

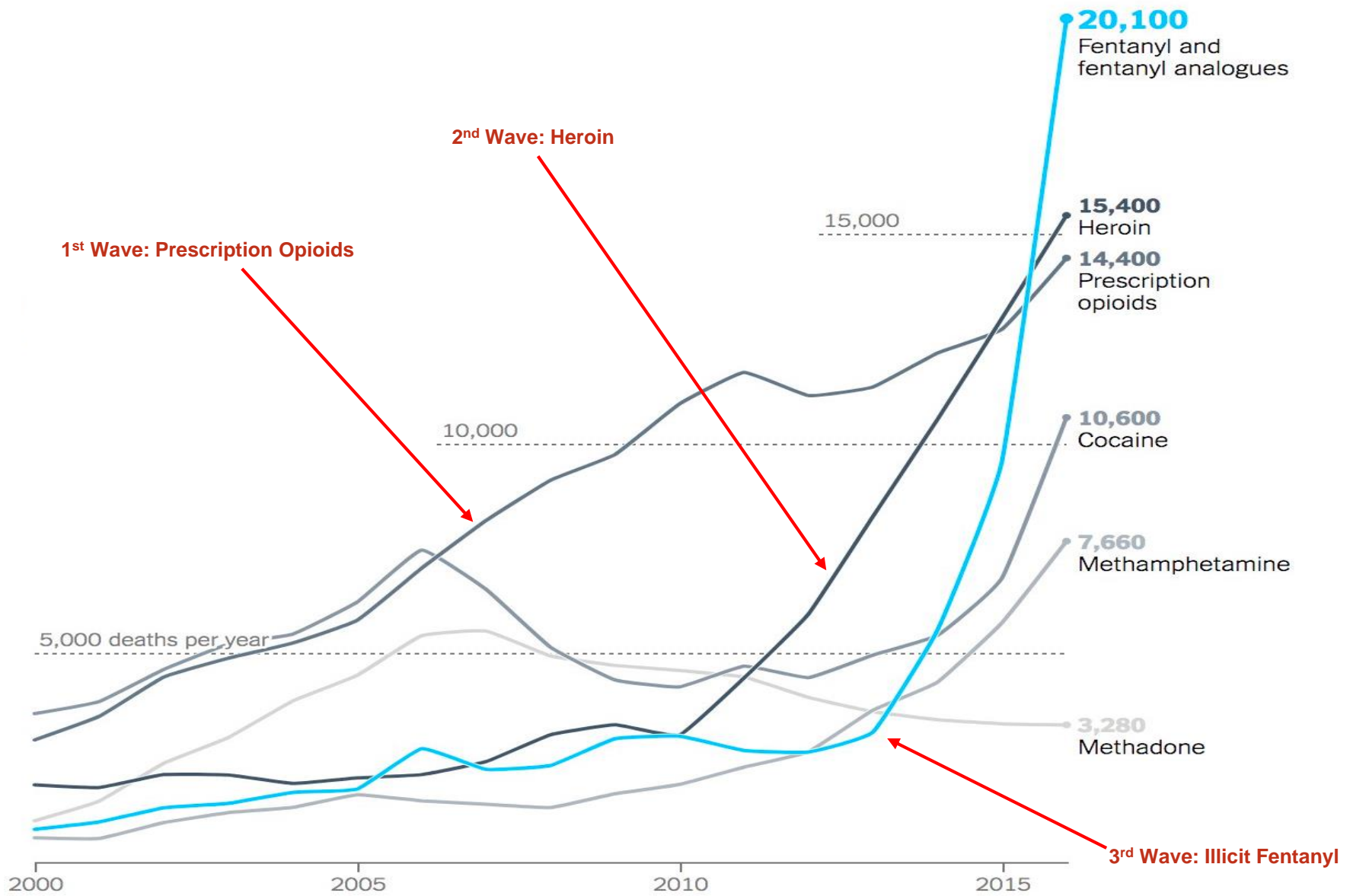


A Surging Illicit Stimulant Crisis During a Fentanyl Epidemic: America's Fourth Mortality Wave

Jon E. Zibbell, PhD

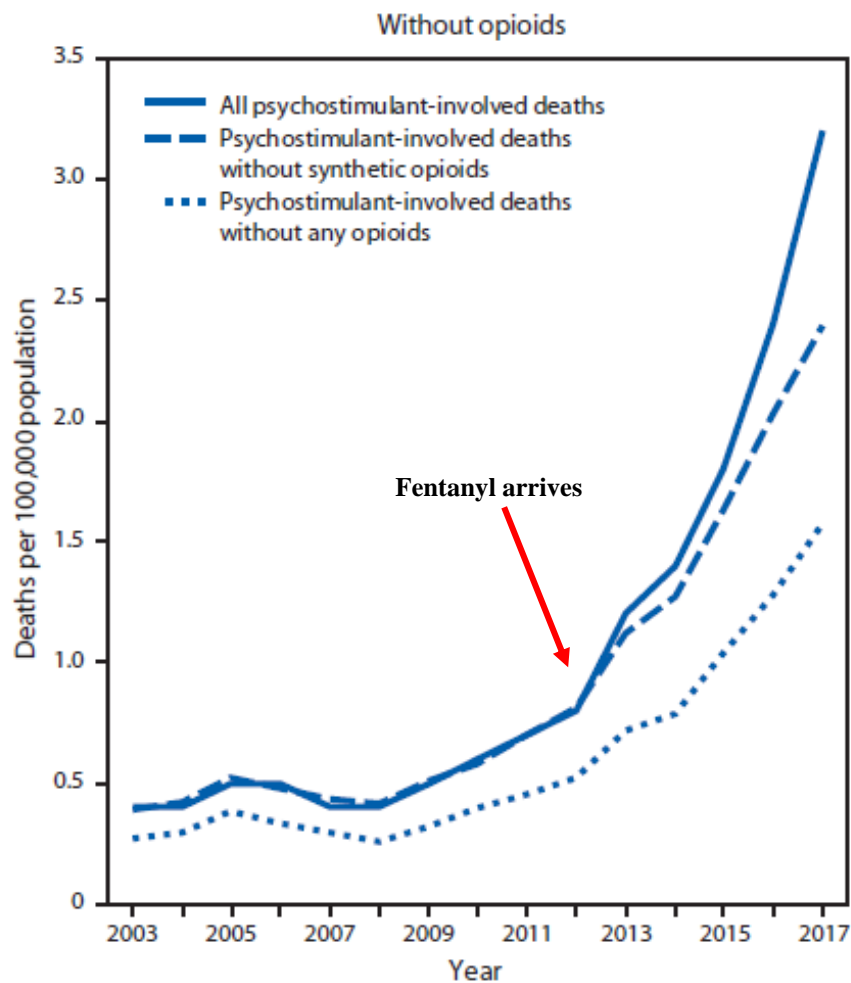
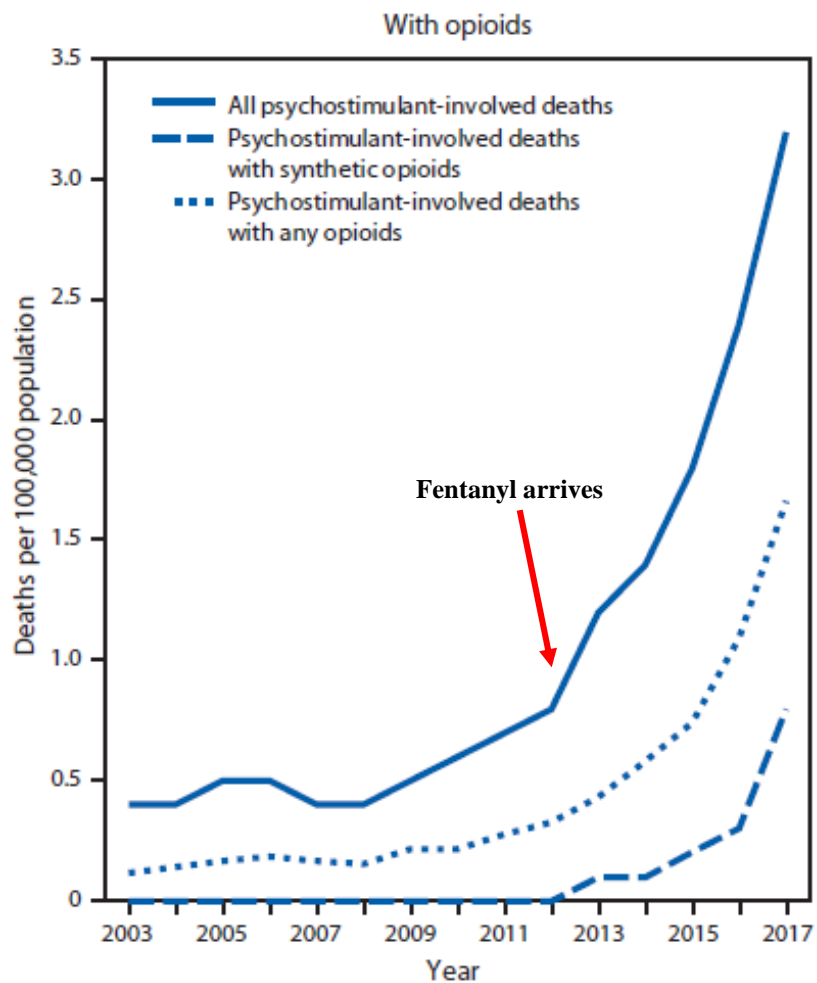
Senior Public Health Scientist
Behavioral Health Research Division
RTI International
Atlanta, GA

Drugs Involved in OD Deaths, U.S., 2000-2016*

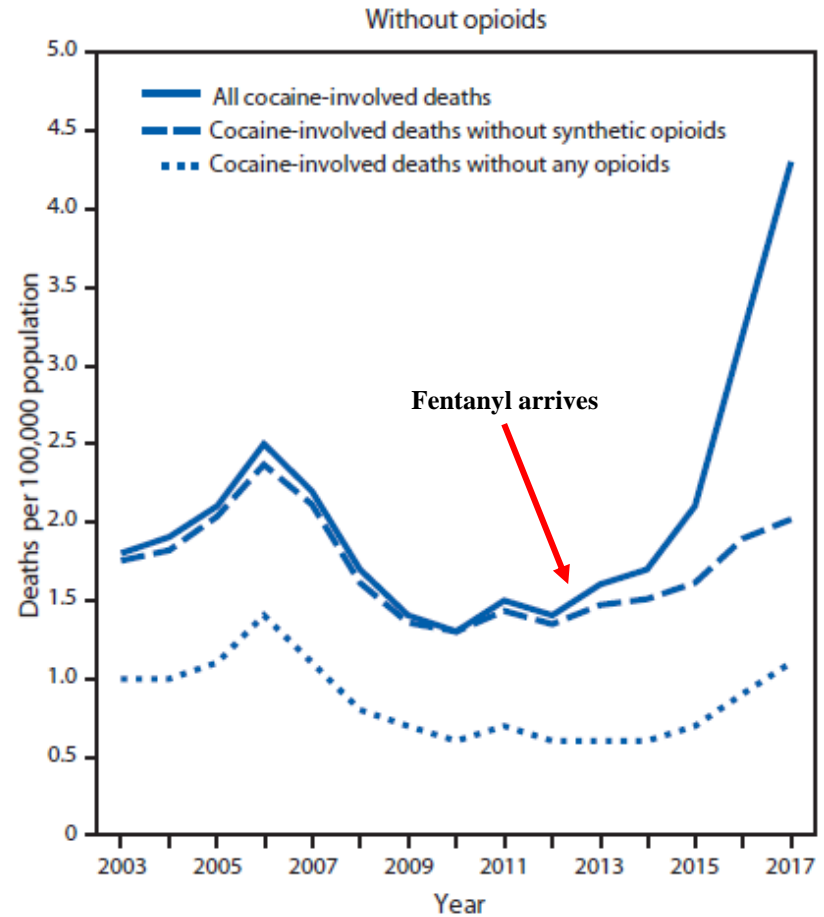
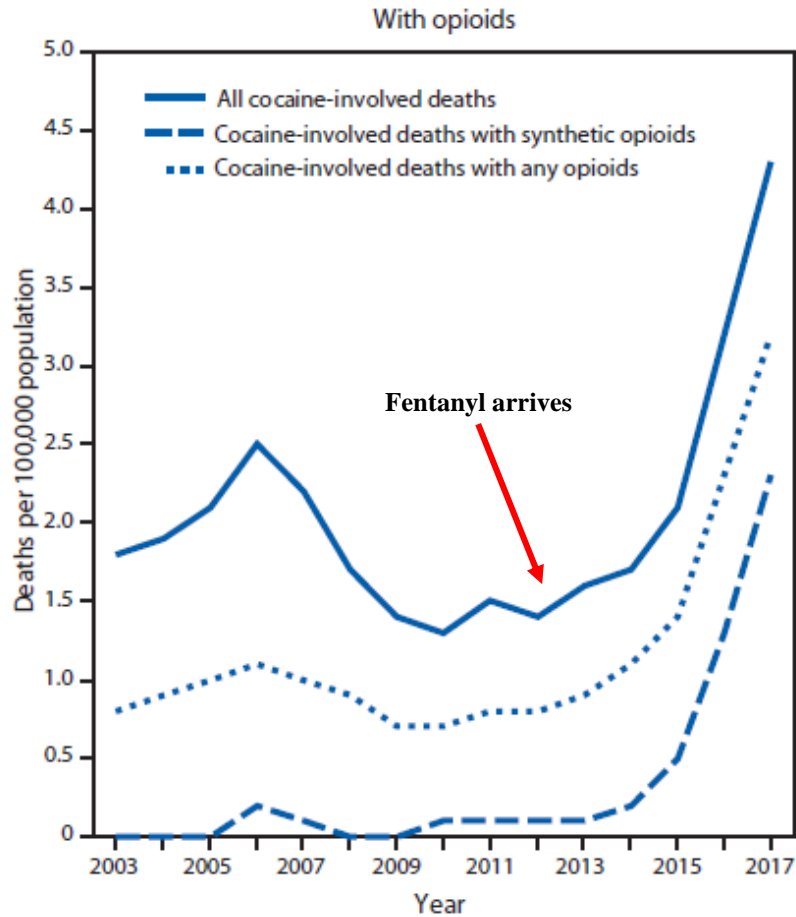


*NYT Interactive, 09/02/2017, National Center for Health Statistics

Drug OD Deaths Involving Psychostimulants, US, 2003-2017



Drug OD Deaths Involving Cocaine, US, 2003-2017



Illicit Stimulants: Cocaine and Methamphetamine

- ❖ The stimulants drugs responsible for the growing ‘psychostimulant’ crisis involve primarily cocaine and methamphetamine—not prescription stimulants
 - ❖ e.g., Adderall [dextroamphetamine] or Ritalin (methylphenidate).
- ❖ Terminology: illicit stimulants vs. psychostimulants
- ❖ Cocaine and meth are both central nervous system (CNS) stimulants that imitate naturally-occurring neurotransmitters in the brain (dopamine) with comparable properties related to intoxicating effect, abuse potential, administration routes, and cessation symptoms
 - ❖ Differ in toxicity and pharmacokinetic profile
- ❖ Domestic meth production has decreased dramatically over the past decade⁸ as a torrent of inexpensive, highly-pure (90%), Mexican-sourced meth flowed into heroin supply chains trafficked alongside fentanyl
 - ❖ Law enforcement meth seizures growing 83% from 2001 to 2017
- ❖ Cocaine production has also increased steadily over the past decade to become the second more prevalent drug seized by DEA in 2019
 - ❖ with retail prices falling sharply and purity rising steeply (-41% and 82%, respectively)
- ❖ Deaths involving meth increased 5-fold from 2010 to 2019
- ❖ Cocaine deaths doubled from 2006 to 2019

Brief History of Amphetamines in the United States

- Amphetamines were developed in the late 1920s by pharmaceutical industry and medical research while searching for decongestant and bronchodilator as substitute for ephedrine
- Benzedrine first appeared in the early 1930s and sold as an antidepressant. Available as an inhaler containing 325mg of amphetamine base and very little else
- 1937 AMA approved advertising of Benzedrine sulphate tablets for narcolepsy
- US military supplies Benzedrine to servicemen for routine use in aviation and general medical supply
- The war years saw an explosion of 5mg amphetamine tablets sold for weight loss
 - 500,000 Americans consuming for weight loss; 30 million tablets manufactured monthly
 - Dexedrine introduced in the early 1950s
 - Largest consumer group is white women between the ages of 36 to 45
 - Late 1950s: *Dexamyl* included barbiturate to overcome unpleasant agitation/anxiety (prescription 'speedball')
 - Legal prescriptions meant consumers were medical patients and not labeled deviant or thrill-seeking
- By the 1960s, widespread consumption starts to produce negative health outcomes:
 - Amphetamine psychosis and paranoia
 - Latent schizophrenia
 - Iatrogenic amphetamine addiction in 2.2% to 3.3% of patients receiving prescriptions
- By 1970, the US had nearly 1 million 'dependent' amphetamine users with 320,000 identified as 'addicts'
- The first amphetamine epidemics were iatrogenic, created by pharmaceutical industry and assisted by medical profession (Similar to the role of prescription opioids in the current opioid epidemic)
- Methamphetamine was scheduled as a category II narcotic in 1970

Amphetamines Mass-Marketed in the 1950s

IN MILD PSYCHOGENIC DEPRESSIVE STATES . . .

this
IN MINUTES!
... WITH

**RAPHETAMINE
PHOSPHATE**
Brand of Amphetamine Phosphate

CHEERFULNESS
MENTAL ALERTNESS
OPTIMISM

● Smooth, fast acting Raphetamine Phosphate aids in restoring normal affects, cheerfulness and optimism in mild psychogenic depressive states . . . and in the management of obesity.

With contraindications chiefly limited to hypertension, cardiac defects, or hypersensitivity to ephedrine-like compounds, benefits may be prolonged.

Newly accepted parenteral Raphetamine Phosphate can successfully be used in treating barbiturate intoxication because of its immediate action.

Clinical supply of both dosage forms available on request. Write to Medical Service Department, R. J. Strassenburgh Co., Rochester 14, N. Y.

parenteral: Raphetamine Phosphate, parenteral, containing 10 mg. racemic racemic amphetamine phosphate per cc. in sterile aqueous solution is available in 10 cc. multidose vials.

tablet: Raphetamine Phosphate tablets containing 5 mg. racemic racemic amphetamine phosphate per tablet are available in bottles of 100, 100 and 1000.

Strassenburgh
FOUNDED IN 1911

“...if the individual is depressed...”

“ . . . If the individual is depressed or anhedonic . . . you can change his attitude . . . by physical means just as surely as you can change his digestion by distressing thought . . . In other words, *drugs and physical therapeutics are just as much psychic agents as good advice and analysis* and must be used together with these latter agents of cure.”

Meyerson, A.—*Feboldin*—
Am. J. Psychiat., July, 1922.

When this was written—in 1922—the only stimulant drugs employed in the treatment of simple depression were of limited effectiveness.

Only in the last decade has there been available—in Benzedrine Sulfate—a therapeutic weapon capable of alleviating depression, overcoming “chronic fatigue” and breaking the vicious circle of anhedonia.

**BENZEDRINE
SULFATE TABLETS**
(racemic amphetamine sulfate)

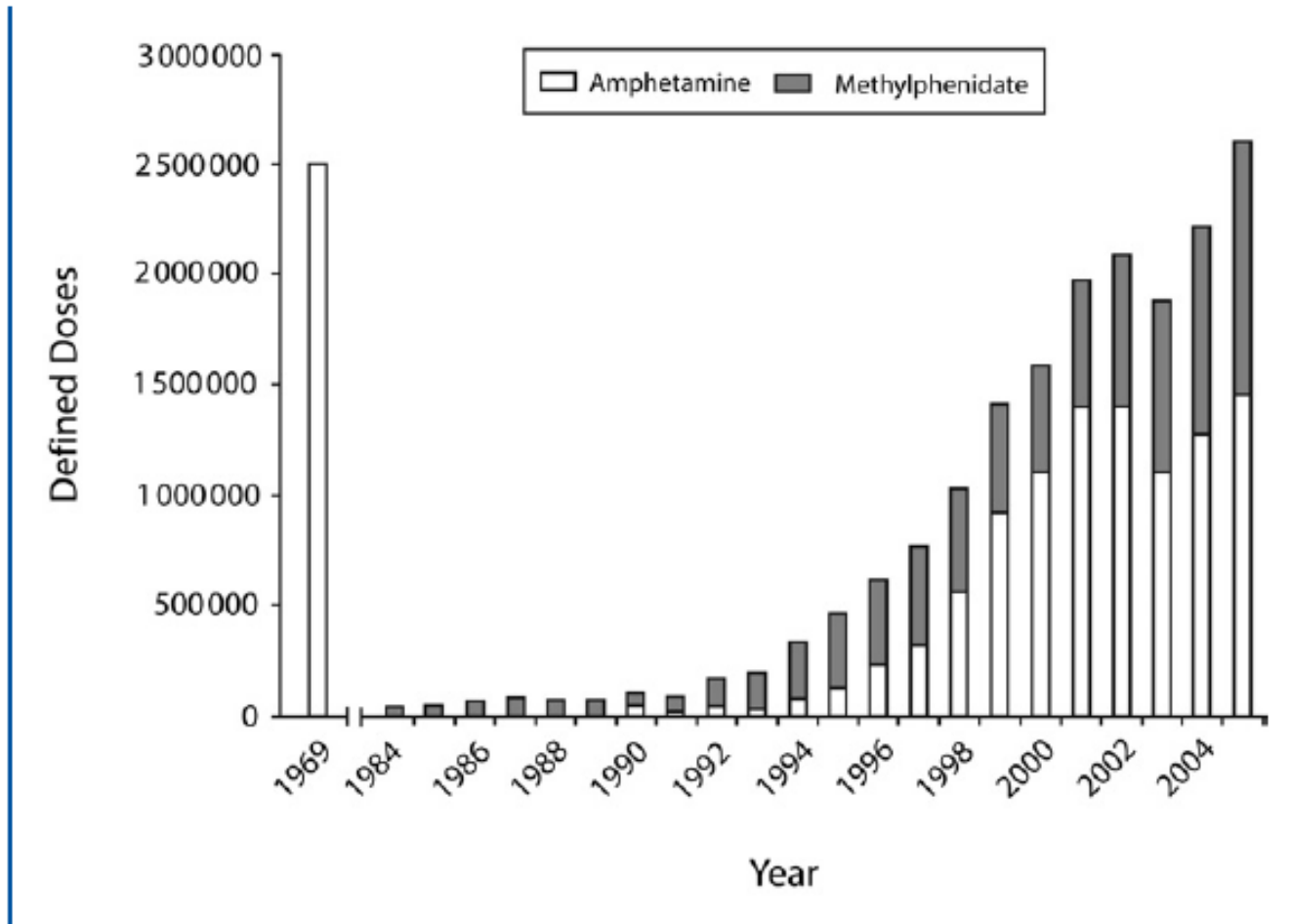
SMITH, KLINE & FRENCH LABORATORIES, PHILADELPHIA, PA.

XIII

Recent Trends and Preceding Crises (1970s-1990s)

- Methamphetamine epidemics since the 1970s began through a combination of recreational use and increased illicit supply
- Treatment admissions show that methamphetamine abuse:
 - Doubled from 1983-1988
 - Quintupled between 1988-1992
 - Quintupled again from 1992-2002
- The [Combat Methamphetamine Epidemic Act of 2005](#) was passed as part of the [USA PATRIOT Act](#), putting restrictions on the sale of methamphetamine precursors
 - Made ingredients used in manufacturing harder to obtain
 - more stringent laws to regulate the sale of pseudoephedrine decongestants
 - Increase penalties for selling and use
 - Doubled federal funding to states with 'meth hot spots'
 - Meth first drug to generate national concern in the US in the 21st century (right before the current opioid epidemic)
- According to SAMHSA, by 2004, roughly 3 million Americans consumed amphetamine-type stimulants nonmedically
 - Twice the number from the 1990s
 - 250,000 to 300,000 report being 'addicted'
 - Severity of current crisis on par the first nonmedical epidemic in the 1970s
- While illicitly-manufactured methamphetamine launched the epidemic of the 2000s, the US has witnessed a surge in the legal supply and use of amphetamine-type ADD medications like Ritalin and Adderall
 - According to DEA, medical supply of these drugs has more than quintupled from 1995 to 2007
 - At present, amphetamines are widely accepted as safe even for small children
 - Increased medical normalization undermines public health efforts to limit amphetamine abuse

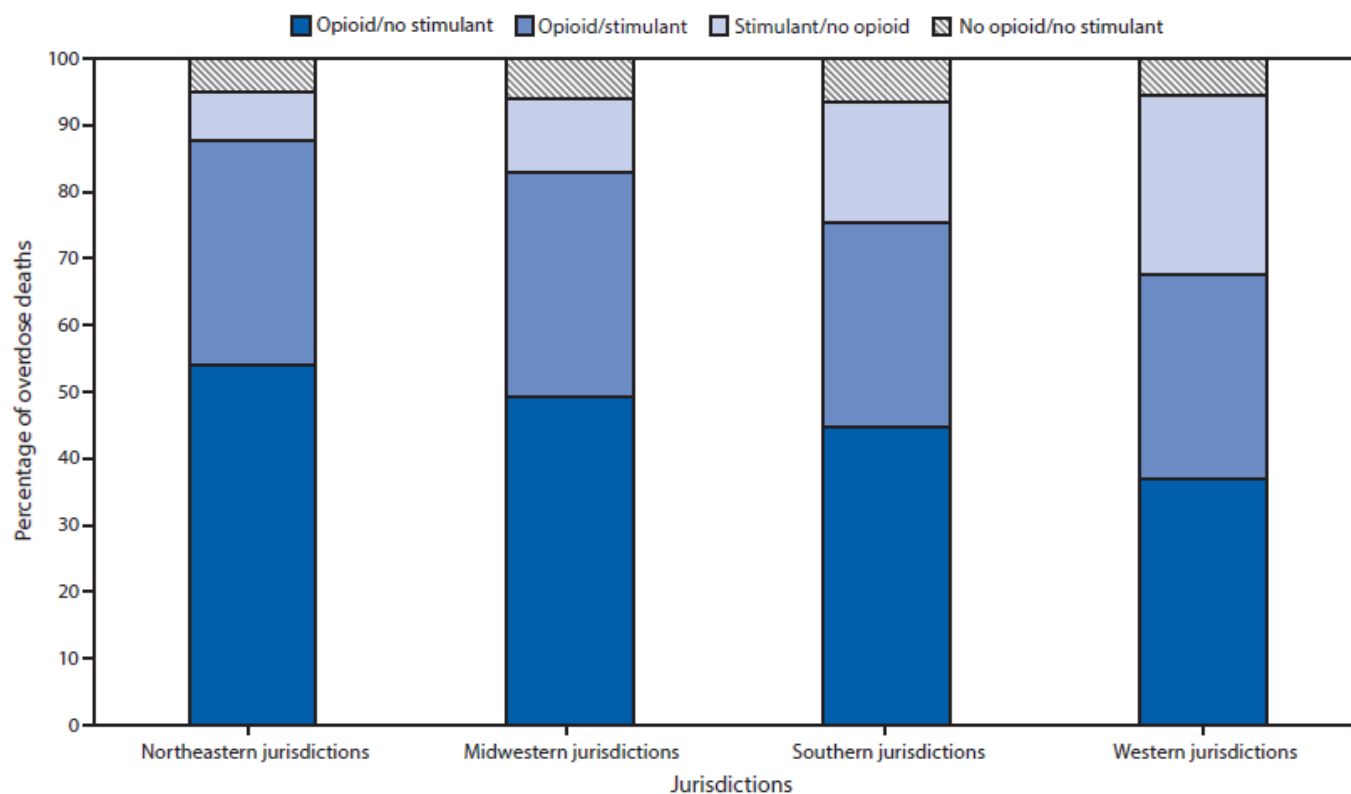
Surge in Consumption of Amphetamine and Methylphenidate



Expressed as common-dose units (10mg Amphetamines; 30mg Methylphenidate) based on DEA production quota figures



Distribution of Opioid/Stimulant Involvement in Drug OD Deaths by Geographic Region, 25 Jurisdictions, Jan-June 2019



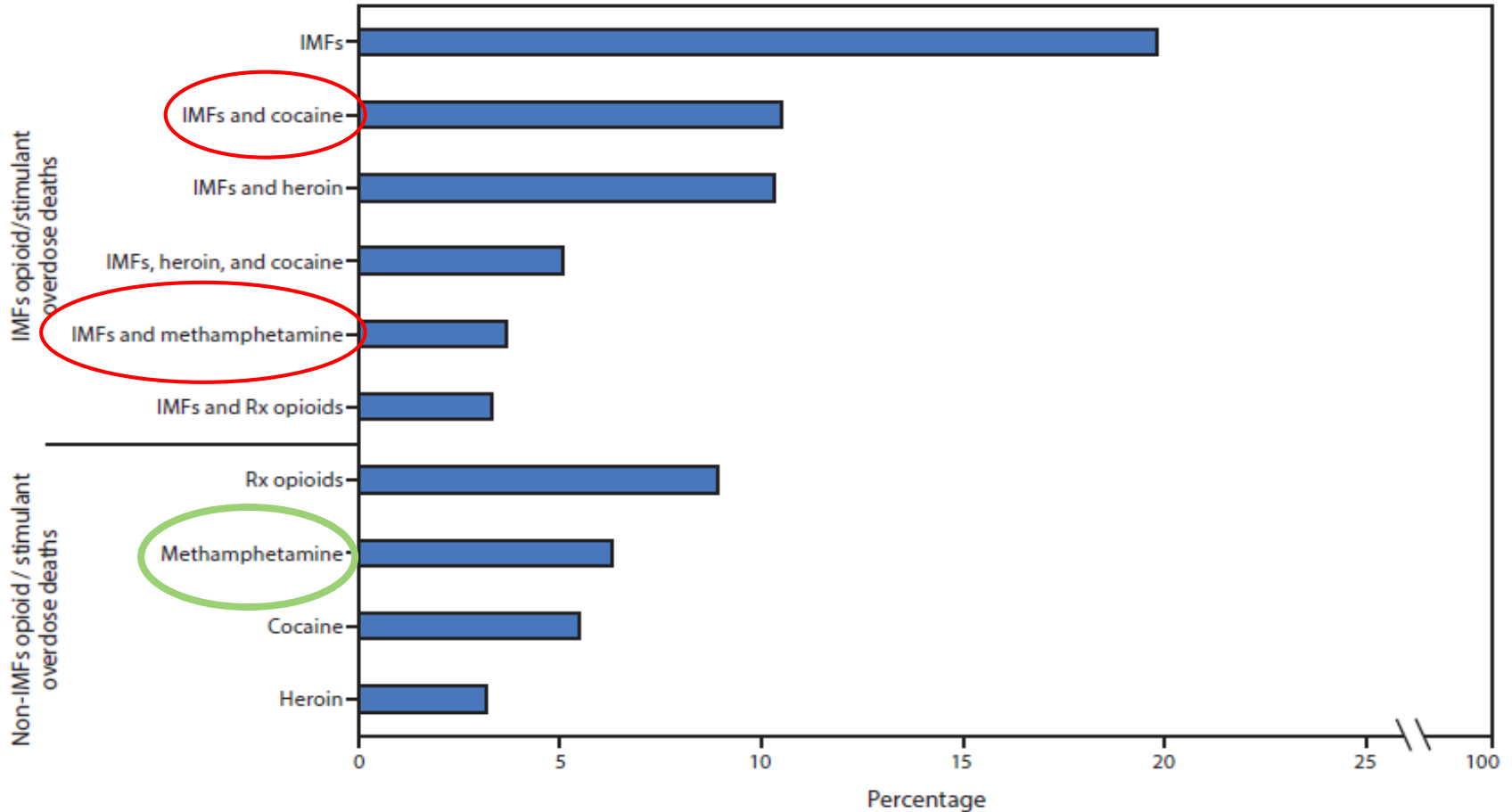
* *Midwestern:* Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin; *Northeastern:* Connecticut, Maine, Massachusetts, New Jersey, Pennsylvania, Rhode Island, and Vermont; *Southern:* Delaware, District of Columbia, Georgia, Kentucky, North Carolina, Oklahoma, Tennessee, and West Virginia; *Western:* Alaska, Nevada, Utah, and Washington.

† Pairwise chi-squared testing found statistically significant differences ($p < 0.01$) for each pairwise comparison of regions.

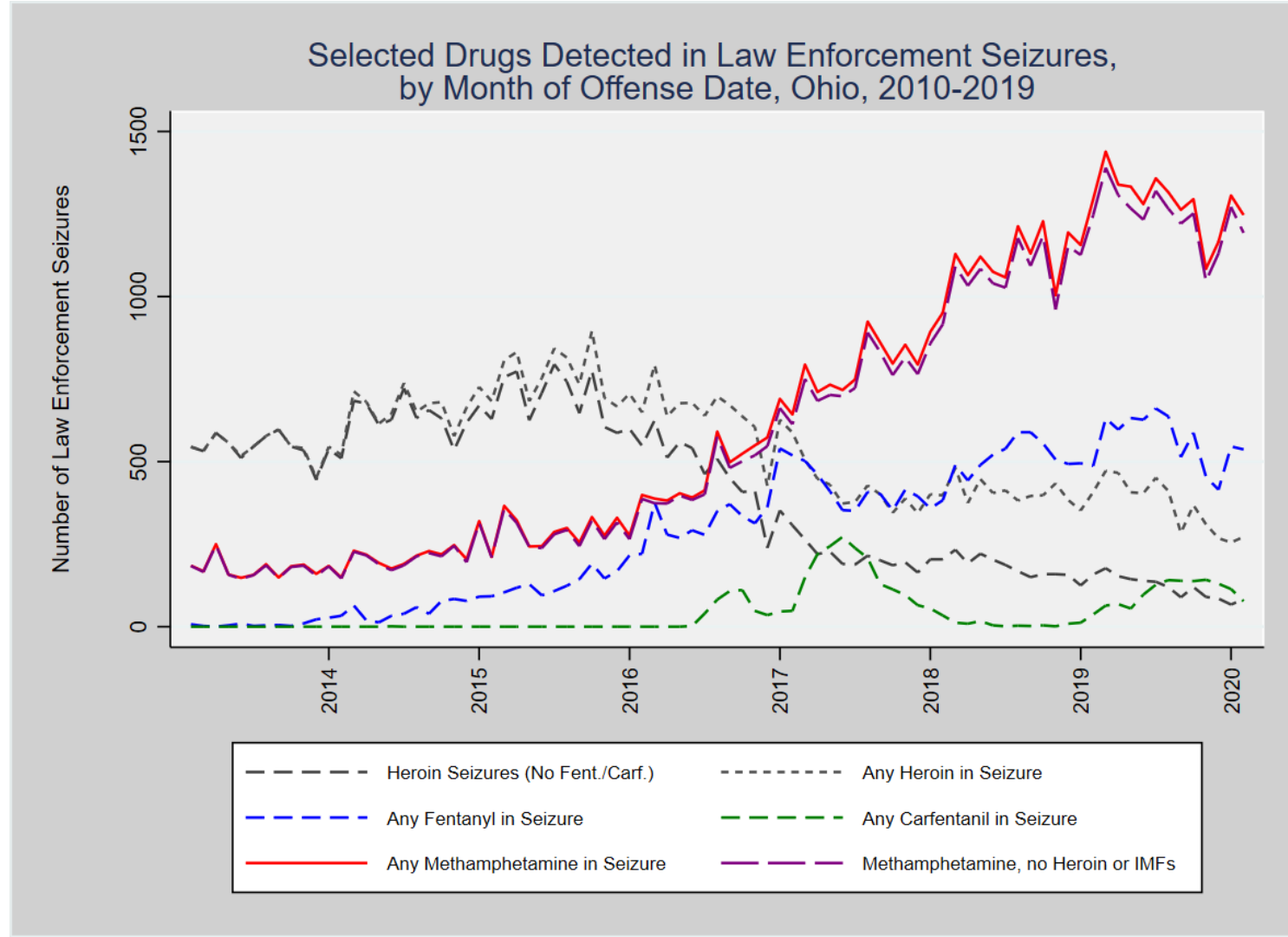
Trends Associated with Current Surge in Illicit Stimulants

- Opioid-involved overdose (OD) deaths with co-occurring cocaine and/or meth grew 429% from 2015-2017
 - ~ 20% involved cocaine (13,942)
 - ~ 15% involved meth (10,333).
- Twillman et al. found a 1280% increase in fentanyl positive screens with co-occurring meth in 2013-2019 from over 1 million urine drug toxicology results
- LaRue et al. revealed an 1850% increase in fentanyl positive screens with co-occurring cocaine in 2013-2018
- Law enforcement seizures of methamphetamine increased nearly 90% from 2015-2019 in mostly in rural areas
 - as cocaine became the second-most seized drug in urban areas behind fentanyl
- Domestic meth production has decreased dramatically over the past decade⁸ as inexpensive, highly-pure (90%), Mexican-sourced meth flowed into illicit supply chains trafficked alongside fentanyl
- During 2015-2017, urban areas witnessed the largest increase in cocaine-involved OD deaths and rural areas experienced the greatest increase in methamphetamine-involved OD deaths

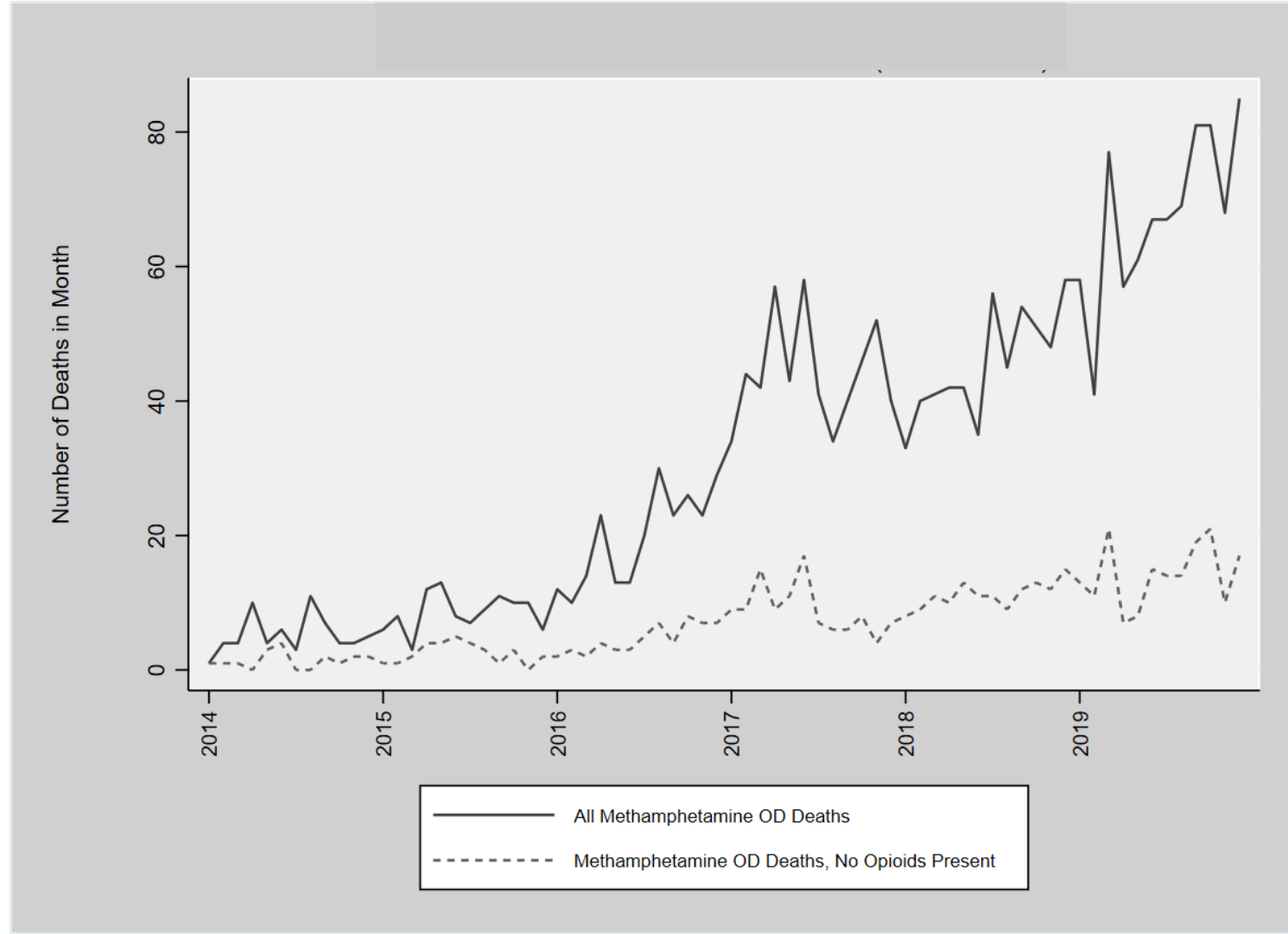
Percentage of Drug OD Deaths Involving 10 Most-Common Combinations of Opioids and Stimulants by Fentanyl, Jan-June 2019



Surge in Illicit Methamphetamine Supply, Ohio, 2010-2019



Concurrent Surge in Illicit Methamphetamine Deaths, Ohio, 2014-2019



Surge in Illicit Stimulants is Part of a Growing Landscape of Polydrug Use

- Cocaine and meth are increasingly being co-used with illicit opioids and non-opioid depressants like alcohol, benzodiazepines or gabapentinoids
- Among trauma patients in San Diego, 41% testing positive for methamphetamine had co-occurring alcohol, cocaine, and heroin, and 41% of heroin and cocaine users reported heavy drinking and “taking pills.”
- Users of cocaine and methamphetamine also report greater use of alcohol and benzodiazepines and higher rates psychological distress
- Among drug OD deaths from 2011 to 2016 that mentioned at least one specific drug, cocaine consistently ranked 2nd or 3rd, with 40% of overdose deaths involving cocaine also mentioning fentanyl and 34% mentioning meth in 2016
- In 2017-2018, 63% of fentanyl overdoses co-involved benzodiazepines, cocaine, and/or meth, and in 2019 cocaine and methamphetamine were the 2nd and 3rd most cited overdose drugs behind fentanyl
- The choice of what drugs and drug combinations to use have been shown to vary by region, race, and socioeconomic status
- Taken together, these data reveal a decade’s-long progression of illicit stimulant use in the context of a protracted opioid epidemic whose intersection may be facilitating increasing co-use of stimulants and depressants and related co-involvement in overdose mortality

Motivation To Use Meth from the Perspective of Consumers

- I think people are using more meth to counteract the fentanyl because it's going to wake you up more. People are, from what I hear they're, you know, doing meth now with their heroin *to counteract the fentanyl* (Female, 35).
- Yeah, as methamphetamine goes now it's, everybody calls it 'ice' and it's, it's definitely out there. I would say eight-out-of-ten people that inject heroin love to do 'ice' because it's a speedball, you know, you speedball it. See me, personally, I like to rush off one and then I wait a while and I like the rush off the other (Female, 33).
- Hey, if you want to get off heroin, you know, meth's a great way to do that. You're going to get sick; you're going to feel the withdrawals from the heroin, because, I mean, meth, what that, it, it gives you a very short lived high but the effects of it last way longer than the high does (Male, 33).
- Heroin's my drug of choice, so that would be what I would fiend for. These days, the meth I do to counteract the, you know, sedation, and, well, just because it's there... (Male, 36).
- Well, I do the meth if I'm sick and can't find no heroin (Male, 44)
- I just don't do this fentanyl by itself. . . . What I'm doing is so strong that if I were just doing it by itself, that I couldn't probably get my head out of my lap and deal with my day. I don't want to be just zonked out, you know (Male, 47).

Conclusion: Items for Consideration

- Vast majority of cocaine and meth-involved OD deaths involve illicit opioids (mostly fentanyl)
- But there is a growing number of methamphetamine deaths *not* involving opioids
- In contrast to cocaine, 100 years of amphetamine-related epidemics have never seen overdose mortality as a component...so why now?
 - Age
 - route of administration (more injectors in the US due to opioid epidemic?)
 - Higher potency of Mexican-sourced meth (compared to domestic manufacturing)
 - polydrug use (with opioids, benzos, alcohol, and other depressants)
 - preexisting conditions (hypertension, obesity, diabetes, etc.)
- ❑ Overdose risk profile
 - Respiratory (opioids) vs. Cardiac (methamphetamine)
 - Metabolism and Toxicity
 - Polydrug Use (contraindications)
 - Pre-existing conditions
- ❑ Treatment for Methamphetamine Addiction
 - No physical dependency
 - People often age-out of stimulant use
 - No agonist therapy approved in US (like methadone for opioid use disorder)
 - Clinical trials in Europe with Methylphenidate (Adderall®) as medicated-assisted treatment (MAT)