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Dr. Alexandra Oschman is a NICU Clinical Pharmacy Specialist and the PGY2 Pediatric Pharmacy Residency Program Director at Children's Mercy Kansas City. She completed her undergraduate degree in Chemistry and Biochemistry at the University of Louisville and her PharmD from Purdue University. She then completed her PGY1 residency at Children's Mercy Kansas City, followed by her PGY2 Pediatrics residency at the University of Kentucky Healthcare. In addition to her direct patient care activities, she participates in research, development of guidelines and policies, and serves as a preceptor to pharmacy and medical residents and fellows. Her areas of interest are varied, but include bronchopulmonary dysplasia, neonatal infections, and pharmacotherapy.



What's New on the Street?

Alex Oschman, PharmD, BCPPS



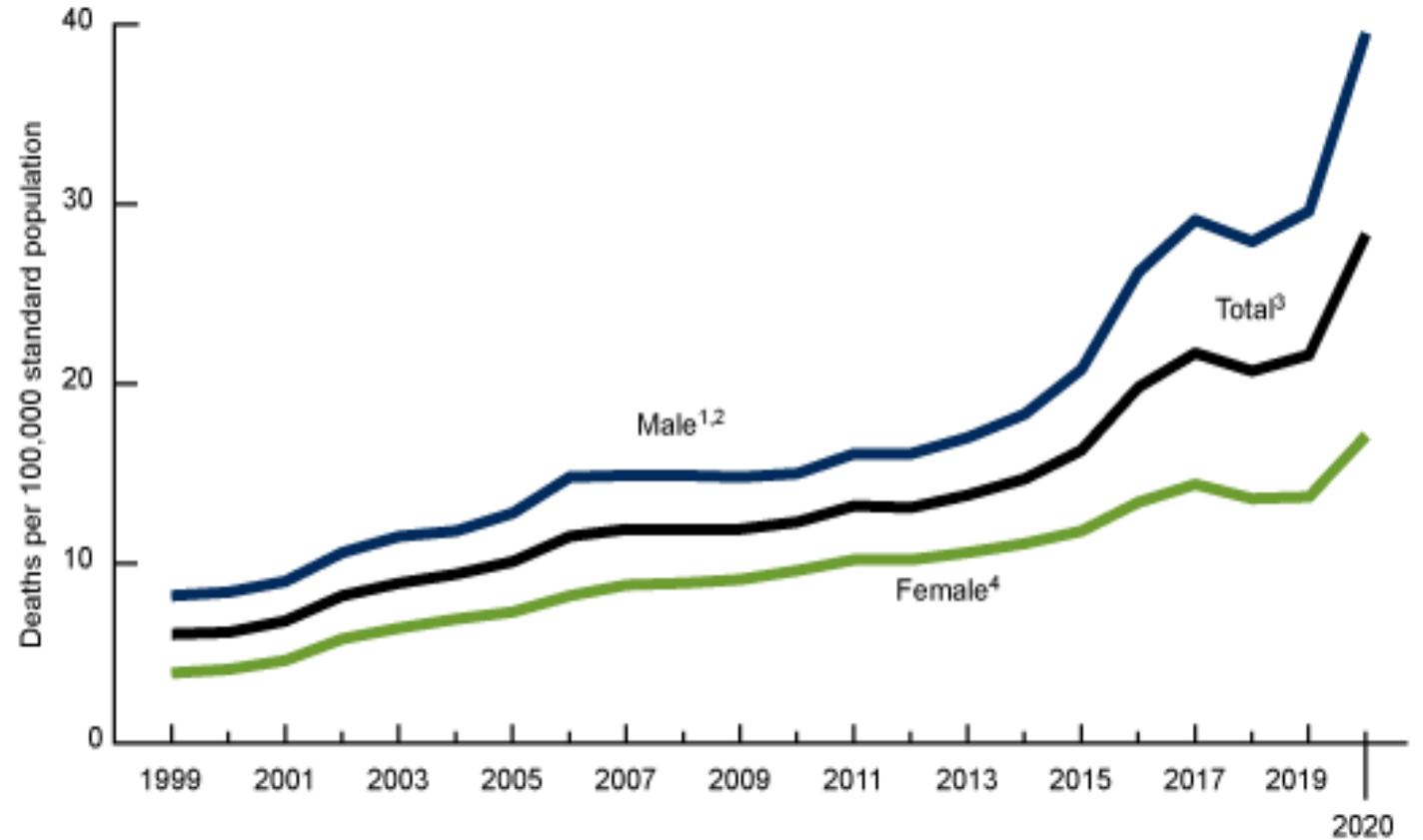
Disclosures

- I have nothing to disclose

Objectives

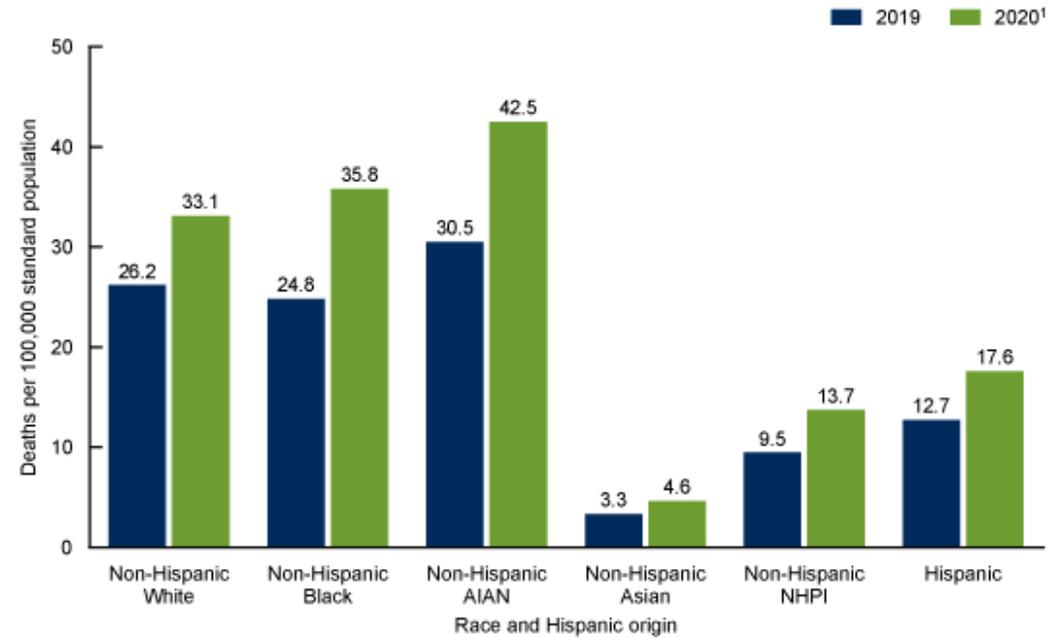
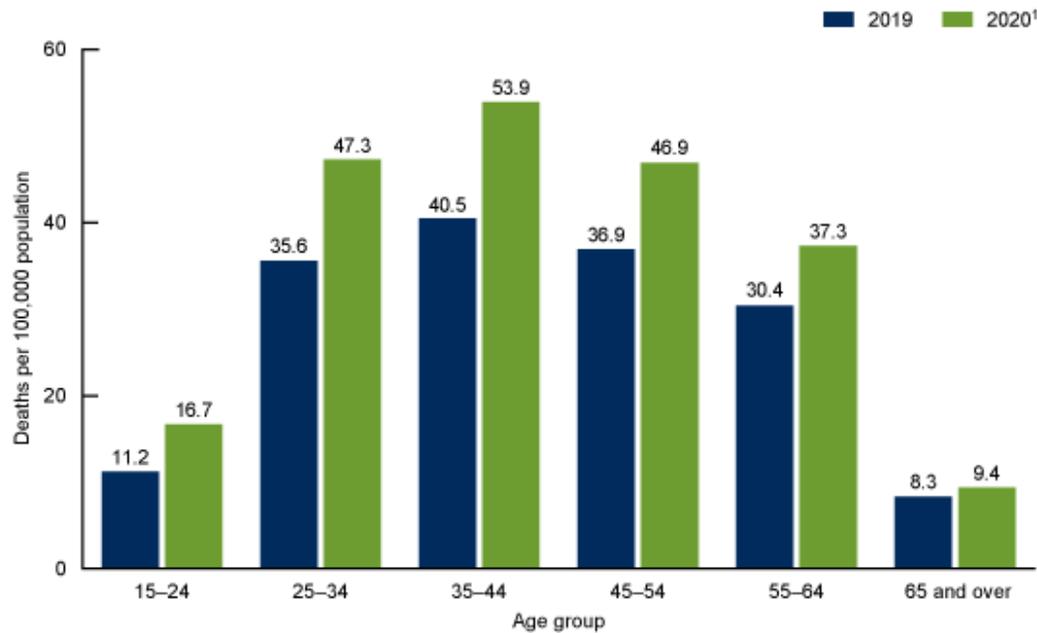
- Identify new and emerging drugs of abuse
- Discuss the effect of these drugs on the newborn and newborn fetus when data is available

US Drug Overdose Death Rates 1999-2020

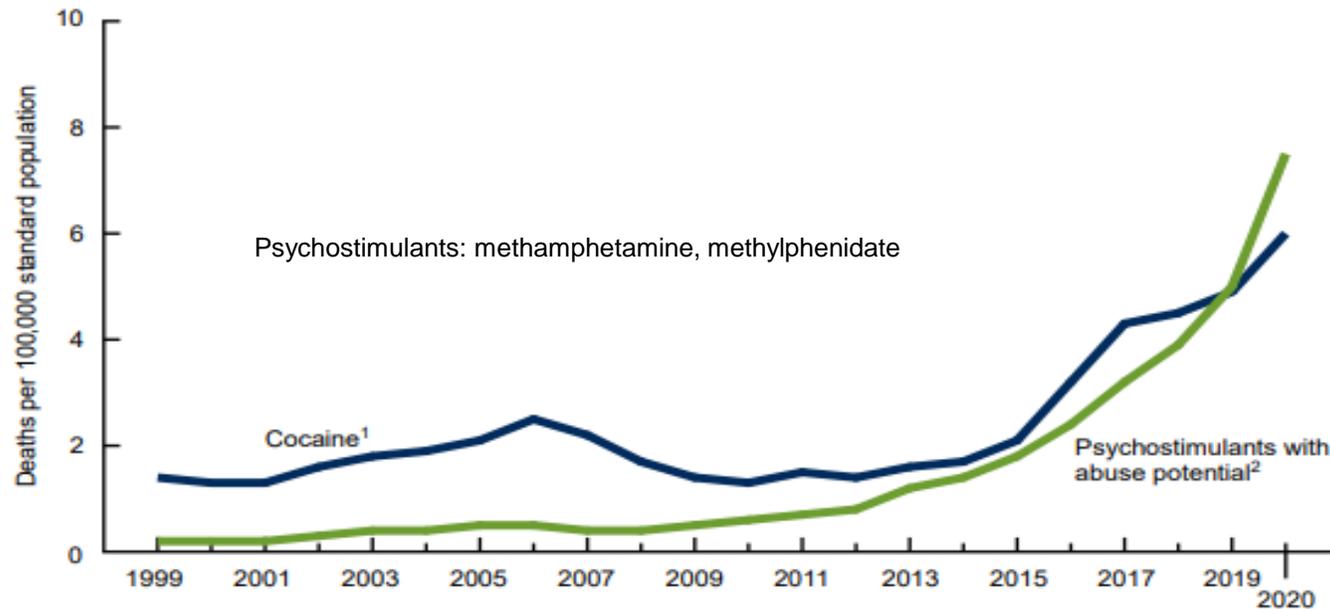
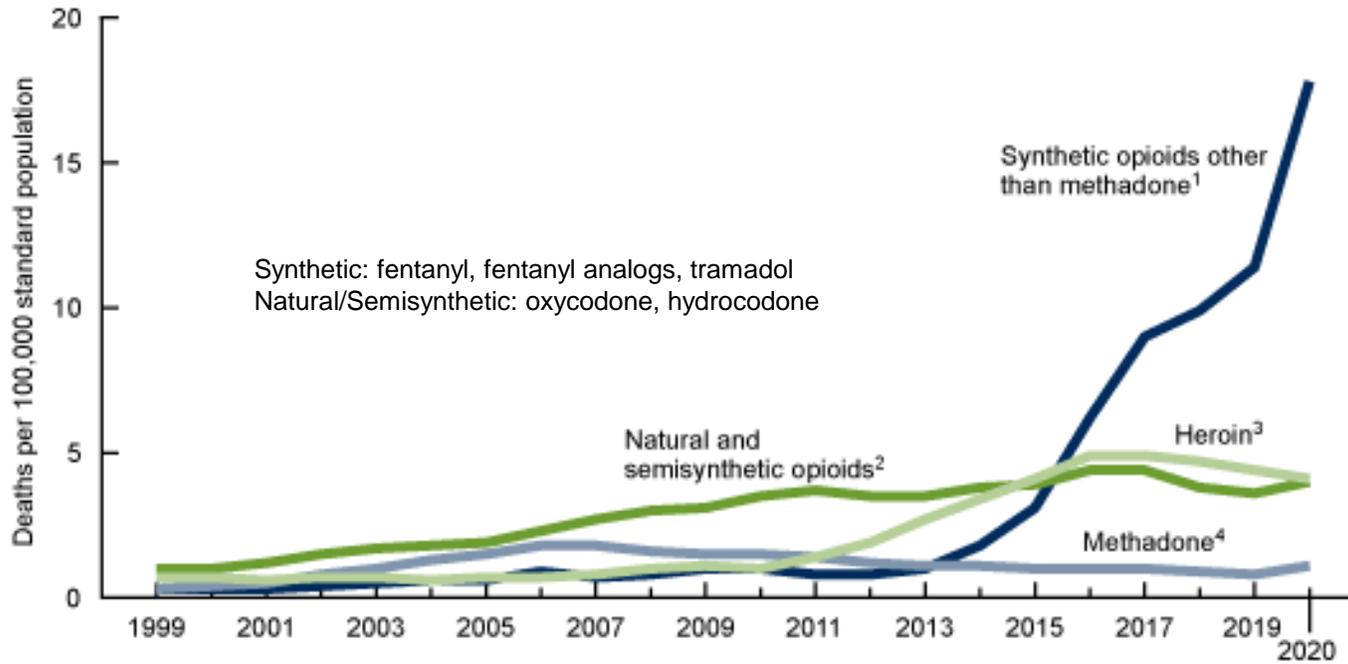


1. Hedegaard H, et al. NCHS Data Brief. 2021; 428: 1-8.

Death by Age and Race



Overdose Deaths By Type of Opioid



New and New Psychoactive Substances (NPS)

- Millions use and misuse illicit street drugs every year
- Commonly known
 - Heroin
 - Methamphetamine
 - Powder/crack cocaine
 - Fentanyl laced drugs
 - Psychedelics (LSD, PCP)
 - Counterfeit pills
 - Inhalants

Nitazenes

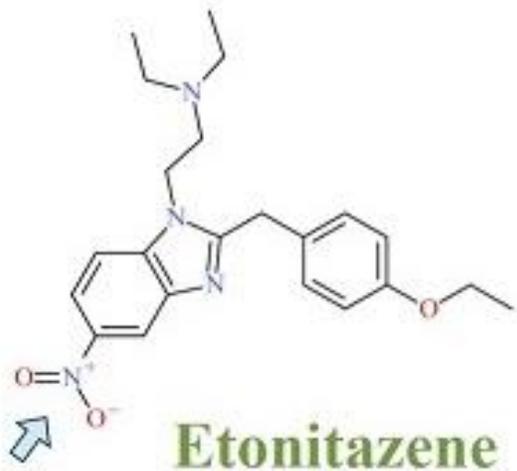
Phenibut

Xylazine

Carfentanil

Cathinone

Nitazenes



First seen in 2019

- Florida, Illinois, Wisconsin
- 4x increase in Tennessee in 2021

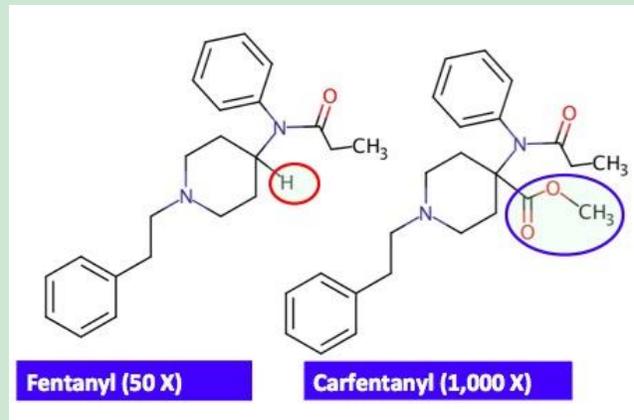
Originally developed 60 years ago

- Abandoned due to high overdose potential
- Opioid (binds mu receptor)
- 20-100x vs fentanyl
- 10 products
- Isotonitazine, Protonitazene, Etonitazene

Street Use

- Usually a powder
- Added/laced with other drugs

Fentanyl & Carfentanil



Fentanyl

- Increasing use in combination drugs

Carfentanil

- 20-100x more potent than fentanyl
- Sedation for elephants, horses
- Handling requires protective gear to prevent skin absorption
- Added to heroin, cocaine, methamphetamine

Mitragynine (Kratom)

Tropical evergreen tree from Southeast Asia

- Thailand, Malaysia, Indonesia and Papua New Guinea

Alternative agent

- Muscle pain, diarrhea, opiate addiction and withdrawal

Stimulant at ↓ doses, opioid effects at ↑ doses

- 25 alkaloids (several are active)
- May bind to serotonin and dopamine receptors
- Mu and Kappa-opioid receptor agonist
 - 13x more potent than morphine
- 3-4 hour half-life



Kratom Adverse Effects

Opioid-like effects

- Sedation
- Nausea
- Constipation
- Dizziness

Hepatotoxicity

- 404 cases
- 8 tied to Kratom
- Jaundice

Miscellaneous

- Jerky limb movements
- Hypothyroidism

Chronic use

- Hallucinations
- Delusion
- Anorexia

High dose

- Tachycardia
- Hypotension

Kratom & Pregnancy

- Very little research
- 2021 report
 - Most use involved other substances as well
 - 5 cases of opioid-like withdrawal in newborns
 - 37 weeks to term gestation
 - Symptoms began 6-8 hrs and up to 4 days after birth
 - Mean length of stay = 10 days (3-12)
 - All 5 treated with a morphine weaning protocol
 - One was changed to clonidine
 - Potentially higher scores than with typical opioids
- Unknown exposure through placenta and breastmilk

Effects on the Baby?

(Nitazenes, Carfentanil, Kratom)



Cathinones

Natural: Khat

- Similar structure to amphetamines
- Enhances norepinephrine, epinephrine, dopamine, and serotonin
 - Blocks re-uptake
- Thought to relieve headaches, help with birth
- Used highly in the middle east
 - 35-60% daily use in females

Synthetic: Flakka, blizzard, gravel, bath salts

- More potent than natural cathinone
- Form: Pale/pinkish crystal
 - Vaporized, snorted, eaten, injected



How Do Cathinones Affect the Body?

Systems affected	Short-term/intermediate effects	Long-term/chronic effects (most effects manifested with short-term/intermediate use also persist here)
<ul style="list-style-type: none"> Central nervous system^{7,11,20,22,23,26} 	<ul style="list-style-type: none"> Mild euphoria, excitement, alertness, insomnia, talkativeness, lethargy, depression, headache/migraine, psychotic reaction (high doses), hallucinations, inability to concentrate, irritability, fine tremor (post khat use), anorexia 	<ul style="list-style-type: none"> Psychosis, depressive reactions, impaired cognitive functioning, increased tremor, seizures
<ul style="list-style-type: none"> Gastrointestinal and hepatic system^{15,18,27-33} 	<ul style="list-style-type: none"> Constipation, polydipsia, gastritis 	<ul style="list-style-type: none"> Gastrointestinal disorders (eg., stomach/duodenal ulcers, inflammation, severe constipation, increased risk of upper gastrointestinal tumors/malignancy, hemorrhoids), liver cirrhosis and fibrosis
<ul style="list-style-type: none"> Cardiovascular system^{11,17,21,22,33} 	<ul style="list-style-type: none"> Tachycardia/palpitation, vasoconstriction, increased blood pressure 	<ul style="list-style-type: none"> Increased cardiovascular disorders, myocardial infarction, heart attack, cerebral hemorrhage
<ul style="list-style-type: none"> Genitourinary system^{6,7,17,19,22,24} 	<ul style="list-style-type: none"> Impotence, libido change (mostly in men) 	<ul style="list-style-type: none"> Impaired male sexual function, impotence, urinary retention
<ul style="list-style-type: none"> Ocular effects^{7,12,22-24,31} 	<ul style="list-style-type: none"> Mydriasis, blurred vision 	<ul style="list-style-type: none"> Mydriasis, blurred vision
<ul style="list-style-type: none"> Metabolic and endocrine systems^{7,12,22-24,26} 	<ul style="list-style-type: none"> Hyperglycemia (inconsistent), hyperthermia, perspiration 	<ul style="list-style-type: none"> Multiple hormonal disorders, malnutrition, weight loss
<ul style="list-style-type: none"> Respiratory system²²⁻²⁴ 	<ul style="list-style-type: none"> Tachypnea 	<ul style="list-style-type: none"> Pulmonary edema, bronchitis
<ul style="list-style-type: none"> Oro-dental effects^{24,27,28,31,33,36} 	<ul style="list-style-type: none"> Oro-dental lesions (eg., dry mouth, caries, periodontal diseases), multiple other moderate oral disorders 	<ul style="list-style-type: none"> More severe oro-dental disorders; oral mucosal keratosis, cancer

Data From Khat Usage

Short duration of action

- Psychological dependence vs physical dependence

Drug interactions?

- Recovery from anesthesia
- Decreased bioavailability of orally administered penicillins
 - Due to interaction with tannins in the GI tract
- Inhibition of anti-platelet effect of aspirin
- Inhibition of CYP 2D6

Breastmilk

- Can decrease breast milk production
- Has several metabolites that pass into breastmilk

What About Baby?

Affect on pregnancy is poorly documented

- Methylenedioxypryovalerone (MDPV) studied in mice
 - 3rd trimester exposure
 - Apoptosis in several areas of the brain
 - Early pregnancy
 - Decreased maternal care
 - Higher agitation/disordered movements
 - Lower survival rates
 - Drug deposition in placenta and brain
 - Higher in fetus than in mom

2 Case reports

- Stillborn
 - 36 week gestational age
- Symptoms similar to opioid withdrawal
 - 37 week gestational age
 - Irritability, jitteriness, high-pitched cry, hyperreflexia
 - Treated with phenobarbital



Miscellaneous Drugs of Abuse

Xylazine (Tranq)

- Strong sedative
 - FDA approved for veterinary use
 - Not a controlled substance
- Often cut with fentanyl
 - Philadelphia: detected in 91% of heroin and fentanyl samples
 - Multiple increased reports of use in 2023
- Alpha-2 Blocker
 - Narcan won't work
 - No antidote
- Adverse effects
 - Hypotension
 - Respiratory depression
 - Hypoglycemia
 - Bradycardia
 - Coma
 - Soft tissue injuries → Amputation

Effect on the Baby

Limited info in humans

Known to cross the placenta

Animal data

- Minimal effect on fetal heart rate
- Contraction of the uterus
- Increased uterine tone
- Decreased fetal weight
- Premature labor
- Developmental delays
- Decreased maternal milk production

Withdrawal Symptoms in Baby?

- Adults
 - Jitteriness, tremors, agitation, respiratory distress
 - Case report
 - Dexmedetomidine, clonidine, tizanidine
 - Discharged on clonidine for symptoms
 - Treatment plan of gabapentin and buprenorphine
 - FDA report states that it is not managed by standard pharmacological therapy for opioid use disorder
 - Doesn't give treatment recommendations

Synthetic Cannabinoids (K2/Spice)

- Often marketed as safe alternatives to marijuana
 - More potent than marijuana
- Unregulated
 - 2015: 84 new synthetic cannabinoids
- Adverse effects
 - Tachycardia
 - Vomiting
 - Agitation
 - Confusion
 - Hallucinations
 - Acute kidney injury
 - Myocardia infarction
 - Stroke
 - Seizures

Cannabinoids: Effects on Pregnancy

Placenta

- May reduce blood flow
- Crosses the placenta

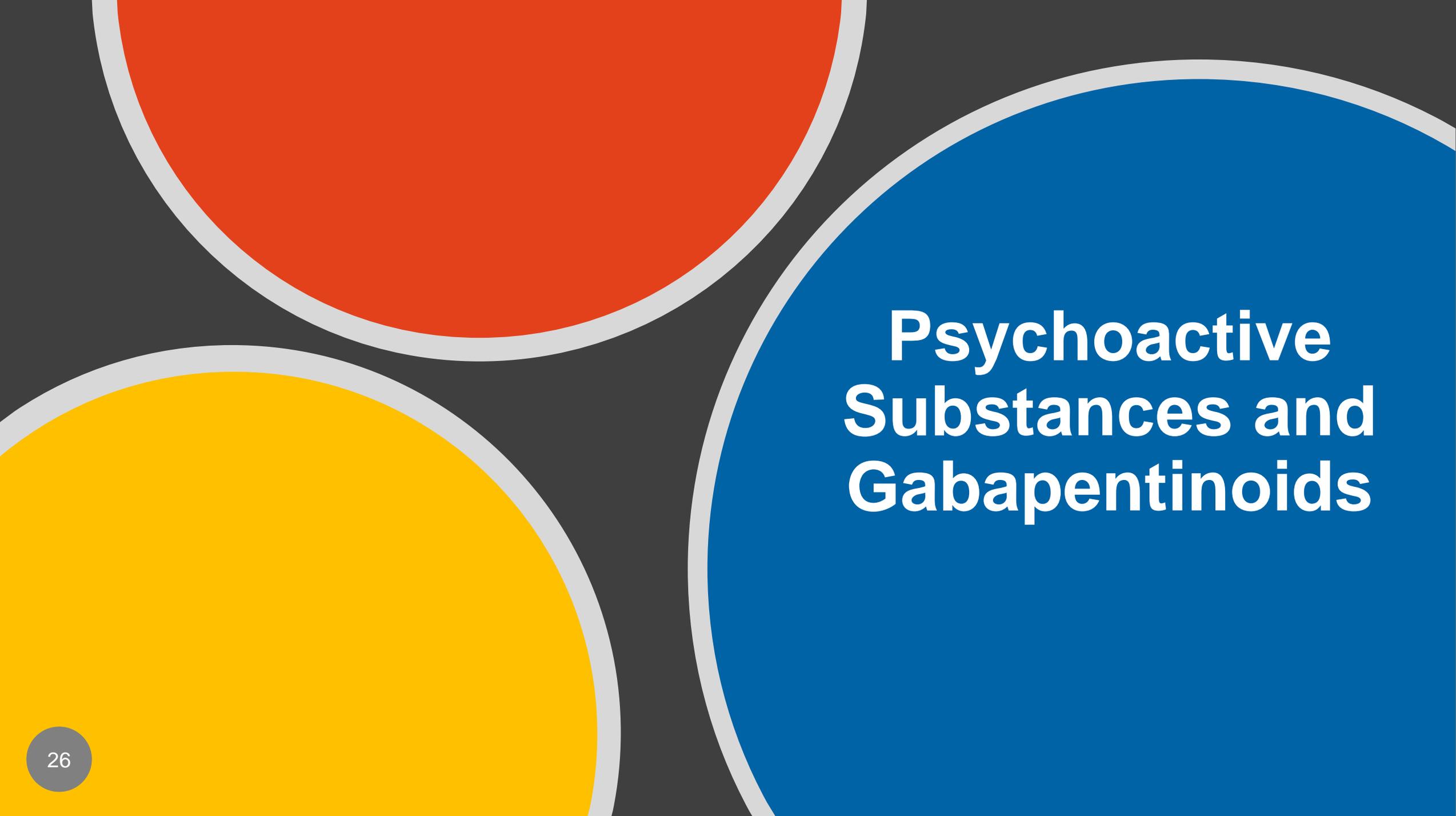
Miscarriage and Preterm Birth

- Cannabis data
- Corrected for confounding factors; increased risk of
 - Stillbirth: 50%
 - PPRM: 46%
 - Preterm birth: 40%
 - Growth restriction: 35%
- No increase in risk
 - Congenital malformation

Cannabinoids: Effects on Pregnancy

Directly affects the fetus

- Impacts on fetal brain development
- Other effects
 - Neurological impairment
 - Hyperactivity
 - Poor cognitive function
 - Changes in dopamine receptors
- Decrease in birth weight
 - Head circumference?
- Fetal anomalies
 - Mixed data with non-synthetic marijuana



Psychoactive Substances and Gabapentinoids

β -phenyl-aminobutyric acid (Phenibut)

Originated in Russia in the 1960s

- Dietary supplement
- Cognitive booster
- Insomnia
- Anxiety
- Performance enhancer

Structurally similar to GABA_B

- Nonselective GABA agonist
- Stimulates dopamine receptors

Adverse effects

- Confusion
- Hypertension
- Tachycardia
- Seizures
- Muscle spasms
- Respiratory depression

Withdrawal symptoms

- Rebound anxiety/depression
- Headaches
- Agitation
- Brain fog
- Tachycardia
- Tremors

Gabapentin/Pregabalin

Structurally similar to GABA

- Mechanism is not completely elucidated
- Does not act on the GABA system
- Binds to calcium channels
- Decreases stimulus triggered excitatory neurotransmitter release

Adverse effects

- Somnolence
- Dizziness
- Fatigue
- Euphoria
- Peripheral edema

Effects on the Baby

Pregnancy

- Crosses the placenta (half-life of 14 hrs)
- Limited outcome data

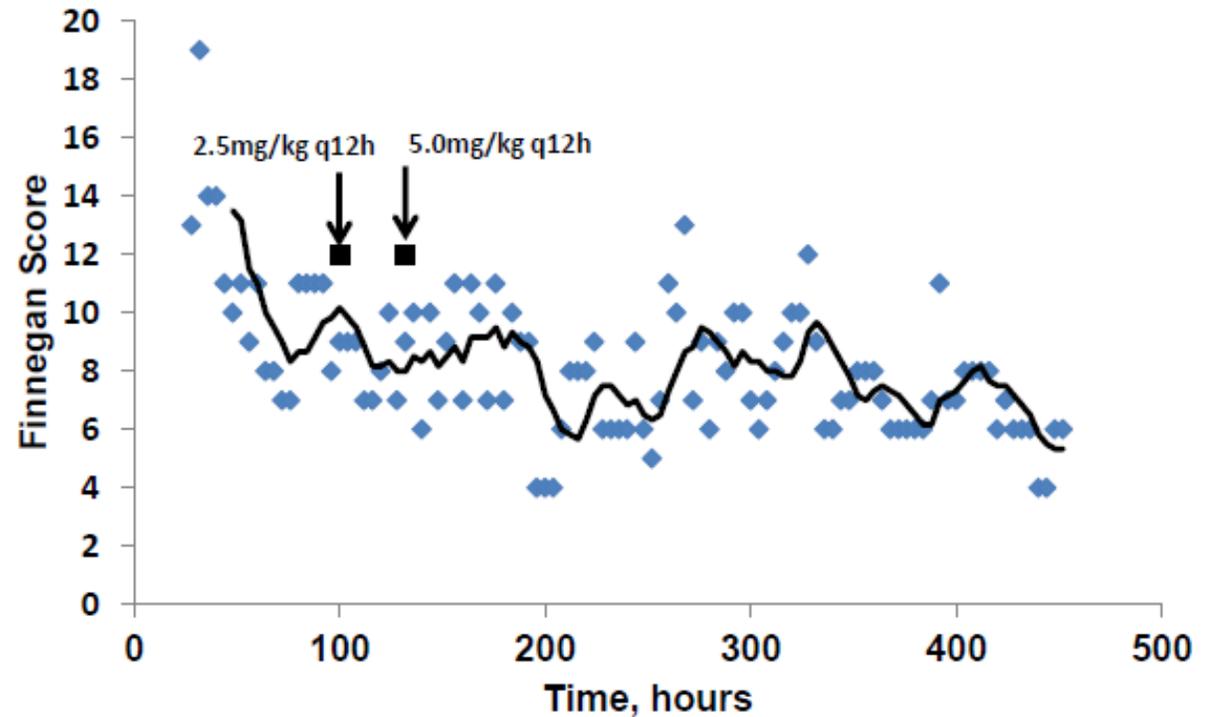
Breastfeeding

- Crosses into breastmilk
- Relative infant dose is 9-13%
- Monitor for drowsiness, adequate weight gain

Effects on the Baby

Case report

- 36 week gestation
- Symptoms around 24 hrs
- Day 1: Lorazepam 0.05 mg/kg every 6 hours
 - Increased to 0.15 mg/kg
- Day 6: gabapentin 2.5 mg/kg BID
 - Titrated to 5 mg/kg BID
- Lorazepam was stopped
- Weaning started on day 15
- Gabapentin stopped on day 48



Gabapentin Neonatal Withdrawal

- 19 infants treated
 - 9 = methadone; 10 = additional therapy
- Additional therapy patients
 - Onset ~ day 3
 - Clonidine was added to methadone
 - Gabapentin 2.5 mg/kg BID
 - Scores decreased to <8 within 48 hours
 - Weaned by 25% every 4 days; methadone every 2 days

Table. Infants treated with gabapentin, 2015

Patients	Maternal Exposure	Mother's dose of gabapentin (mg/day)	DOL gabapentin started	Number of days on gabapentin treatment	Electroencephalogram results	Unique symptoms
1	Heroin, hydromorphone	600-3000	15	30	Normal	Yes
2	Methadone	Unknown	15	37		Yes
3	Subutex	4800	11	45		Yes
4	Subutex	1800	11	37		Yes
5	Hydrocodone, heroin, vistaril, flexeril	Unknown	10	40	Normal	Yes
6	Heroin, hydromorphone	Unknown	23	60	Normal	Yes
7	Subutex, marijuana	Unknown; used daily	19	30		Yes
8	Heroin, oxycodone	400-1200	7	63	Normal	Yes
9	Subutex	12 500	15	52		Yes
10	Subutex, marijuana, (history of heroin before 26 weeks gestation)	Unknown; used daily	26	73	Normal	Yes

Summary

- The realm of drug misuse has significantly changed since 2020
- Drugs with increasing potency along with combination drugs are increasing in popularity
- The effect of most of these compounds on the mother, fetus, and newborn are unknown
 - Several compounds work similarly to opioids and likely have similar effects and treatment
- Unknown if many of the treatment options utilized for neonatal opioid withdrawal syndrome are effective for these other exposures

