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Adina Badea.
Clinical Laboratories Confront a New Wave of Drug Overdose Deaths
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Guest: Dr. Adina Badea from Rhode Island Hospital and The Warren Alpert Medical School of Brown University, in Providence, Rhode Island.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. We are all familiar with the phrase "opioid epidemic," the dramatic increase in opioid overdose deaths beginning in the late 1990s.

What you may not know is that the opioid epidemic has gone through several stages, each characterized by different opioid drugs, different routes of administration, and presenting different challenges for the clinical laboratory. In the first wave, deaths were primarily caused by prescription opioid painkillers. In the second wave, heroin was the primary drug, eventually giving way to a third wave, which was marked by fentanyl and other synthetic analogs.

We have now entered a fourth wave, a period characterized by polysubstance use, the presence of opioids accompanied by other illicit substances. A new News & Views article, appearing in the August 2024 issue of *Clinical Chemistry*, highlights a recent publication studying this fourth wave and proposes ways clinical laboratorians can help stem the tide. In this podcast, we're excited to speak with the article's author.

Dr. Adina Badea is the Director of Toxicology at Rhode Island Hospital and an Assistant Professor of Pathology and Laboratory Medicine at the Warren Alpert Medical School of Brown University. Her research interests center on developing, optimizing, and implementing novel diagnostic methods to address unmet patient needs and public health crises. So, Dr. Badea, let's start off with the basics. What is this fourth wave of the drug overdose crisis?

Adina Badea: Yes, thank you for that introduction. The fourth wave focuses on the co-positivity of fentanyl and stimulants that lead to overdose deaths. There are some regional and geographically specific trends as to when that fourth wave started, but overall, in about 2015, the number of overdoses that are due to co-involvement of fentanyl with stimulants has steadily risen to match by the end of 2021, pretty much match the number of deaths due to fentanyl co-involved with other opioids.

So just to give you a perspective, from about 2020 to about 2021, the rate of deaths from fentanyl combined with stimulants rose from a measly 0.6% of total opioid deaths to 32.3%. So that is a staggering difference, and this is what marks what experts have called this fourth wave of the opioid crisis.

Bob Barrett: Well, just to quickly follow up on that, do you have any more details about the findings?

Adina Badea: Absolutely. And so, as I mentioned a little bit before, there are specific patterns to the four major geographic regions of the United States, and these geographic differences mostly emerge in 2014. In 2014, heroin was still the most commonly co-involved substance with fentanyl in overdose deaths. In the Northeast, this was followed by a shift to cocaine in 2019.

In the West, however, this pattern of having heroin as still the major driver of opioid deaths did not change until 2020, when methamphetamine became the most common co-involved substance with fentanyl. The Midwest and the South exhibited slightly shorter periods of heroin-fentanyl co-positivity, so that was about from 2016 to 2018, and then this lead in opioid deaths shifted entirely to methamphetamine and cocaine by 2021.

Bob Barrett: So how relevant is this information to clinical laboratorians? Should they alter current practices in light of this new information?

Adina Badea: Absolutely. So, the information is relevant because it highlights the fact that these trends are indeed somewhat geographically specific, and so clinical laboratories with their access to clinical samples from their relevant patient populations play a significant role in highlighting geographically specific trends. It also highlights a need for clinical laboratories to tailor their testing services to their specific populations, and while I agree that this study has some limitations, looking at opioid overdose deaths definitely has a bit of a lag in terms of how relevant that information is. So by the time the data from overdose deaths gets analyzed, the picture might be changing on the ground.

These findings do highlight that the drug use landscape, so to speak, is changing, perhaps encourages laboratories to be a little bit more nimble and alter their offerings of drug screen panels or drug confirmation panels to match what is seen in their local population and also what is seen as a general trend in terms of leading causes of opioid overdose deaths.

Bob Barrett: Do clinical labs have a role in responding to this fourth wave?

Adina Badea: Absolutely. These studies that are focused on opioid overdose death statistics have an inherent lag, as I said. This data tends to not be analyzed until about mid-year, the next year, and also it really only captures the population that actually dies from overdose. Clinical labs are at a very interesting point where you have patients that come in with non-fatal overdoses or patients that come in with a substance use disorder before it turns into an overdose event, and the data in terms of drug co-positivity that clinical labs have is a very valuable and complementary piece. With good data analysis and perhaps multiple labs from multiple areas of the country working together, you can piece together another aspect of this crisis or put another piece of the puzzle on the table.

So, by looking at how co-positivity changes between different clinical settings, from treatment clinics for substance use disorder to non-fatal overdose events to even other clinical settings in which drug use is noticed or is becoming to be a comorbidity, clinical labs offer valuable information that is perhaps a little closer in terms of what's happening out there in real time in terms of drug use.

Bob Barrett: Well, finally, doctor, let's look ahead. What do you see as the future of drug testing in clinical laboratories?

Adina Badea: Yes, this is very exciting, actually. When you look at the information that is out there, especially the information that can be extracted from post-mortem, drug overdose, toxicology testing, the testing menus at this time seem to be rather limited. The study reference does not include any information on fentanyl analogs or novel psychoactive substances that may also be and has been noted that they have been important drivers in morbidity and mortality. That piece of information is missing.

It's also a piece of information that is currently not always available in clinical drug testing as well. In my opinion, what clinical labs should start doing, and what the future is, to look at drug use or substance use in a comprehensive manner. I see these typical panels of drugs of abuse or urine drug screens followed by static confirmation panels.

I see this strategy morphing towards a more comprehensive drug screen testing strategy in which these novel psychoactive substances or cuts in the drug supply such as xylazine, novel opioids other than fentanyl, such as the nitazenes, are included in the panel or there's an easy way to see the presence of these substances. For instance, by high resolution mass spectrometry, no matter how comprehensive the panel, typically drug detection is done in an untargeted fashion, which allows retrospective query of the data when knowledge of a novel drug supply adulterant or a novel analog

comes to the surface. I see clinical labs approaching this crisis in a more novel and comprehensive way to gather even more information and to lead the front in terms of dictating what these drug panels should be looking like for postmortem analysis as well in order to make sure that our postmortem data is up to date in terms of what is out there in the drug supply.

Bob Barrett: That was Dr. Adina Badea from the Warren Alpert Medical School of Brown University in Rhode Island. She wrote a News & Views article on the fourth wave of drug overdose deaths in the August 2024 issue of *Clinical Chemistry*. She's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.