Welcome to the Biannual Bulletin from the Center for Addiction Research! The biannual bulletin contains news stories and summaries provided by CAR members about the great work they are doing. Thank you to those who shared stories for this edition! To have your work included in the next issue, coming in late January 2026, please send a brief summary/story accompanied by pictures or graphics (if available) to Jen Rowe (roweji@ucmail.uc.edu) any time prior to January 15th. Thank you!

CAR Biannual Bulletin

July 2025

Member Research Updates

2026 Next Bulletin Release Date:
- Late January

2026 Next Deadline for Submitting Stories:
- January 15th

Register Now! Center for Addiction Research Summer Speaker Series, final session, Wednesday, August 13, 2025, at 12:00 PM, featuring Dr. Davide Amato and Jon Kostas, "Psychedelics as Therapeutics for Substances Use Disorder: A Perspective on Their Neurobiology and Future Clinical Applications."
Sponsored by: Center for Addiction Research

Prenatal Opioid Exposure Linked to Smaller Brain Volume

Opioid exposure in the second or third trimester was associated with smaller brain volumes in newborns, a prospective U.S. study found.

Total brain volume averaged nearly 5% smaller among 173 newborns with antenatal opioid exposure than 96 without such exposure after controlling for birth weight, postmenstrual age at MRI, and maternal factors (387.51 vs 407.06 cm3, 95% CI 8.75-30.35, adjusted P=0.002), according to Catherine Limperopoulos, PhD, of Children's National Hospital in Washington, D.C., and colleagues.

The exposed group also had significantly smaller volume compared to the control group for cortical gray matter, deep gray matter, white matter, cerebellum, brainstem, and the right and left amygdala, they reported in JAMA Pediatrics.

"Antenatal opioid exposure has been associated with adverse neurodevelopmental consequences in children," lead author Yao Wu, PhD, also of Children's National Hospital, told MedPage Today in emailed remarks. "However, the effects of antenatal opioid exposure on the developing brain remain poorly understood."

"Our findings of impaired regional brain growth in newborns with antenatal opioid exposure may serve as early biomarkers of later neurodevelopmental dysfunction in this high-risk population," Wu added.

The study is a rigorous "first dive" into long-term impact of exposure, wrote Nethra Madurai, MD, and Lauren L. Jantzie, PhD, both of Johns Hopkins University School of Medicine in Baltimore, in an accompanying editorial.

"Indeed, we must shift our focus beyond the initial withdrawal symptoms associated with POE [prenatal opioid exposure] if we are to improve the lifelong health and well-being of infants and children impacted by the opioid epidemic," they wrote.

The results affirm the vulnerability of the developing brain and lay a foundation "that will hopefully lead to meaningful interventions and improved outcomes" for affected children, although not yet sufficient to suggest any change in medication-assisted opioid use in pregnancy, the editorialists suggested.
The most common opioids used during pregnancy in the study were buprenorphine (68.8%) and methadone (26%).

Methadone-exposed newborns had significantly smaller white matter volume compared with controls (155.87 vs 166.64 cm3, adjusted P=0.01), while buprenorphine-exposed newborns had significantly smaller right amygdala volume compared with controls (0.50 vs 0.55 cm3, adjusted P=0.008). Additionally, newborns exposed to opioids alone and those exposed to opioids plus other substances both had significant reductions in volumes compared to controls for total brain volume (opioid-only: 389.77 vs 407.15 cm3, adjusted P=0.03; polysubstance: 386.49 vs 407.15 cm3, adjusted P=0.005). The same pattern was seen for cortical gray matter, deep gray matter, cerebellum, brainstem, and right amygdala volume.

Furthermore, polysubstance-exposed newborns had smaller volumes in white matter (159.27 vs 166.71 cm3, adjusted P=0.02) and the left amygdala (0.48 vs 0.51 cm3, adjusted P=0.04) compared with controls.

The prospective Outcomes of Babies with Opioid Exposure (OBOE) study recruited newborns with antenatal opioid exposure in the second or third trimester and contemporary, unexposed controls seen at four U.S. sites from August 2020 to December 2023.

MRIs were performed at a mean age of about 43 postmenstrual weeks for exposed and unexposed infants. Slightly less than half of the infants were female.

While findings were adjusted for postmenstrual age at MRI, sex, birth weight, maternal smoking status, and maternal education, limitations included lack of detailed data on the amount and duration of opioid exposure and not controlling for maternal mental health disorders.

"Finally, although we are prospectively collecting outcome data," the researchers further noted, "the short- and longer-term impact of decreased brain volumes on later neurodevelopment in this cohort is not yet known."

Read the article from MedPage Today:
"Prenatal Opioid Exposure Linked to Smaller Brain Volume"

Read the study published in the journal *JAMA Pediatrics*

Machine learning brings new insights to cell's role in addiction, relapse
UC, University of Houston collaborate on research published in Science Advances

Object recognition software is used by law enforcement to help identify suspects, by self-driving cars to navigate roadways and by many consumers to unlock their cell phones or pay for their morning coffee.

Now, researchers led by the University of Cincinnati's Anna Kruyer and the University of Houston's Demetrio Labate have applied object recognition technology to track changes in brain cell structure and provide new insights into how the brain responds to heroin use, withdrawal and relapse. The research was published April 30 in the journal Science Advances.

Kruyer's lab focuses on relapse to heroin use, as many overdose deaths occur when people overestimate their capacity for drug use during relapse. The team has developed an animal model of relapse over the past seven years, studying interactions between brain cells and the reward center of the brain that orchestrates the relapse process.

"We want to understand the neurons that are involved and all of the different cells and molecules that can shape that activity," said Kruyer, PhD, assistant professor in the Department of Pharmaceutical Sciences in UC's James L. Winkle College of Pharmacy. "The idea would be if you can interfere with relapse, you can help someone stay clean."

"Essentially the Holy Grail is how to find treatments that prevent opioid users from relapsing," added Michela Marini, a University of Houston doctoral student who was the lead author on the study.

While neurons are a more commonly studied brain cell, Kruyer has focused on another cell called an astrocyte. Astrocytes have many functions, including metabolic support for neurons, providing molecules that neurons turn into neurotransmitters, and shielding or uncovering different receptors during synaptic activity.

"Astrocytes are a kind of protective cell that can restore synaptic homeostasis," Kruyer said. "They are super dynamic relative to the synapse, and they're moving toward and away from the synapse in real time in a way that can impact drug seeking. So if you prevent this reassociation with synapses during relapse, you can increase and prolong relapse."

Labate is an applied mathematician with expertise in harmonic analysis and machine learning.

"A central focus of my research is the development and application of mathematical techniques to uncover meaningful patterns in non-Euclidean data, such as the analysis of complex shapes," said Labate, PhD, professor in the University of Houston Department of Mathematics. "The study of astrocytes provides an ideal setting for this type of investigation: these cells are highly heterogeneous, varying widely in size and shape, and are capable of dynamically remodeling their morphology in response to external stimuli."

While animal model studies have produced results, Kruyer and her colleagues faced a barrier in that the techniques used could not be translated for human subjects. To work around this issue, they focused on an astrocyte protein that essentially acts as the cell's skeleton.

"We thought if we could figure out a way to translate what we're seeing at the synaptic level to changes in the cytoskeleton, maybe we could see if astrocytes are doing something critical during relapse in humans," Kruyer said.

A team of mathematicians led by Labate trained object recognition machine learning models on hundreds of astrocyte cells until the technology could accurately detect an astrocyte within an image, similar to how object recognition software works.

“Machine learning techniques have been widely applied in the literature to image classification tasks, where the objective is to assign each cell to a specific category,” Labate explained. “In such contexts, machine learning is particularly powerful for identifying image-based cellular features that are difficult to capture using traditional geometric descriptors, yet serve as effective discriminators between classes.”

Once the program could identify astrocytes, the team trained it to analyze specific structures based on 15 different criteria, including astrocyte cytoskeletal density (similar to bone density), size, length versus sphericalness and number of smaller branches coming off of the main branch.

“You can think about this like if you gave a computer a bunch of images of street scenes, it would commonly see pedestrians, cars and buildings,” Kruyer said. “If you give a computer 1,000 images of astrocytes, there are things it would commonly see. This is the segmentation process whereby a computer can now start to make measurements of the different features of the astrocyte.”

Using all 15 measurements weighted by their importance in the computer’s precision to detect astrocytes, researchers developed a single metric to quantify the characteristics of each astrocyte.

“In previous work, I have utilized machine learning for both cell classification and segmentation problems,” Labate said. “In this paper, however, we address a more nuanced question: are there specific subpopulations of astroglia that exhibit more pronounced morphological changes compared to the rest? To investigate this, we introduced the concept of distance to compare the shape characteristics of individual astrocyte cells while accounting for the inherent heterogeneity within the population.”

Applying the model

After developing the machine learning model to identify astrocytes and report the new metric, the team looked at astrocytes specifically within an area of the brain called the nucleus accumbens (NAc) that is active during drug relapse.

The model was able to predict exactly where in the NAc an astrocyte came from based on its structure with 80% accuracy.

“This tells us that astrocyte structure varies by anatomy,” Kruyer said. “Astrocytes have been considered to be this homogenous type of cell, but this indicates to us that astrocyte structure varies significantly by location — perhaps the shape and the size have something to do with their function.” Using animal models and the new knowledge gained from the computer models, the team found that astrocytes appear to shrink and become less malleable after exposure to heroin.

“These data suggest that heroin is doing something molecularly that makes astrocytes less able to respond to synaptic activity and maintain homeostasis,” Kruyer said.

“This paper exemplifies the strength of interdisciplinary collaboration, where innovative quantitative tools are developed or adapted to tackle complex biological questions,” added Labate. “The success of this research lies in the effective communication between disciplines and in our

willingness to push the boundaries of traditional machine learning to address biologically meaningful and timely challenges."

Next steps
Kruyer said she is most excited about the application of machine learning to a biological question, which eliminates human error and biases and makes the research more easily translatable from animal models to humans.

"We're asking open-ended questions, and it's giving us all of these really fine-grained detailed answers, and then what we do with that is up to us," she said. "Human astrocytes are much larger, much more complex and way more abundant than in the animal models, so applying a tool like this is really cool to carry forward in humans."

Moving forward, the team wants to learn more about the specific mechanisms of astrocytes in each region within the NAc and train new models using human tissue samples. Long term, the knowledge gained could help develop new treatments for addiction focused on restoring or replacing astrocytes to their functions prior to being exposed to heroin.

"Collaborating with the University of Cincinnati on this groundbreaking study has been incredibly rewarding," Marini said. "By uncovering how astrocytes are altered by heroin use, we're opening new doors not just for addiction research, but for understanding the brain's response to a wide range of drugs and neurological conditions. This kind of work is essential for developing better treatments in the future."

Labate said the machine learning method his team developed can additionally be adapted and applied to other types of cells with intricate structures.

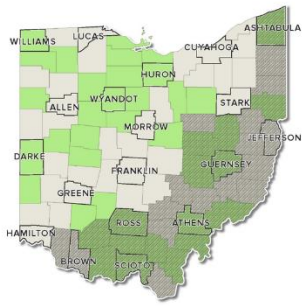
"By enabling precise quantification and comparison of single-cell morphological features, this approach opens the door to the development of novel techniques for identifying cellular or molecular biomarkers that reflect biological processes, disease states or responses to therapeutic interventions," he said. "More broadly, our work introduces a new quantitative framework for uncovering and validating fundamental mechanistic models underlying complex brain conditions, such as addiction to drugs of abuse."

Read a related article from Medical Xpress:
"Machine learning brings new insights to astrocytes' role in heroin addiction and relapse"

Read the study published in the journal *Sciences Advances*

Communities That HEAL (CTH) Intervention

Ohio Healing Communities Study



The Communities That HEAL (CTH) intervention was created by a team of opioid-overdose reduction experts from academic and medical institutions in the four states where the HEALing Communities Study took place: Ohio, Kentucky, Massachusetts, and New York. The CTH is a step-by-step process that puts community members at the center of all decision making and action to reduce overdose deaths. The intervention mirrors similar programs that have worked in communities to inspire change. The CTH stands apart from other approaches to community overdose reduction in two important ways:

1. The CTH is a data-driven approach, meaning that community members are presented with current information about the extent to which overdose death are happening in their area to inform their selection of evidence-based practices.

2. The CTH is a community-engaged approach, meaning that public health officials assist and empower communities to make choices, coordinate action, and put practices into place that will effectively reduce overdoses.

(Dr. T. John Winhusen is HEALing Communities Study, Ohio co-Principal Investigator)

Read a related study published in the journal *Prehospital Emergency Care*

Read a related study published in the *International Journal of Drug Policy*

Thirdhand Smoke Poses Hidden Risks to Children

CINCINNATI (WKRC) - New research from Cincinnati Children's Hospital reveals that thirdhand smoke, the residue left by tobacco smoke in environments, poses a significant health risk to children, even in homes where no one currently smokes.

Dr. Melinda Mahabee-Gittens, a researcher at the hospital, explained, "Thirdhand smoke is the residue that is leftover by folks who have smoked in different environments."

The study examined over a thousand children, aged zero to eleven, living in homes where someone had previously smoked. Despite the absence of active smoking around them, these children exhibited high levels of hand nicotine.

"They still had pretty high levels of hand nicotine," said Mahabee-Gittens.

The findings are concerning because previous studies have linked higher hand nicotine levels in children to an increased risk of respiratory and other illnesses, traditionally associated only with secondhand smoke exposure.

"Also have increased risk of respiratory illnesses and other illnesses that previously we thought were only due to exposure to secondhand smoke," Mahabee-Gittens noted.

The study found that nine out of ten children tested showed signs of thirdhand smoke exposure, with toddlers being the most affected due to their tendency to touch their eyes, mouths, and faces. Given that no level of tobacco smoke exposure is considered safe, Mahabee-Gittens recommends that individuals moving into new housing inquire about the enforcement of indoor smoking rules.

"What I would recommend is asking the landlord, are indoor smoking rules strictly enforced?" she said, adding that stricter rules could reduce exposure to thirdhand smoke.

Mahabee-Gittens hopes that policy changes will eventually mandate the disclosure of previous tobacco use in homes, potentially reducing the impact of thirdhand smoke on children.

Read the article from Local12:
"Thirdhand smoke poses hidden risks to children"

Read the study published in the journal *Environmental Health Perspectives*

UC-UC Health Addiction Center (UCAC) Pilot Research Program

Deadlines:

Letter of Intent Due: September 22, 2025
Full Applications Due: November 3, 2025 (before 8 am)
Notification of Awards Made: February 2026 (date TBD)
Award Dates: March 1, 2026 – February 28, 2027

Dr. T. John Winhusen, Donald C. Harrison Endowed Chair in Medicine, Director, Center for Addiction Research, and Professor; Vice Chair of Addiction Sciences, is pleased to announce a new pilot research program. Applications will be accepted from any full-time faculty member, resident, clinical fellow, or post- doctoral scholar whose appointment is at the University of Cincinnati College of Medicine. Any resulting application for funding to an outside agency must be submitted from UC. Investigators at CCHMC are not eligible for submission as PIs but can be Co-Is on proposals. The UCAC pilot program encourages applications that include interactions between basic scientists and clinicians to foster the development of translational investigations for addiction. In addition, interdisciplinary studies and studies that include participation of basic scientists or clinical researchers from other UC colleges and affiliates are encouraged.

To be considered, proposals need to focus on important problems in the field of addiction. A wide spectrum of projects can be considered relevant. Priority will be given to those projects that carry the highest potential for scientific contributions and are most likely to lead to successful application for extramural funding. Projects with well-developed concepts and innovative ideas requiring additional data for an extramural proposal submission, particularly if an NIH study section requested such data, will be given high priority. The strategy for advancing the research project as an extramural research grant or mentored training award submission should be clearly indicated.

After initial peer review within the UC/UC Health Addiction Center (UCAC), with written critiques, the College of Medicine Office of Research will select 1 to 2 proposals to fund for a maximum of $25,000 each. To be eligible for these funds, the Principal Investigator on the application must either hold a full-time faculty appointment at UC College of Medicine or be employed as a resident, clinical fellow, or post-doctoral fellow at UC (or by permission of the UCAC director). Eligible applicants who submit an LOI will receive instructions for full application submission in CCAPS.

Review full details and submission guidelines.

2025 New Publications and Newly Funded Grants

The synthetic opioid fentanyl increases HIV replication in macrophages
Janani Madhuravasal Krishnan, Ling Kong, Heidi L. Meeds, Krishna M. Roskin, Mario Medvedovic, **Kenneth E. Sherman**, **Jason T. Blackard**

PLOS One
DOI: https://doi.org/10.1371/journal.pone.0298341

Prefrontal cortical microglial transcriptome relates to mouse offspring executive function deficits after perinatal opioid exposure in a sex-dependent manner
Brittany L. Smith, Brandon Brooks-Patton, Justin L. Bollinger, Tess A. Guzman, Alexander H. Brendle, Samuel C. Woodburn, Anna G. Makela, Eric S. Wohleb, **Teresa M. Reyes**

Brain, Behavior, and Immunity
DOI: https://doi.org/10.1016/j.bbi.2025.03.016

Effects of the Communities That HEAL Intervention on Initiation, Retention, and Linkage to Medications for Opioid Use Disorder (MOUD): A Cluster Randomized Wait-List Controlled Trial
Jennifer L. Brown, Marc R. Larochelle, Laura C. Fanucchi, Deirdre C. Calvert, Aimee N.C. Campbell, Redonna K. Chandler, Daniel J. Feaster, LaShawn M. Glasgow, Erin B. Gibson, JaNae Holloway, Michelle R. Lofwall, Aimee Mack, Nicole Mack, Edward V. Nunes, Jeffery C. Talbert, Sylvia Tan, Nathan Vandergrift, Jennifer Villani, Kat Asman, Hermik Babakhanlou-Chase, Sarah M. Bagley, Tracy A. Battaglia, Derek Blevins, Carly Bridden, Debbie M. Cheng, Mia Christopher, Lindsay W. Cogan, Chinazo O. Cunningham, Barry Eggleston, Naleef Fareed, Soledad Fernandez, Darcy A. Freedman, **Caroline E. Freiermuth**, Bridget Freisthler, Louisa Gilbert, Lindsey Hammerslag, Daniel Harris, Timothy Hunt, Shazia Hussain, Phuong Huynh, Rebecca D. Jackson, Emily B. Kauffman, Charles Knott, Hannah K. Knudsen, R. Craig Lefebvre, Frances R. Levin, Rick Massatti, Ann Scheck McAlearney, Jake R. Morgan, Rosie Munoz Lopez, David W. Lounsbury, Lisa Newman, Katrina Nickels, Emmanuel A. Oga, Devin A. Oller, Theodore V. Parran, Maria Quinn, Kelly S. Ramsey, Bruce D. Rapkin, Pamela Salsberry, Michael Stein, Jessica L. Taylor, Julie Teater, Scott T. Walters, Gary A. Zarkin, Nabila El-Bassel, **T. John Winhusen**, Jeffrey H. Samet, Sharon L. Walsh

Drug and Alcohol Dependence
DOI: https://doi.org/10.1016/j.drugalcdep.2025.112785

Protocol Commentary for the SUCCESS (Successful Recruitment and Retention in a Randomized Controlled Trial of Pregnant Participants with Opioid Use Disorder) Study
Ashley M Snyder, Sanila Math, Kristine Campbell, Davida M Schiff, Alexindra Wheeler, Kristi Carlston, Adam J Gordon, **T John Winhusen**, Gerald Cochran, Marcela C Smid

Substance Use and Addiction Journal
DOI: https://doi.org/10.1177/29767342251334490

Ending the HIV Pandemic 2025-2026
PI: **Richard J. Ryan, MD**
Grant Sponsor: Centers for Disease Control and Prevention
- Ending the HIV Epidemic project focuses on reducing the number of new HIV infections in the US. The three main objectives for this EHE site is to identify people living with HIV not currently in care, provide linkage to care and referrals PrEP.

HIV Prevention Activities Grant 2025-2026
PI: **Richard J. Ryan, MD**
Grant Sponsor: Centers for Disease Control and Prevention
- Reduce risk and improve receipt of medical care and services by PLWHA not in care (newly and previously diagnosed) throughout region 8 inclusive of WOC, youth 15-29 and IDU. Also to improve primary prevention for MAM and HRHs who are HIV neg throughout region through risk reduction counseling, testing and PrEP education/referral.

The Ohio Valley Node (OVN) of the Clinical Trials Network (CTN) 2025 - 2032
PI: **T. John Winhusen, PhD**
Grant Sponsor: National Institute on Drug Abuse (NIDA)
- The Ohio Valley Node (OVN) joined NIDA's Clinical Trials Network (CTN) in September of 2000 as one of the CTN's second wave of awardees and has been funded continuously since then. Funds in the current 7-year award cycle (3/1/2025 - 2/29/2032) support OVN infrastructure, project development, and support to all OVN performance sites.

New NIDA funded R01 grant ***Single cell opioid (fentanyl) responses in the context of HIV.*** CO-PIs: **Dr. Jason Blackard** and Dr. Krish Roskin (CCHMC). Collaboration with Dr. Mariana Baum at Florida International University.

ABSTRACT

The number of drug overdose deaths has increased significantly in recent years. By 2019, 70.6% of drug overdose deaths involved opioids, and in Ohio, >90% of unintentional overdose deaths involved fentanyl. Opioid receptors are expressed in multiple peripheral blood mononuclear cell (PBMC) types that are susceptible to HIV infection but poorly studied, particularly in those with HIV and fentanyl use. We previously identified multiple differentially expressed genes related to apoptosis, antiviral/interferon response, chemokine signaling, NFκB signaling, viral gene expression, and hepatocarcinogenesis that were differentially regulated in the presence/absence of fentanyl in several cell types *in vitro*. In a separate NIDA-funded R61/R33 focused on fentanyl and viral infections, we collected peripheral blood samples from >100 persons with HIV and/or HCV and active drug use, as well as healthy controls. Using a novel liquid chromatography-tandem mass spectrometry-based approach, fentanyl was detected in 100% of patients presenting with opioid overdose. Single cell transcriptome analysis identified multiple differentially expressed genes in fentanyl-positive versus fentanyl-negative participants in CD4+ and CD8+ T lymphocytes, monocytes, B lymphocytes, dendritic cells, and natural killer cells. Translational research on opioid-cell and opioid-virus interactions is essential for optimized treatment and limiting viral reactivation. Thus, we propose a multi-*omics* approach and complementary *in vivo* and *ex vivo* studies in well-characterized patient cohorts to directly evaluate the impact of fentanyl on markers of the single cell transcriptome and microRNA profile.

Center for Addiction Research 2025 Summer Speaker Series

To view the completed sessions recordings and presentation slides, or to register for the final virtual August session, please visit the 2025 Summer Speaker Series webpage.

Forming an Interprofessional Workforce to Address Opioid Use Disorder Among At-Risk Youth

Wednesday, June 11, 2025
12:00–1:00 p.m.

Michael D. Brubaker, PhD, LICDC-CS, NCC, University of Cincinnati

Kaycia Spenser, LISW, Cincinnati Children's Hospital

Participants ≈≈ 37

Survey Rating:

91% rated the session as being very good or excellent

Endocannabinoid Regulation of Repeated Stress-Cocaine Interactions

Wednesday, July 9, 2025
12:00–1:00 p.m.

Jayme McReynolds, PhD, University of Cincinnati

Participants ≈≈ 28

Survey Rating:

86% rated the session as being very good or excellent

Center for Addiction Research (CAR)

University of Cincinnati
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CAR Director:
Dr. T. John Winhusen

CAR Mission

To accelerate scientific progress in the prevention and treatment of substance use disorders and their consequences by fostering research collaborations across:

- UC departments, colleges, and centers including Cincinnati Children's Hospital Medical Center
- Local, regional, and state community and governmental partners
- Other academic institutions and industry

The CAR includes three research concentrations (cores):

Changing outcomes, saving lives through work on opioid, stimulant, cannabis, and alcohol use disorders

University of CINCINNATI
CENTER FOR ADDICTION RESEARCH

- Addiction Treatment Development and Testing (ATT)
- Perinatal Addiction/Developmental-consequences (PAD)
- Population Health and Health Services (PHHS)

Find out more about the CAR using the website link below: https://med.uc.edu/institutes/CAR/home

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