reflects changes in executive brain function that contribute to alcohol craving and loss of control over drinking.

Several years ago, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) established an Addictions Neuroclinical Assessment (ANA), a framework to better understand individual differences in AUD. The ANA incorporates measures related to incentive salience, negative emotionality, and changes in executive function. The current study built on previous research on these three addiction cycle domains and aimed to determine if a simplified assessment, which would be easier to implement in a broad range of clinical settings, could also be effective.

The researchers used existing data from two of the largest AUD treatment clinical trials ever conducted—Project MATCH, a national, multisite, randomized clinical trial of treatment matching for AUD; and the COMBINE Study (often referred to as COMBINE), the largest alcohol pharmacotherapy trial conducted in the United States. Using these data, the researchers selected 15 measures corresponding to the three domains of the addiction cycle to determine if the domains could predict treatment outcomes among the participants. They found that the 15-measure assessment was specific enough—and generalizable enough across sociodemographic groups—to predict treatment outcomes.

Specifically, the researchers found that individuals with higher negative emotionality and incentive salience prior to receiving treatment were more likely to have a higher intensity and frequency of drinking at one and three years after treatment. Additionally, individuals with high negative emotionality prior to treatment had the lowest overall functioning at three years post-treatment. Moreover, while executive function measures were not related to later drinking patterns, individuals with more self-control and greater executive function were more likely to maintain a non-abstinent recovery. Future research will determine if individualized profiles such as these could help drive the use of tailored behavioral or medication treatment approaches for AUD.

References:

Witkiewitz K, Stein ER, Votaw VR, Hallgren KA, Gibson BC, Boness CL, Pearson MR, Maisto SA. Constructs derived from the addiction cycle predict alcohol use disorder treatment outcomes and recovery 3 years following treatment. Psychol Addict Behav. 2022 Aug 11. Epub. PubMed PMID: 35951419

NIAAA [Internet]. The cycle of alcohol addiction [cited 2022 Oct 24]. Available from: https://www.niaaa.nih.gov/publications/cycle-alcohol-addiction

Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997 Oct 3;278(5335):52–58. PubMed PMID: 9311926

Kwako LE, Momenan R, Litten RZ, Koob GF, Goldman D. Addictions Neuroclinical Assessment: a neuroscience-based framework for addictive disorders. Biol Psychiatry. 2016 Aug 1;80(3):179–189. PubMed PMID: 26772405

Project MATCH Research Group. Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. J Stud Alcohol.1997 Jan;58(1):7–29. PubMed PMID: 8979210

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A, COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006 May 3;295(17):2003–2017. PubMed PMID: 16670409

HEART MEDICATION SHOWS POTENTIAL PROMISE AS TREATMENT FOR ALCOHOL USE DISORDER

Spironolactone, a medication for heart problems and high blood pressure, may also be effective for treating alcohol use disorder (AUD), according to a new National Institutes of Health study. The study presents converging evidence from experiments in rodents, as well as electronic health data from humans, suggesting that spironolactone may play a role in reducing alcohol drinking. The research, published in *Molecular Psychiatry*, was led by scientists at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and Yale School of Medicine in New Haven, Connecticut.

"Seeing similarities across species and research designs gives us confidence that we are onto something potentially important scientifically and clinically," said Lorenzo Leggio, M.D., Ph.D.,

chief of the Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, a joint laboratory of NIDA and NIAAA, and one of the study's senior authors.

Less than 10 percent of people with AUD receive any treatment, despite the availability of behavioral treatments and three safe and effective medications approved by the U.S. Food and Drug Administration. Given the diverse biological processes that contribute to AUD and the variability in the presentations of the disorder across individuals, research to identify new medications is needed to provide a broader spectrum of treatment options that can be tailored to individual needs.

Previous preclinical research suggests that signaling through a specific corticosteroid receptor (mineralocorticoid receptors), which can be blocked by spironolactone, might play a role in alcohol consumption and craving. In the present study, researchers showed, through experiments performed in mice and rats, that spironolactone decreases alcohol consumption. Moreover, in a complementary analysis of health records of a large sample of people from the U.S. Department of Veterans Affairs health care system, the researchers found that individuals who had been prescribed spironolactone (for reasons such as heart problems or high blood pressure) were more likely to self-report reductions in alcohol consumption.

"These results are encouraging," said NIAAA Director George F. Koob, Ph.D., a co-author of the study. "This study provides scientific support for clinical studies to understand how the medication may reduce alcohol consumption and assess the safety and potential efficacy of spironolactone in humans with AUD."

References:

Farokhnia M, Rentsch CT, Chuong V, McGinn MA, Elvig SK, Douglass EA, Gonzalez LA, Sanfilippo JE, Marchette RCN, Tunstall BJ, Fiellin DA, Koob GF, Justice AC, Leggio L, Vendruscolo LF. Spironolactone as a potential new pharmacotherapy for alcohol use disorder: convergent evidence from rodent and human studies. Mol Psychiatry. 2022 Nov;27(11):4642–4652. Epub 2022 Sep 20. PubMed PMID: 36123420

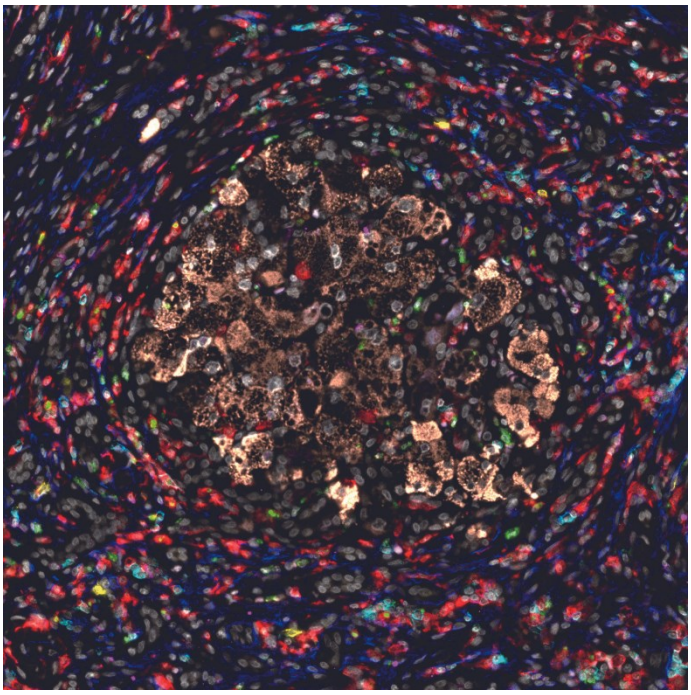
NIAAA [Internet]. News Release: Heart medication shows potential as treatment for alcohol use disorder. 2022 Sept 20. [cited 2023 Jan 10]. Available from: https://www.niaaa.nih.gov/news-events/news-releases/heart-medication-shows-potential-treatment-alcohol-use-disorder

NIAAA [Internet]. Alcohol Treatment Navigator. What medications are available for treating AUD? [cited 2022 Oct 24] Available from: https://alcoholtreatment.niaaa.nih.gov/FAQs-searching-alcohol-treatment#topic-what-medications-treat-aud

A CLOSER LOOK

RESEARCHERS GAIN NEW INSIGHT INTO THE DEVELOPMENT OF SEVERE ALCOHOL-ASSOCIATED HEPATITIS

Alcohol misuse can lead to alcohol-associated hepatitis (AH), a form of liver disease with a high short-term mortality rate in severe cases. Currently, no medications have been approved by the U.S. Food and Drug Administration to treat AH, and liver transplantation is often required due to liver failure. A better understanding of how AH develops could help improve AH treatment and prevent progression to severe disease. A recent study has shown a positive correlation among neutrophilic



The image above shows staining of liver tissue from a patient with severe AH using different fluorescent colors to label different cell types. The staining reveals a broad array of inflammatory cells surrounding liver cells located in the center of the image.

infiltration and the model for end-stage liver disease score (MELD score, a scoring system predicting prognosis of liver disease) and serum alanine aminotransferase (ALT) levels. Researchers found a mechanism by which neutrophils—a type of white blood cell—contribute to liver injury in AH. Published in the *Journal of Clinical Investigation*, the study was supported by the National Institute on Alcohol Abuse and Alcoholism.

A growing body of evidence indicates that various types of cells in the body's immune system are involved in AH, including neutrophils. When a person develops severe AH, the levels of neutrophils increase in the liver, but how these cells contribute to the development of the disease is not clear. To gain insight, the researchers examined neutrophils and other immune cells in the livers of 40 patients with severe AH. The authors showed that neutrophil-derived reactive oxygen species (ROS) promoted liver injury and inflammation in the experimental model. This suggests that neutrophil-generated ROS is one of the mechanisms that contribute to liver injury and dysfunction in severe AH in addition to many other cell types involved in severe AH pathogenesis.

More specifically, the researchers found increased expression of neutrophil cytosolic factor 1 (NCF1), a gene involved in controlling ROS. To gain insight into the mechanism of NCF1 in severe AH with high neutrophil levels, the researchers examined NCF1 in an animal model of liver injury. They found that NCF1 contributes to higher levels of ROS and thus liver inflammation/injury by inhibiting adenosine monophosphate-activated protein kinase (AMPK, a key regulator of lipid metabolism) and by inhibiting microRNA-223 (a key anti-inflammatory microRNA). MicroRNAs are non-coding RNA molecules thought to play a key role in the regulation of gene expression.

These findings provide important insight into the mechanisms that may drive liver injury, and ultimately liver failure, in individuals with severe AH. Additional clinical and translational research is needed to more fully characterize the pathological mechanisms that contribute to severe AH and to identify novel therapeutic targets for this devastating disease.

Reference:

Ma J, Guillot A, Yang Z, Mackowiak B, Hwang S, Park O, Peiffer BJ, Ahmadi AR, Melo L, Kusumanchi P, Huda N, Saxena R, He Y, Guan Y, Feng D, Sancho-Bru P, Zang M, Cameron AM, Bataller R, Tacke F, Sun Z, Liangpunsakul S, Gao B. Distinct histopathological phenotypes of severe alcoholic hepatitis suggest different mechanisms driving liver injury and failure. J Clin Invest. 2022;132(14):e157780. PubMed PMID: 35838051

SPOTLIGHT

NATIONAL CONFERENCE FOCUSES ON HEALTH ISSUES AFFECTING WOMEN AND GIRLS

In October, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Interagency Work Group on Drinking and Drug Use in Women and Girls (IWG) hosted the 2022 National Conference on Alcohol and Other Substance Use in Women and Girls: Advances in Prevention, Treatment, and Recovery. More than 400 attendees participated in the two-day virtual conference, which featured plenary lectures by NIAAA Director George F. Koob, Ph.D., National Institute on Drug Abuse Director Nora Volkow, M.D., and National Institute of Mental Health Director Joshua Gordon, M.D., Ph.D. Valerie A. Earnshaw, Ph.D., of the University of Delaware gave a keynote address on stigma and substance use.

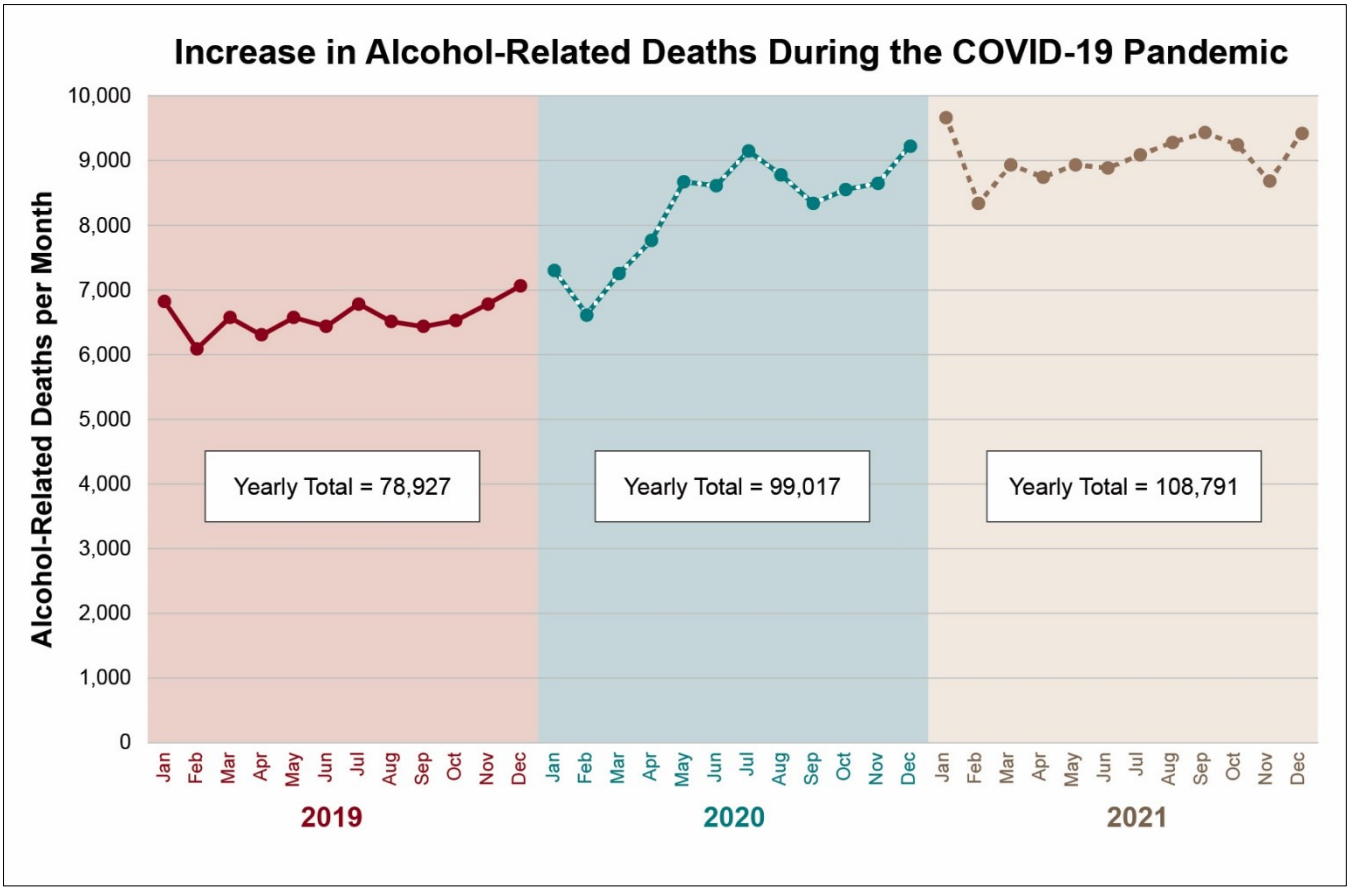
The conference highlighted the importance of reducing stigma and other health barriers and featured panels on harmful substance use in women, harmful substance use among adolescent girls, model programs for mothers with substance use disorders and children with prenatal substance exposure, prevention and treatment for special populations, and co-occurring substance use and mental health disorders. In addition, breakout sessions included topics such as adolescents, pregnant and pre-conception women, women of color, people living with HIV, post-menopausal women, legal-involved populations, military families, children and adults living with fetal alcohol spectrum disorders, and LGBTQIA+ populations.* Discussions focused on opportunities for building effective community-based participatory research, working with Black churches and other faith-based partnerships, and incorporating personal spirituality into treatment planning.

According to conference co-chairs Deidra Roach, M.D., and Joan Romaine of NIAAA, the working group is planning future webinars and other follow-up opportunities. News about upcoming events, links to a recording and summary of the conference, and contact information for the conference organizers will be posted on the IWG section of the NIAAA website.

LGBTQIA+ stands for lesbian, gay, bisexual, transgender, queer, intersex, and asexual. The plus sign includes other members of the community, such as genderfluid, nonbinary, or two-spirit individuals, among others.

BY THE NUMBERS

ALCOHOL-RELATED DEATHS CONTINUED TO INCREASE IN 2021



The figure above shows the number of alcohol-related deaths each month in 2019, 2020, and 2021. The annual total number of deaths increased 25% between 2019 and 2020 (from 78,927 to 99,017). The annual total number increased another 10% between 2020 and 2021 (from 99,017 to 108,791). A death was considered alcohol-related if alcohol was listed in a death certificate as the primary cause (e.g., alcohol-associated liver disease) or a contributing factor (e.g., death from a fall while intoxicated).

Rates of deaths involving alcohol increased by less than 2.5% per year in the two decades leading up to the COVID-19 pandemic. The 25% leap in 2020 was unprecedented. Per capita consumption of alcohol, measured as gallons of pure alcohol per person, increased by 2.9% in 2020. This was the largest increase in more than 50 years, since a 3.4% increase in 1968.

"The fact that alcohol-related deaths continued to climb in 2021 is truly concerning," said Aaron White, Ph.D., Senior Scientific Advisor to the NIAAA Director. "NIAAA's hope is that continuing to educate the public and the health care community about the potential health risks of excessive alcohol consumption and that continuing to emphasize the importance of alcohol screening and brief intervention can help bring these numbers down."

References:

U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC) [Internet]. National Center for Health Statistics Mortality Data on CDC WONDER. Multiple cause of death, 2018–2021. 2023. [cited 2023 Feb 9]. Available from: https://wonder.cdc.gov/controller/saved/D157/D324F825

NIAAA. Surveillance report #119: apparent per capita alcohol consumption: national, state, and regional trends, 1977–2020. [cited 2023 Jan 19]. Available from: https://pubs.niaaa.nih.gov/publications/surveillance119/CONS20.htm

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