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A Better Way

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A BETTER Way

An addiction specialist and a statistician team up to develop groundbreaking treatment for opioid-addicted pregnant women

By Gerry Boyle ’78

Photography by Ben Wheeler

Before she became an addiction-medicine specialist, Alane O’Connor ’96 studied environmental economics at Colby, and for several years consulted on pollution cleanup and nuclear waste storage. Associate Professor of Statistics Liam O’Brien first studied physics and mathematics, eyed medical school, and early on put his analytical skills to work for a psychiatric hospital.

Together the pair has combined their broad experience to produce groundbreaking research that is changing the way clinicians around the world treat pregnant and opioid-addicted women and their unborn children.

O’Connor, who went on to earn a doctorate in nursing practice at Vanderbilt and specializes in addiction treatment in Maine, and O’Brien, a Harvard-educated biostatistician and chair of Colby’s Mathematics and Statistics Department, have spearheaded studies that have yielded important developments in the use of a drug called buprenorphine, an opioid substitute used to suppress symptoms of withdrawal and cravings from powerfully addictive opioids like heroin and fentanyl, and sold commercially as Suboxone.

In just a few years, their work—with coauthors that include Colby student researchers—has been published in the world’s most prestigious journals in the field. O’Connor’s first paper (co-written with physician William Alto) was published in 2011 in the *American Journal of Obstetrics and Gynecology* and is a go-to reference for those treating pregnant women with opioid addiction.

What makes the work—and associated treatment—even more remarkable is that all of these studies emanated, not from a major research university and hospital, but from a family medicine residency based in Waterville, Maine (albeit one of the largest and most reputable in New England).

“I am surprised that some of the larger centers didn’t have the foresight to try very early on to create the kind of resources that Alane’s been able to create to study the problem,” said Greg Feero, an M.D. and Ph.D. geneticist who oversees research at Maine-Dartmouth Family Medicine Residency and is an associate editor of the *Journal of the American Medical Association*.

O’Connor, who has practiced at Maine-Dartmouth for 13 years, can date her entry into this specialty to 2007, when a patient who was pregnant confided that she was addicted to opioids and did not want to be on methadone, the traditional choice for pregnant women. O’Connor and her colleagues had been using buprenorphine on nonpregnant patients and looked around to see what research had been done on treatment of pregnant ones. “There was nothing. Zero,” O’Connor said. “We said,

Associate Professor of Statistics Liam O'Brien, left, and Alane O'Connor '96, doctor of nursing practice and addiction-medicine specialist, confer in O'Brien's office at Colby. O'Brien does statistical analysis of data O'Connor gleans from her Waterville-based practice, which focuses on women who are pregnant and addicted to opioids.

'Alright. We'll try to figure this out.'"

Fortunately for countless mothers and infants, she was equipped in multiple disciplines to do just that. And when the sophistication of the work outstripped her statistical analysis chops, O'Brien stepped in.

This wasn't always the plan.

O'Connor grew up in central Maine (she was an alpine ski racer at Colby), majored in economics and minored in mathematics, and was mentored by renowned environmental economist Thomas Tietenberg. At Colby she did an economic work-up of the potential labor impact of a proposed clear-cutting ban, then went on to work for a major environmental consulting firm in Boston. There she trained her analytical eye on Superfund cleanups and major oil spills, among other projects.

But after five years, O'Connor was ready for a change and recalled the time she spent volunteering at the community hospital in Farmington, Maine. "I really liked the idea of service," she said. "Making a difference in people's lives."

She earned her master's degree in nursing practice at Boston College, then returned to Maine to practice and stepped into what would soon become the vortex of an overwhelming public health problem—opioid addiction.

Spurred by rampant use of the highly addictive prescription pain reliever OxyContin, the opioid problem swept the country—especially rural areas. Maine soon ranked as one of the worst states in opioid abuse and overdose death as the drugs of choice expanded from prescription narcotics to heroin and fentanyl.

It wasn't long before pregnant women started presenting with addiction issues, and Maine is now one of the top three states (along with West Virginia and Vermont) in the rate of babies born drug affected. Eight percent of babies born in Maine last year were substance exposed. O'Connor found herself treating more and more of these patients—and also saw their

CHARTING
A PATH FORWARD

Even as she was still adding the head-circumference measurements for all 137 babies to the data set, Lilly Watson '20 liked the trend that was emerging.

Before birth the infants had been exposed through their opioid-addicted mothers to buprenorphine, an alternative to methadone, the more commonly used opioid replacement. Methadone had been linked to smaller head circumference—and associated problems—in babies. The effects of buprenorphine had not been scrutinized.

"We had the baseline for a normal head circumference," Watson said, "so I had a little bit of an idea as I saw the results coming in."

Those results, which Watson so meticulously gathered and recorded, would be scrutinized by Alane O'Connor '96, a doctor of nursing practice at Maine-Dartmouth Family Medicine Residency and Watson's mentor last summer. The numbers would then be subjected to rigorous statistical analysis by Liam O'Brien, biostatistician and chair of the Department of Mathematics and Statistics at Colby.

The conclusion: for this cohort of infants there was no relationship between head circumference at birth and the mother's buprenorphine dose, nor was there a relationship at birth between head circumference and the severity of withdrawal. The study—coauthored by O'Connor, O'Brien, and Watson and being considered for publication by the *Journal of Maternal-Fetal & Neonatal Medicine*—provided one more reason for pregnant women with opioid addiction to be given buprenorphine, not methadone.

"I wasn't surprised," Watson said, "but I was happy."

That was just one of the rewarding and even life-changing experiences during her internship last summer. Long interested in children's health, she considered becoming a pediatric surgeon. Coming to Colby from Yarmouth, Maine, outside of Portland, she was aware of the scourge of opioid addiction in the state.

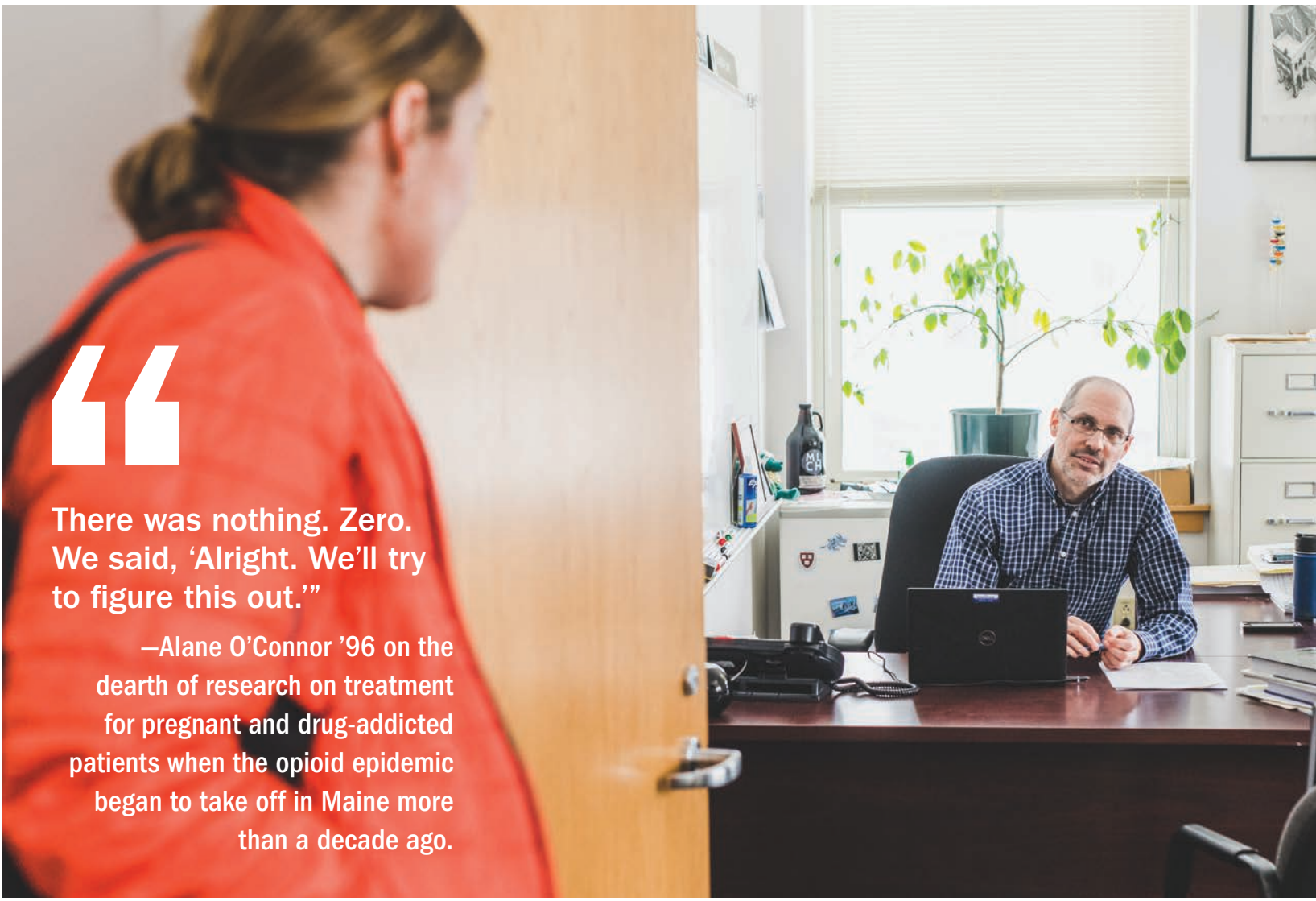
Watson used DavisConnects' "Handshake" database to connect to the Maine-Dartmouth Family Practice Residency in Waterville, which led to O'Connor. That turned into an opportunity to assist with O'Connor's research, and to shadow doctors at MaineGeneral Medical Center in Augusta. Now Watson's plan is to take a year to work and another year to prepare for MCATs and apply to medical school.

And as she finished the 10-week intensive internship, another piece was falling into place.

In addition to working on the groundbreaking head-circumference study, she shadowed O'Connor as she met with patients, listened to them discuss their pregnancies—and their drug use. Watson sat in with groups of new mothers, talked to them about their lives. On one occasion a mom asked her to hold her baby—and for Watson, her goal became clearer. She would become a pediatric hospitalist.

"All the data points I was collecting—this was one of them," Watson said. "That cemented it for me. It was an incredible experience."

—Gerry Boyle '78



> There was nothing. Zero. We said, 'Alright. We'll try to figure this out.'"
>
> —Alane O'Connor '96 on the dearth of research on treatment for pregnant and drug-addicted patients when the opioid epidemic began to take off in Maine more than a decade ago.

newborns suffering from withdrawal and the possibility of longer-term effects.

It's a thorny health problem, complicated by social stigma, a large number of uninsured patients, the potential state intervention from child protective services due to drug use during pregnancy, and the availability of buprenorphine, also known as Suboxone, on the street. Women fear losing custody of their infants if they seek addiction treatment during pregnancy, so many attempt to acquire buprenorphine from other sources. They see others who have used "subs" during pregnancy and their babies seem fine, O'Connor said.

"So they may think 'I'll just take this drug off the street.' In reality, that is a potentially dangerous option as the withdrawal syndrome infants experience after birth is very treatable, but only if we know to look for it."

Because withdrawal doesn't peak until 72 hours after birth, O'Connor worries about newborns that might be sent home too early, since untreated withdrawal in infants can have catastrophic consequences.

Pregnant women in addiction treatment also experience significant stigma and pressure to get off all opioids during pregnancy—including buprenorphine—but in utero withdrawal can cause complications, including fetal demise, she said. Keeping these patients on buprenorphine and getting them into intensive counseling with close obstetrical follow-up is by far the safest option, O'Connor said. "Most women are terrified at their first visit, but I work hard to make them feel that this is a safe place in their otherwise entirely chaotic lives," she said.

That trust is key, not only to the welfare of individual patients, but also for the far-reaching clinical studies, Feero said. "I don't think she could achieve what she has been able to achieve without a strong bond between her and the patients she cares for. She's incredibly dedicated to them."

Said Lilly Watson '20, who spent last summer as an intern with O'Connor and sat in on meetings with patients where drug use was discussed, "It's more of a conversation than an inquisition."

As a clinician, O'Connor was dedicated to treating individual patients, but her economics background left her looking for ways to have broader impact. "I knew that to make a meaningful difference in healthcare, I needed more skills, research skills, M.B.A.-type skills. How to think about health policy, how to look at legislation, how to look at systems of care."

She went back to school, earning her Vanderbilt doctorate and working to hone her understanding of the economic forces that drive the ways healthcare is provided. She also considered how individual cases can be folded into data that can result in more effective treatment for countless patients, not only her own.

O'Connor put this knowledge to use in rural Maine, which was emerging as one of the epicenters of the opioid crisis. She and her colleagues serve a largely working-class population, and many of those patients—including some 400 who were pregnant—were entangled in addiction. O'Connor and her colleagues decided then that "This is not somebody else's problem. This is our problem," she said.

At the time, a dozen years ago, the preferred opioid substitute was methadone, which was dispensed at clinics across Maine and the country. As a result, the literature was scant about buprenorphine effectiveness. But O'Connor had observed that buprenorphine, used as she prescribed, resulted in fewer medical complications for the women than with methadone, and that infants experienced milder withdrawal symptoms.

She also knew that buprenorphine can be prescribed in a doctor's office, while methadone, dispensed through the identifiable clinics, required pregnant women to be exposed to public scrutiny. The prospect of running that gauntlet could lead some women to deny drug use, to buy drugs on the street, or to try to quit mid-pregnancy, exposing the unborn child to serious physiological stresses. "Somebody had to write this," O'Connor said.

So she and Alto did just that, publishing the seminal article in 2011 on the management of women treated with buprenorphine during pregnancy. But there were many deeper questions to be answered. And O'Connor knew it was time to bring in a research partner who could glean the answers from the growing and unprecedented data set that was being collected at her practice.

Feero introduced O'Connor to O'Brien, who consults on everything from autism to housing discrimination to school nutrition to validating psychological assessment tools. O'Brien's path to biostatistics was in some ways just as indirect as O'Connor's was to medicine, and the experiences and interests he developed along the way would help create a research team that punches far beyond its weight.

O'Brien grew up in a tough suburb of Denver and excelled in high school academics. With encouragement from his mother and his teachers, he applied to and was accepted to the Colorado School of Mines, which specializes in earth sciences and engineering. As an undergraduate, he majored in mathematics and physics and again excelled, expected to graduate and find a job. When an advisor suggested graduate school, his reaction was, "What are you talking about? I can't afford graduate school." His advisor replied, "'No, they're going to pay you.'"

> **"You make a mistake and somebody reads that paper and it either leads them down a wrong research avenue, or in some cases it could cause a doctor to make a recommendation that's wrong. In the extreme case—it sounds awful but it's true—it could kill somebody."**
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> —Associate Professor of Statistics Liam O'Brien

He considered medical school but thought that with his math skills perhaps he could find a way to make a difference at a broader public health level. O'Brien had done an internship at the University of Colorado's University Hospital as an undergraduate and later identified a training program at Harvard funded by the National Institutes of Health that focused on biostatistics in psychiatry.

O'Brien was accepted to the doctoral program in biostatistics at the university's T.H. Chan School of Public Health. Through the NIH psychiatric training grant, he was able to work in the genetics lab at Massachusetts General Hospital, followed by a stint at the Massachusetts Mental Health Center, consulting for the psychiatrists there. Ultimately, O'Brien—who had not studied biology or statistics before Harvard—graduated with a doctorate in biostatistics and a minor in psychiatric epidemiology, with an emphasis on maternal and child health.

"I see the work with Alane as related to that because I see addiction research as an important piece of psychiatric research," O'Brien said.

The perfect match on paper turned out to be just that.

It's an oversimplification to say that O'Brien's role is to work with the numbers. In fact, his analysis begins, not with numbers, but with careful consideration of the words used to express the question being asked. "I have to translate the words used by the researcher into the appropriate data analysis, so I need to know how to bridge that divide," he said.

O'Brien first translates the question into the variables that will need to be considered, and then considers what types of variables they are. Is it a binary variable, like are you on buprenorphine or not? Or is the variable on a continuum, like the babies' gestational age or birth weight, that would mean analysis of a variable that spans an interval. "That dictates the type of statistical test I would start to think about," he said.

The catch, O'Brien said, is that the conditions attached to the tests have to be satisfied. "If they are, great. I run the test and I give her the results."

If not? The question may have to be rephrased or refocused. And working with O'Connor, that discussion is less complicated than it can be. "Alane is great because she does understand the statistics side more than other researchers that I work with," O'Brien said. "She can understand when I tell her, 'We need to look at other confounders.' No other researcher I work with understands my concerns as well as she does. She understands what you can or can't say with the data."

Some studies are more complicated than others. The head-circumference study, the most complex statistical analysis thus far, required that O'Brien generate "bootstrap percentiles," which call for data to be resampled over and over (in this case one million times) to produce a simulated data set of babies exposed to buprenorphine so that it could be used as a proxy for the population of babies in Maine who had been exposed. In that case, and others, he had to explain his process to the peer reviewers so they were satisfied that the conclusions were sound.

And O'Brien has to be satisfied as well, in terms of data integrity and ethics. In the case of buprenorphine, a statistical stretch or muddy conclusion could have dangerous results.

"You make a mistake and somebody reads that paper and it either leads them down a wrong research avenue, or in some cases it could cause a doctor to make a recommendation that's wrong," he said. "In the extreme case—it sounds awful but it's true—it could kill somebody."

His biostatistics and his maternal and child health background reinforced the importance of the work of the buprenorphine study, which is affecting the lives of countless women and children. "I care a lot about this project," said O'Brien, who also is adjunct faculty of the University of New England College of Graduate and Professional Studies. "I work on all kinds of stuff. People come up to me, they want me to work on school nutrition data, they want me to work on sleep data. You name it, I'll try to help with it. But this is the one that I'm most interested in by far."

The addiction-medicine world is interested as well. The Maine studies, and others, supporting the safety and effectiveness of buprenorphine have caused the drug to be designated by the American College of Obstetricians and Gynecologists and the World Health Organization as a first-line treatment along with methadone, rather than as a second choice, O'Connor said. Increasingly, women are becoming aware of its benefits for infants and are preferring it to methadone.

The Findings

O'Brien and O'Connor, with coauthors, have collaborated on papers that have been published in the world's most prestigious addiction-medicine journals almost every year since 2011. Their conclusions:

Women who are able to access addiction treatment early in pregnancy were more likely to remain in treatment a year after giving birth—*Journal of Substance Abuse Treatment*

There is no need to limit or reduce buprenorphine dosing during pregnancy to prevent adverse outcomes in infants —*European Addiction Research*

Breastfeeding appears safe in infants exposed to buprenorphine during pregnancy, and an integrated obstetric and addiction treatment program reduces the barriers that many women in recovery encounter with breastfeeding —*Journal of Midwifery & Women's Health*

Marijuana use in the third trimester does not complicate pregnancy or the delivery process for infants exposed to buprenorphine during pregnancy but may have an impact on the severity of infant withdrawal syndrome —*Drug and Alcohol Dependence*

When compared to female infants, male infants were more likely to have severe withdrawal syndrome after exposure to buprenorphine during pregnancy—*Journal of Perinatal Medicine*

Concurrent exposure to antidepressants and buprenorphine during pregnancy has been associated with a longer duration of infant withdrawal symptoms —*Journal of Maternal-Fetal & Neonatal Medicine*

Buprenorphine, unlike methadone, does not appear to be associated with reduced head circumference at birth (and related potential cognitive problems)—*Journal of Maternal-Fetal & Neonatal Medicine*

And women and infants are the bottom line.

The Maine-Dartmouth Residency has become one of the leading centers for addiction medicine, and Feero attributed much of that progress to O'Connor and her clinical care and research instincts. O'Connor is sought after to present at national conferences, and the resident physicians are benefiting from her knowledge, insight, and experience.

O'Connor, meanwhile, said that while it's imperative that the buprenorphine studies are disseminated to the medical community at large, she still loves her one-on-one work with patients, providing the right medication so they are stabilized enough emotionally and physically to work on re-establishing a normal life. A small number of mothers have tapered off opioids entirely. Some have been referred to a higher level of care. Some did not survive the disease. "The vast majority are still with us," she said.

Recently a patient returned to O'Connor's office with her six-year-old daughter. The woman had been pregnant with the child and addicted when she first came for treatment. Now, with buprenorphine and very hard work, she was off opioids entirely and her daughter was healthy. O'Connor said they hugged and cried before the woman left to continue her drug-free life. ©