Can pharmacogenetic enhance our understanding and management of Opioid Use Disorder?

Jon E. Sprague, RPh, PhD
Director of Science & Research for the Ohio Attorney General
BCI Eminent Scholar
Bowling Green State University

DAVE YOST

Objectives

- Explain the impact of the COVID-19 pandemic on the opioid crisis in Ohio and United States
- Describe the chemical modifications made to fentanyl
- Describe the effects of opioids on the dopamine reward pathways in the brain
- Explain the pharmacogenetics in the context of OUD
- Discuss the Ohio pharmacogenetic study of OUD

National Data: Opioid Overdose Deaths

U.S. Drug Overdose Deaths

- More than 100,000 deaths from June 2020 to May 2021
- ~170 fatalities/ day primarily in those 18 to 45
- Primary driver is illicit forms of fentanyl
- Estimated annual economic cost to the U.S. is $1 trillion
- Drug traffickers in Mexico produce most of the counterfeit tablet

New Challenges to the United States

- Illegal drug manufacturing has become easier to conceal by moving from the field to the laboratory.
- Serious geopolitical issues significantly impede actions to disrupt supply.
- Synthetic opioids are highly potent and easy to make, and small amounts can be transported for large profits.
- Social media and encryption platforms, as well as established logistics systems, make distribution difficult to disrupt.
- COVID-19

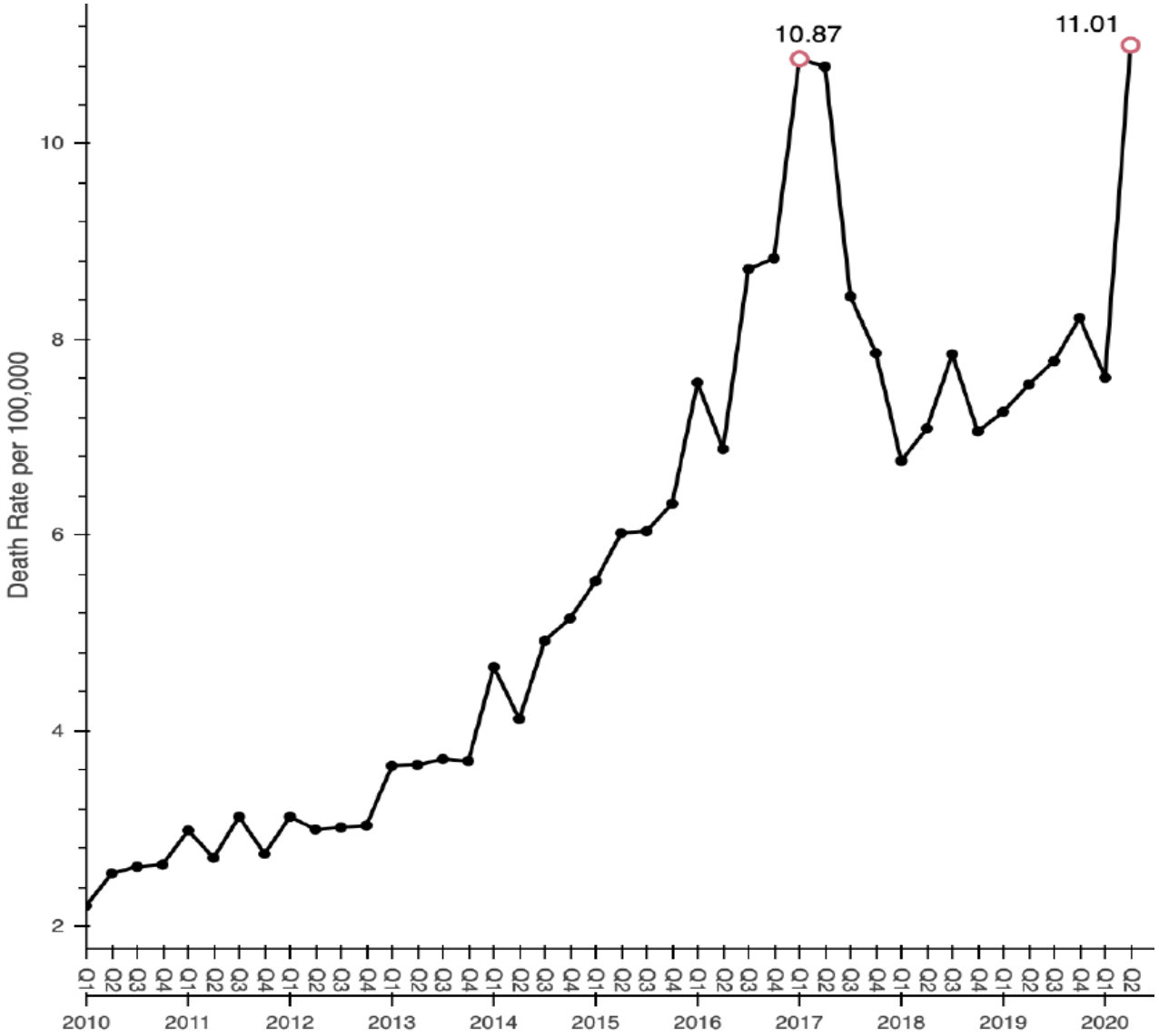
Source: U.S. Commission on Combating Synthetic Opioid Trafficking

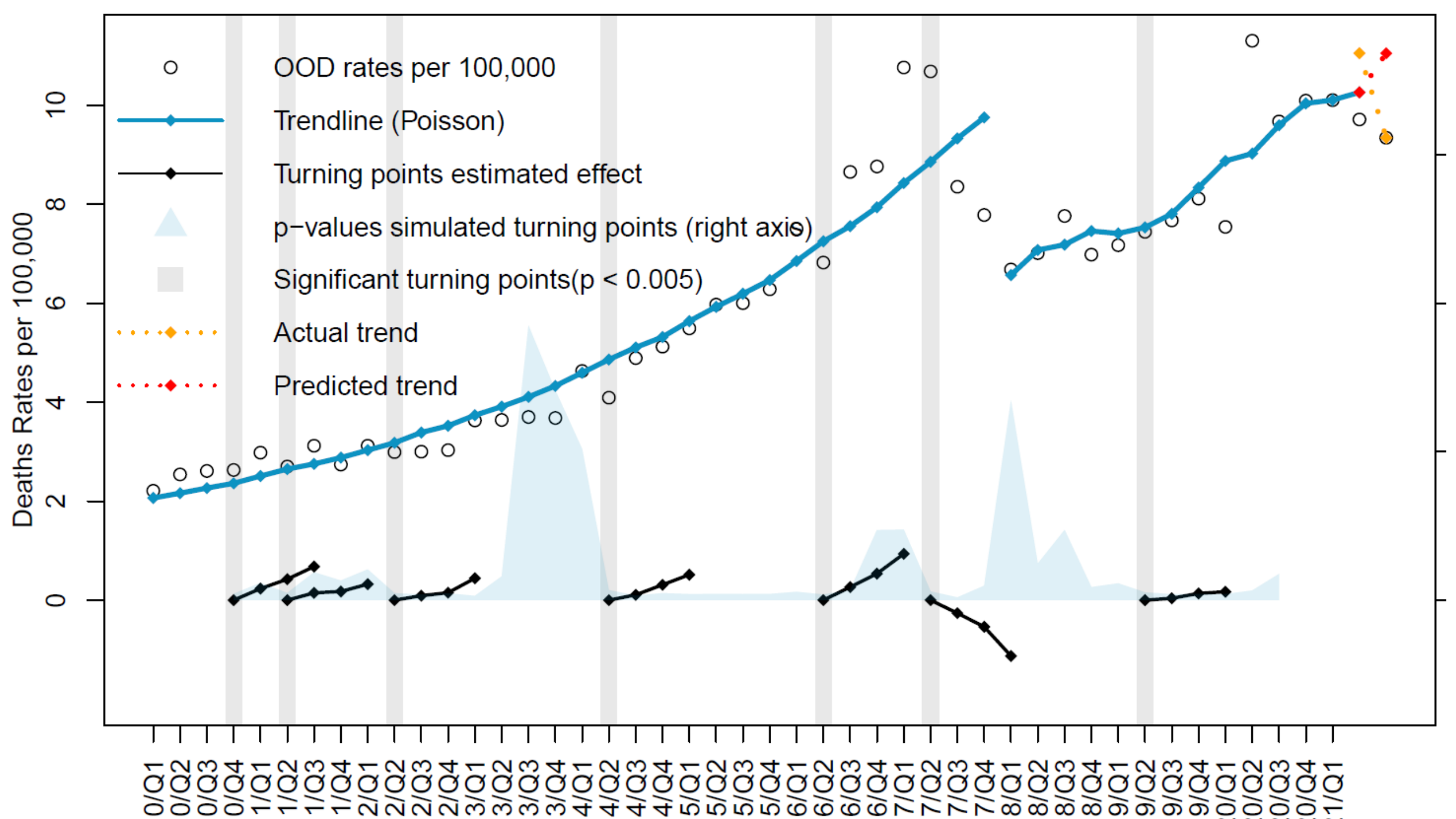
Ohio Data: Opioid Overdose Deaths

Methods

- The ODH database was quarried
- Mortality dataset for deaths in Ohio related to opioids
- Temporal trend analyses were utilized to identify significant changes in trends of the quarterly OOD rate per 100,000 from Q1 of 2010 to Q2 of 2020.

Results


10.87
11.01
Death Rate per 100,000
2
4
6
8
10
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020


OOD rates per 100,000
Trendline (Poisson)
Turning points estimated effect
p−values simulated turning points (right axis)
Significant turning points(p < 0.005)
Actual trend
Predicted trend
Deaths Rates per 100,000
0
2
4
6
8
10
0/Q1
0/Q2
0/Q3
0/Q4
1/Q1
1/Q2
1/Q3
1/Q4
2/Q1
2/Q2
2/Q3
2/Q4
3/Q1
3/Q2
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8/Q2
8/Q3
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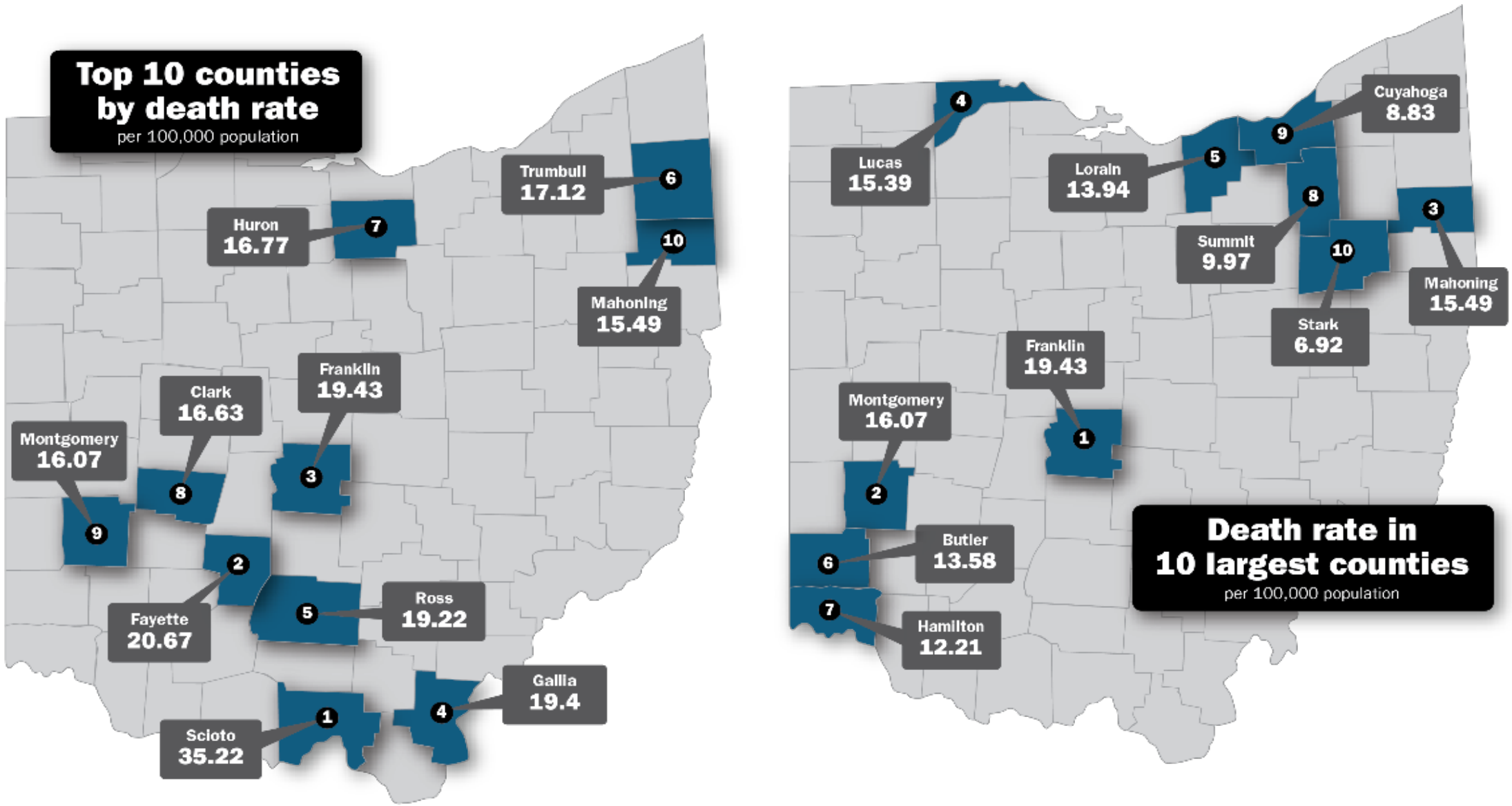
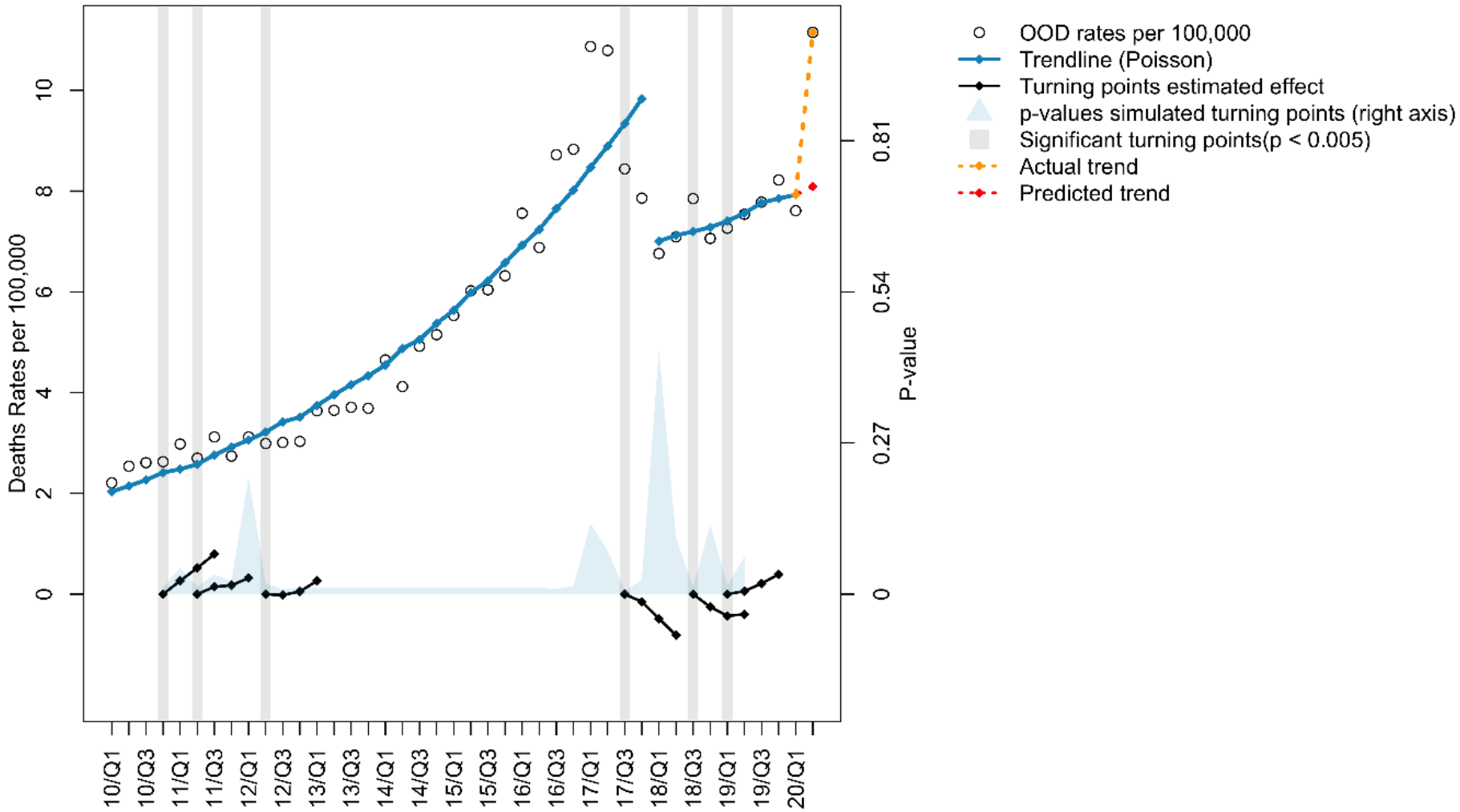
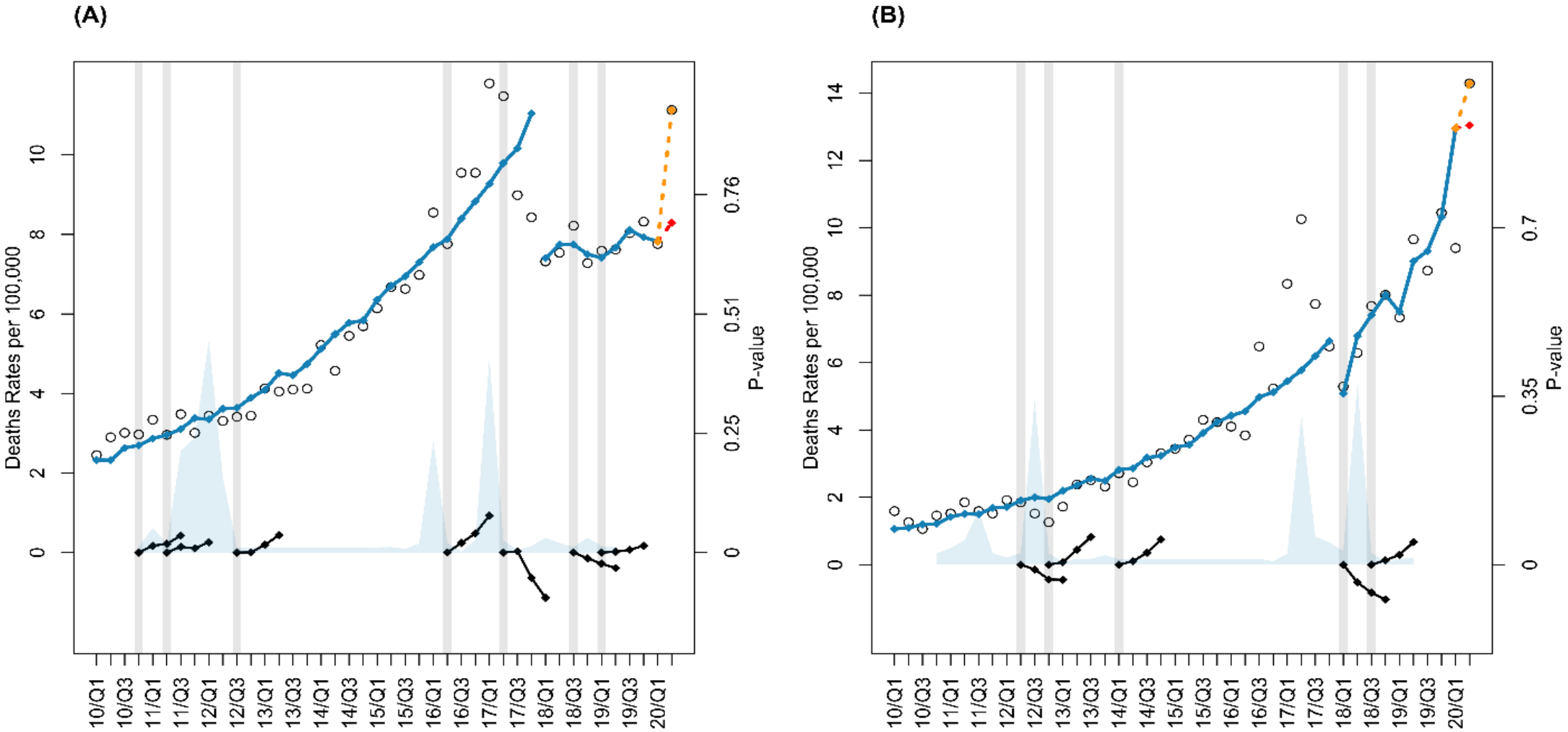
10/Q1
10/Q2
10/Q3
10/Q4
11/Q1


Top 10 counties by death rate
per 100,000 population
Trumbull 17.12
6
Huron 16.77
7
10
Mahoning 15.49
Franklin 19.43
Clark 16.63
Montgomery 16.07
3
8
9
2
Fayette 20.67
5
Ross 19.22
Gallia 19.4
4
Scioto 35.22
1
4
Lucas 15.39
Lorain 13.94
5
9
Cuyahoga 8.83
8
Summit 9.97
3
10
Mahoning 15.49
Stark 6.92
Franklin 19.43
Montgomery 16.07
1
2
Butler 13.58
6
7
Hamilton 12.21
Death rate in 10 largest counties
per 100,000 population

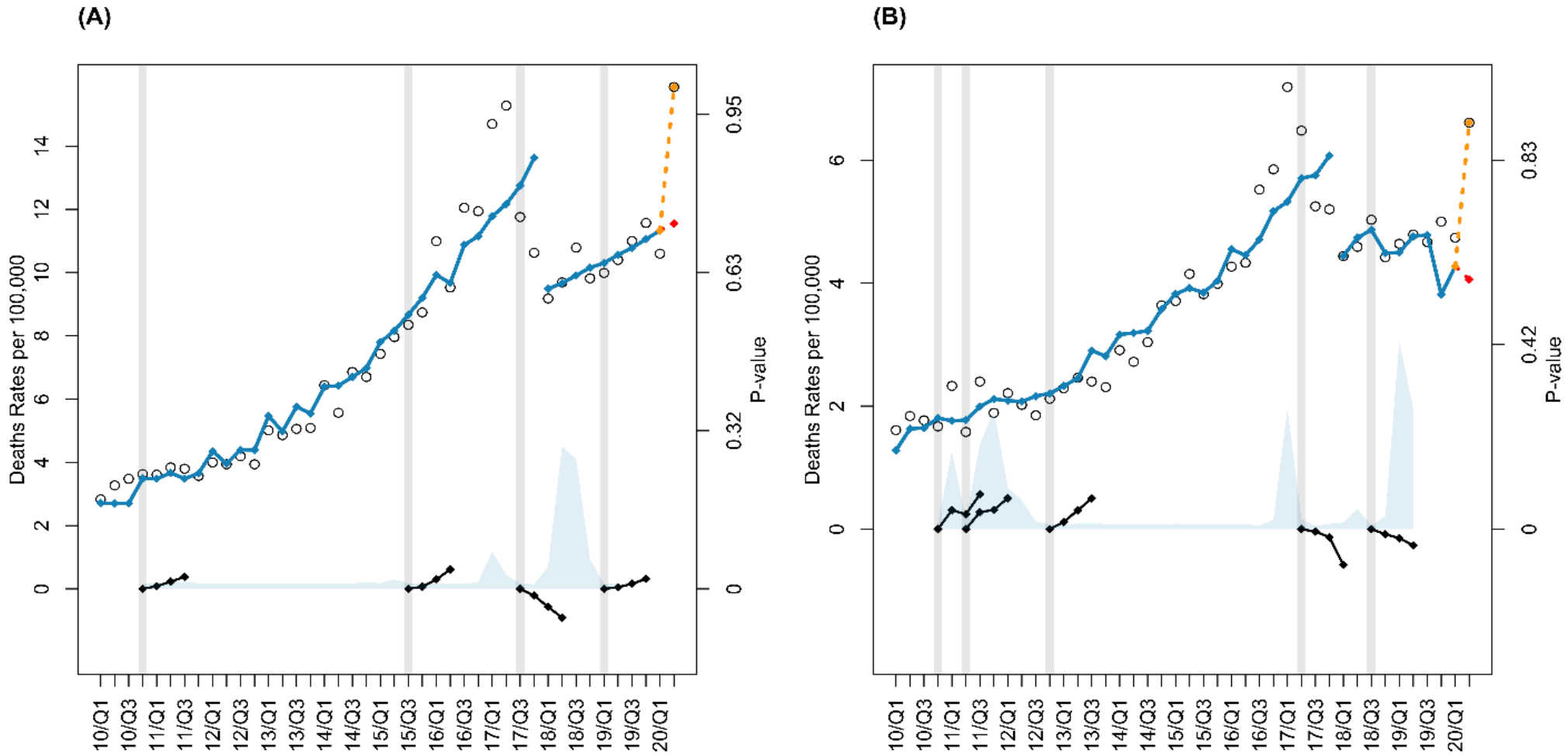
Temporal Trend Analysis of the Overall Quarterly OOD Rate per 100,000



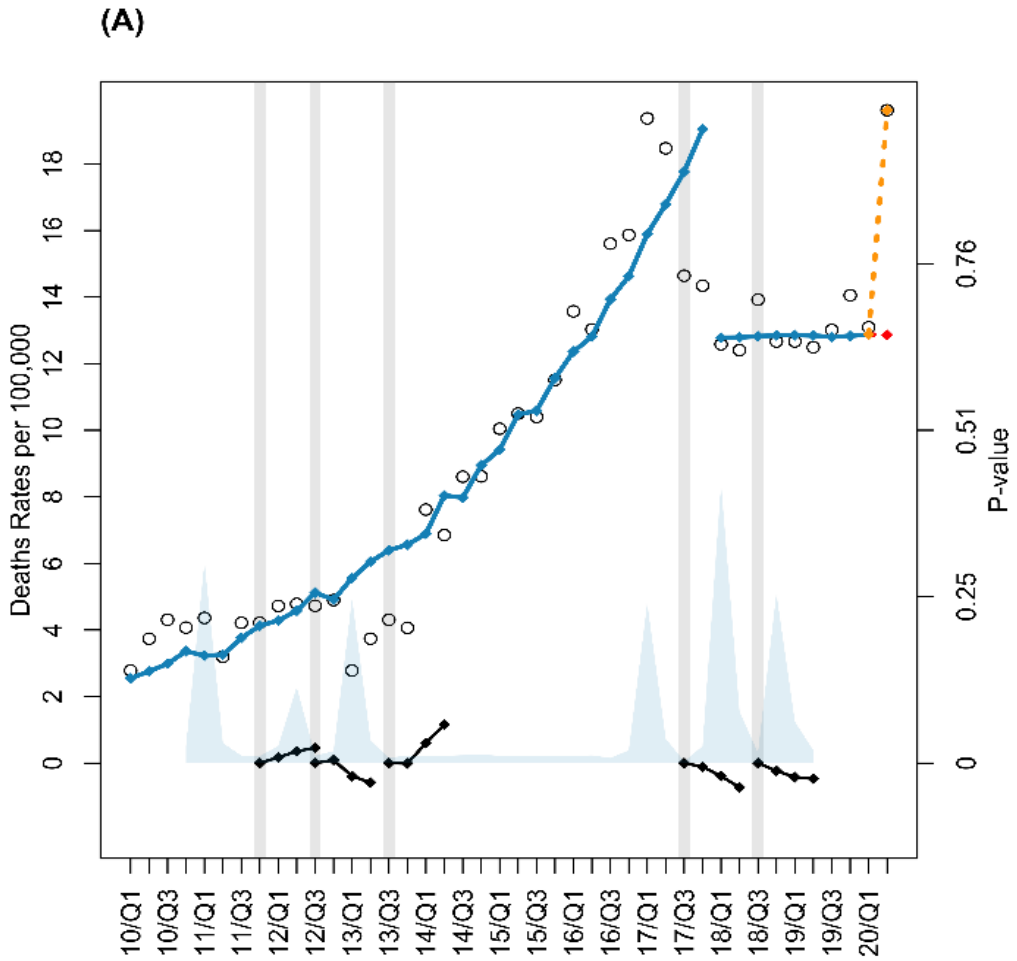
Temporal Trend Analysis of the Quarterly OOD Rate per 100,000 for the White (A) and Black (B) populations

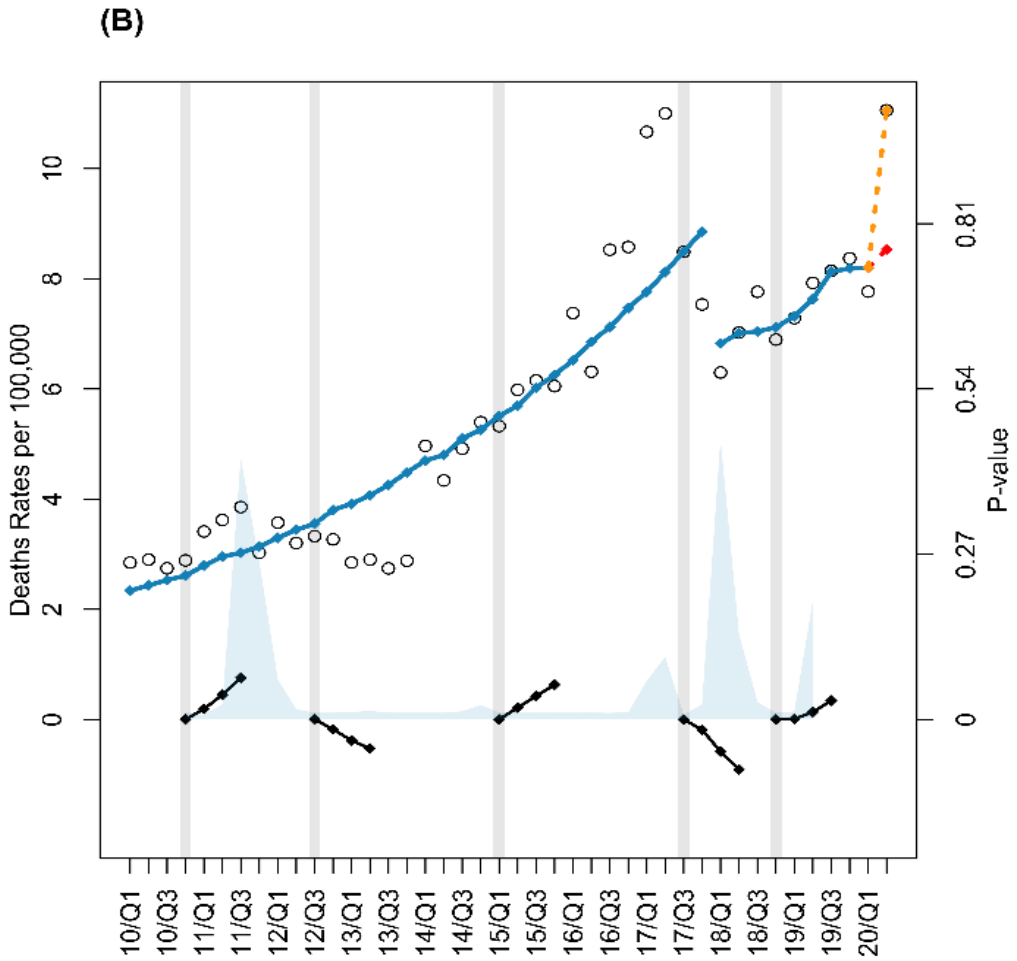


Temporal Trend Analysis of the Quarterly OOD Rate per 100,000 for males (A) and females (B)



Temporal Trend Analysis of the Quarterly OOD Rate per 100,000 for age groups (A) 18-39 and (B) 40+



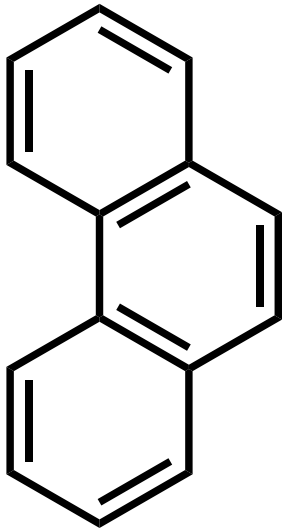


The Pharmacophore Rule

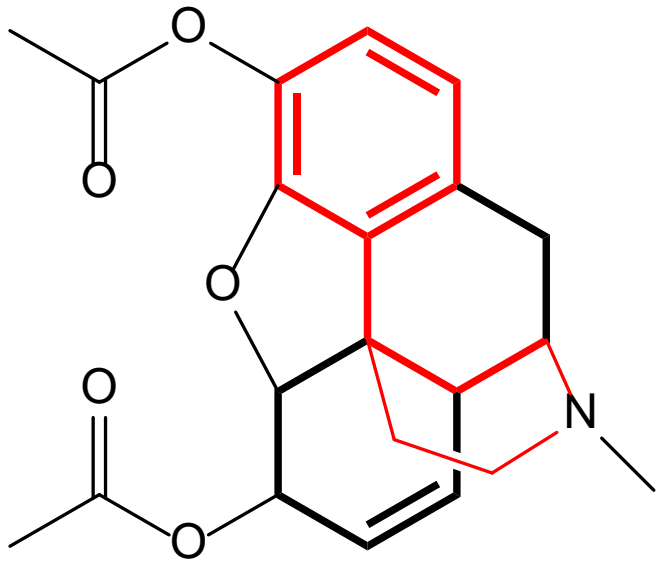
The Pharmacophore Rule was written so chemists would be able to identify the basic structural elements required for a compound to bind to their drug targets.

What is a pharmacophore?

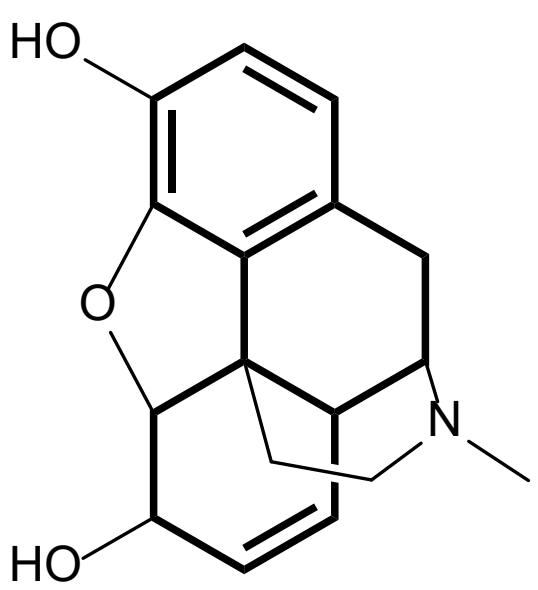
- the portion of drug molecule required for pharmacological activity



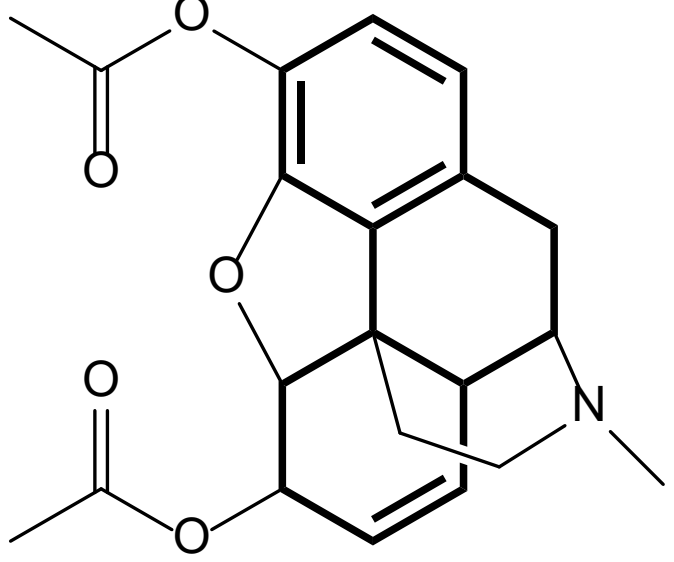
Phenanthrene



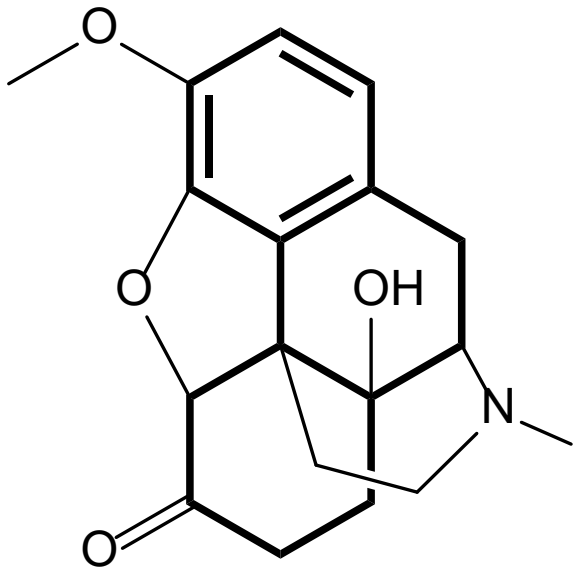
Heroin



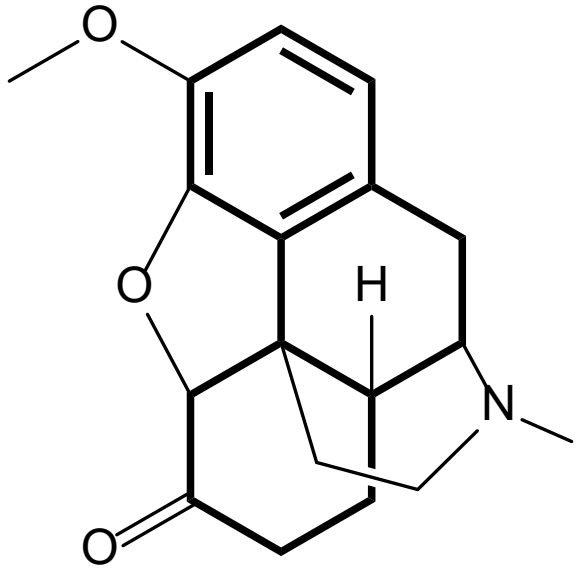
Morphine



Heroin

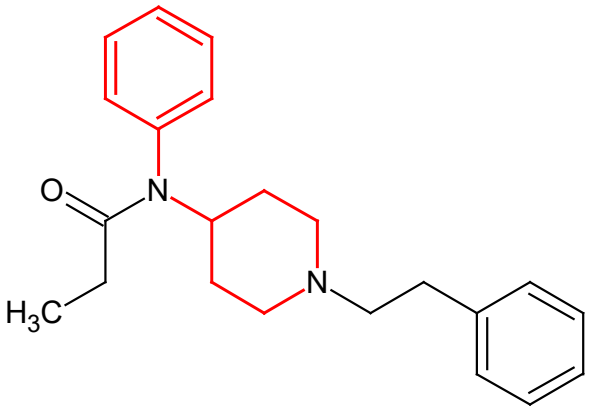


Oxycodone

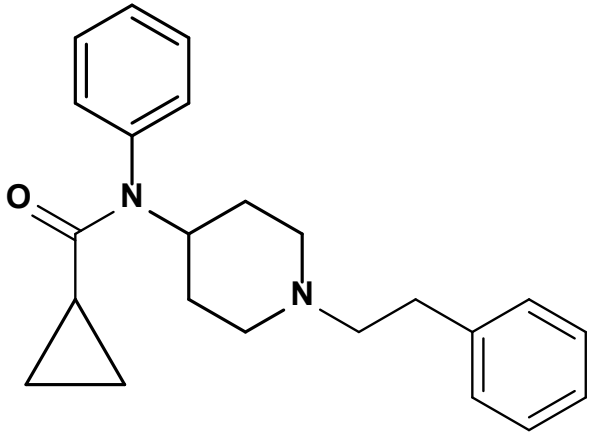


Hydrocodone

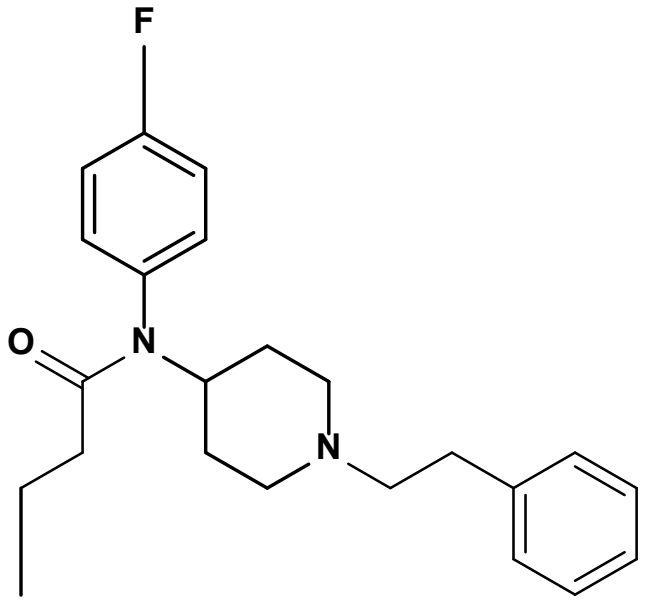
Example Fentanyl Pharmacophores



Fentanyl



Cyclopropyl fentanyl

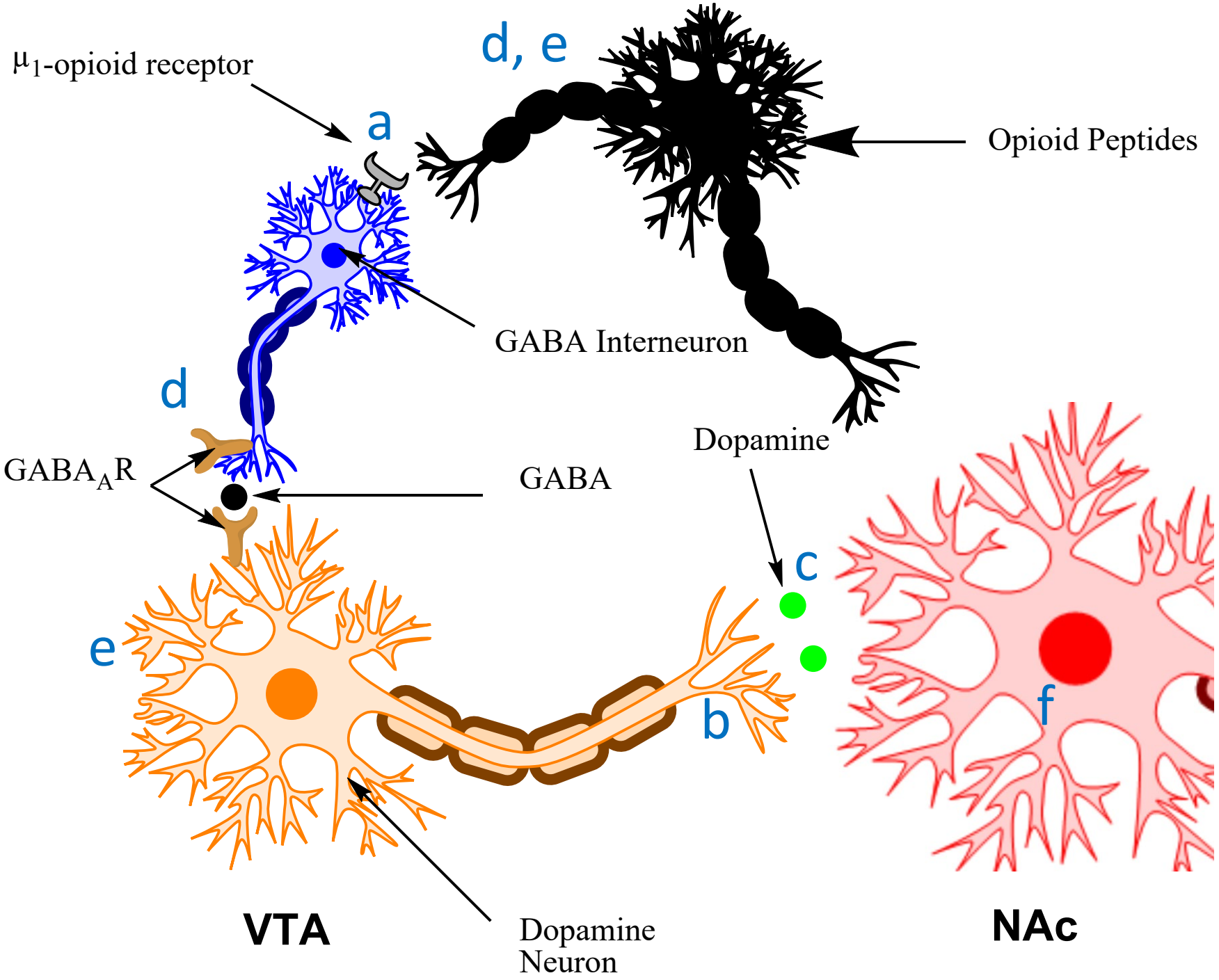


para-fluorobutyryl fentanyl

Dangerous Counterfeit Prescription Tablets

https://www.dea.gov/sites/default/files/2021-05/Counterfeit%20Pills%20fact%20SHEET-5-13-21-FINAL.pdf

The Dopamine Reward Pathway

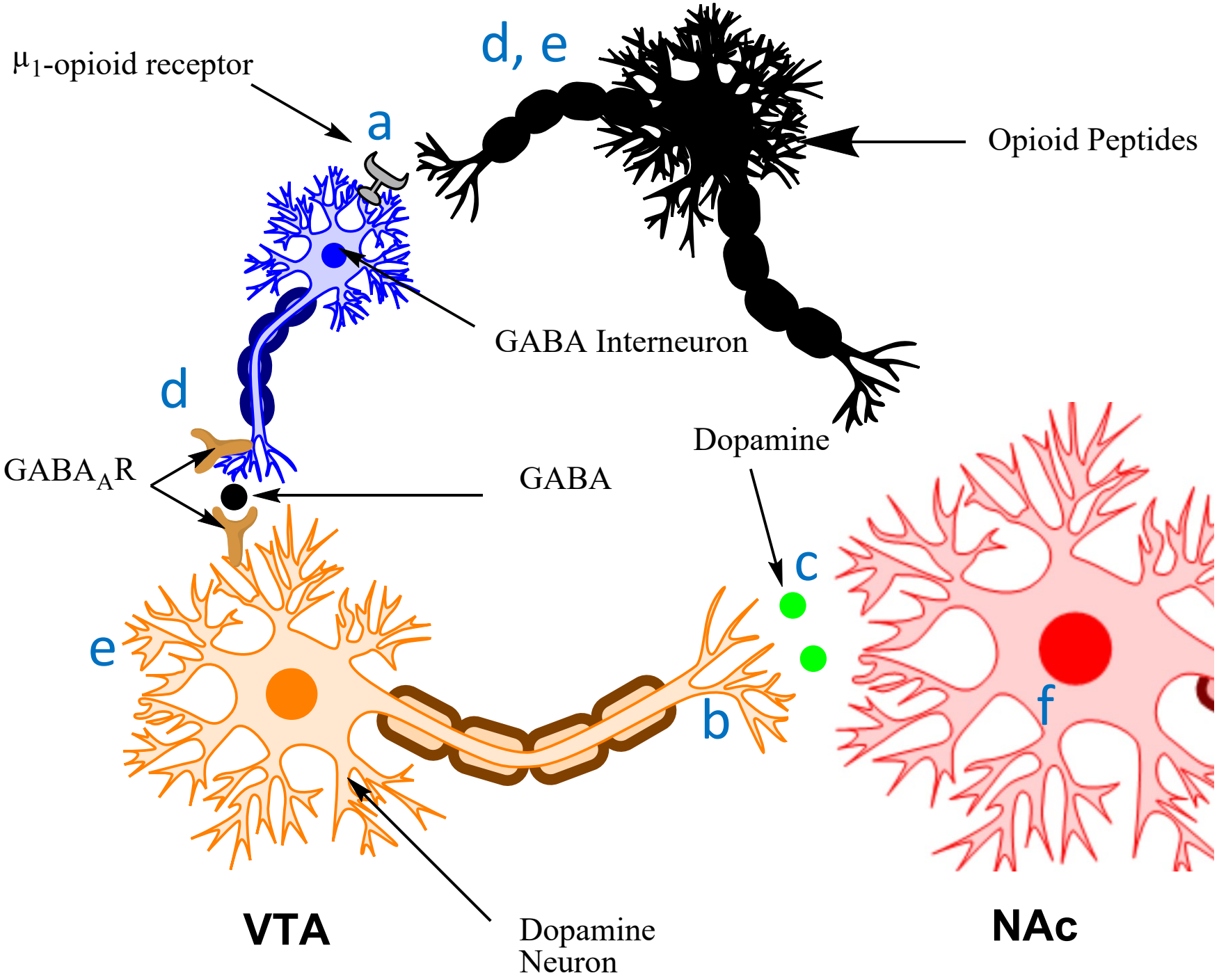

μ1-opioid receptor
a
d, e
Opioid Peptides
GABA Interneuron
d
GABAAR
GABA
Dopamine
c
e
b
f
VTA
Dopamine
Neuron
NAc

Pharmacological Targets of Drugs of Abuse

Drugs	Target
a. Opioids	Agonists at mainly the μ_1 receptor
b. Cocaine	Increase DA levels by blocking DAT
c. Amphetamine	Stimulate DA release
d. Ethanol	Facilitates $GABA_A$ receptor function
e. Nicotine	Agonist at NAChR
f. Cannabinoids	Agonists at CB_1 receptors
g. Hallucinogens	Agonists at 5-HT_{2A} receptors

Common Cellular & Molecular Adaptation

Translational Changes


μ1-opioid receptor
a
d, e
Opioid Peptides
GABA Interneuron
d
GABAAR
GABA
Dopamine
c
e
b
f
VTA
Dopamine
Neuron
NAc

Epigenetic Changes

1. Increases in histone deactylase in the NAc & VTA

2. Decreases in histone methyltransferase in the NAc

Genetic Changes

1. D2 receptors (D2R)
2. D4 receptors (D4R)
3. Catechol-O-methyltransferase (COMT)

Pharmacogenomic Application

Structure of DNA

- DNA is composed of 4 nucleotide bases
- Matched A-T and C-G

5’-CATGTACCTGGGCCG-3’
3’-GTACATGGACCCGGG-5’

Definitions

Molecular Level

- Pharmacogenomics: The study of variations of DNA and RNA characteristics as related to drug response.[1]
- Pharmacogenetics: The study of variations in DNA sequence as related to drug respose.[1]

Clinical Level

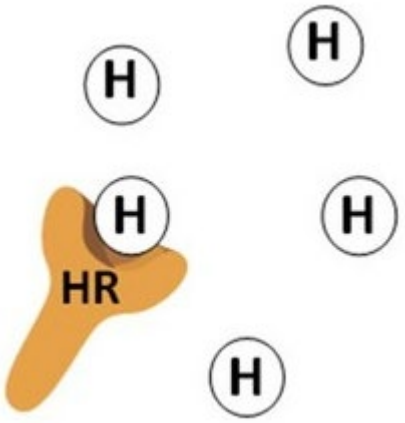
- Pharmacogenomics: The study of many genes, in some cases the entire genome, involved in response to a drug.[2]
- Pharmacogenetics: The study of a gene involved in response to a drug.[2]

[1]E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available at www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073162.pdf. Accessed November 4, 2016.

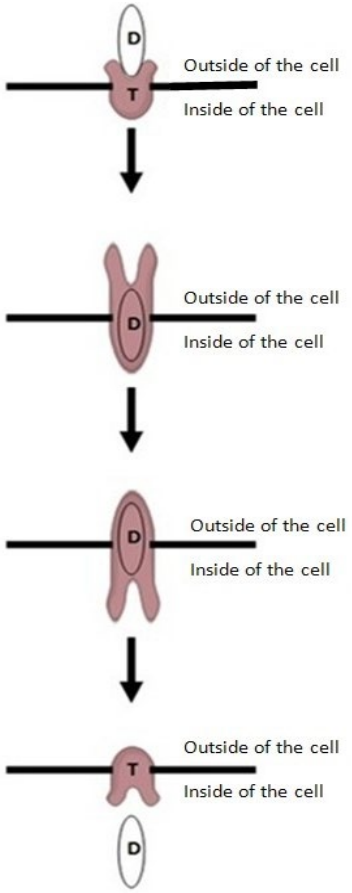
[2] Kisor DF, Kane MD, Talbot JN, Bright DR, Sprague JE. Pharmacogenes: Scientific Background and Clinical Applications. 2017. Reproduced with permission.

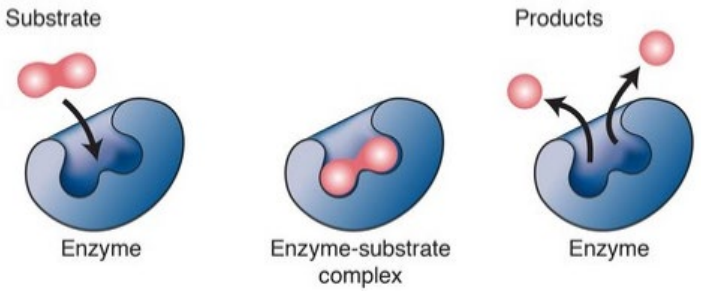
DNA to Protein Drug Targets: Pharmacogenes

Receptors or Transporters or Enzymes



Examples:
Histamine
β-adrenergic
Estrogen





Examples:
CYP2D6

Examples:
OATP1B1 (influx)
P-glycoprotein (efflux)

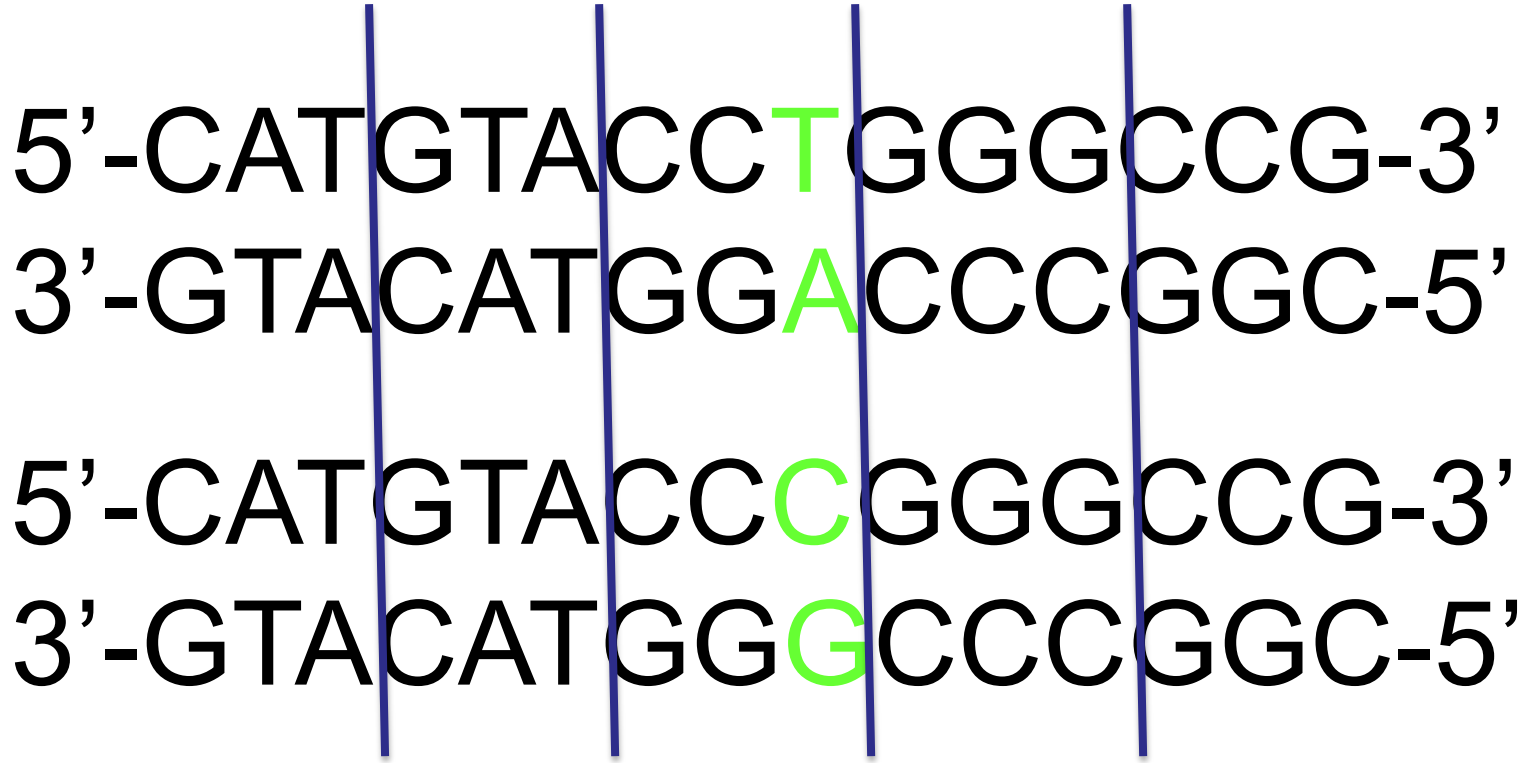
Sources: drugsandgenes.com, Leja, D. Enzyme. National Human Genome Research Institute.

Structure of Genes

- A segment of DNA containing all the information needed to encode for one protein is called a gene.

Single Nucleotide Polymorphisms (SNPs)

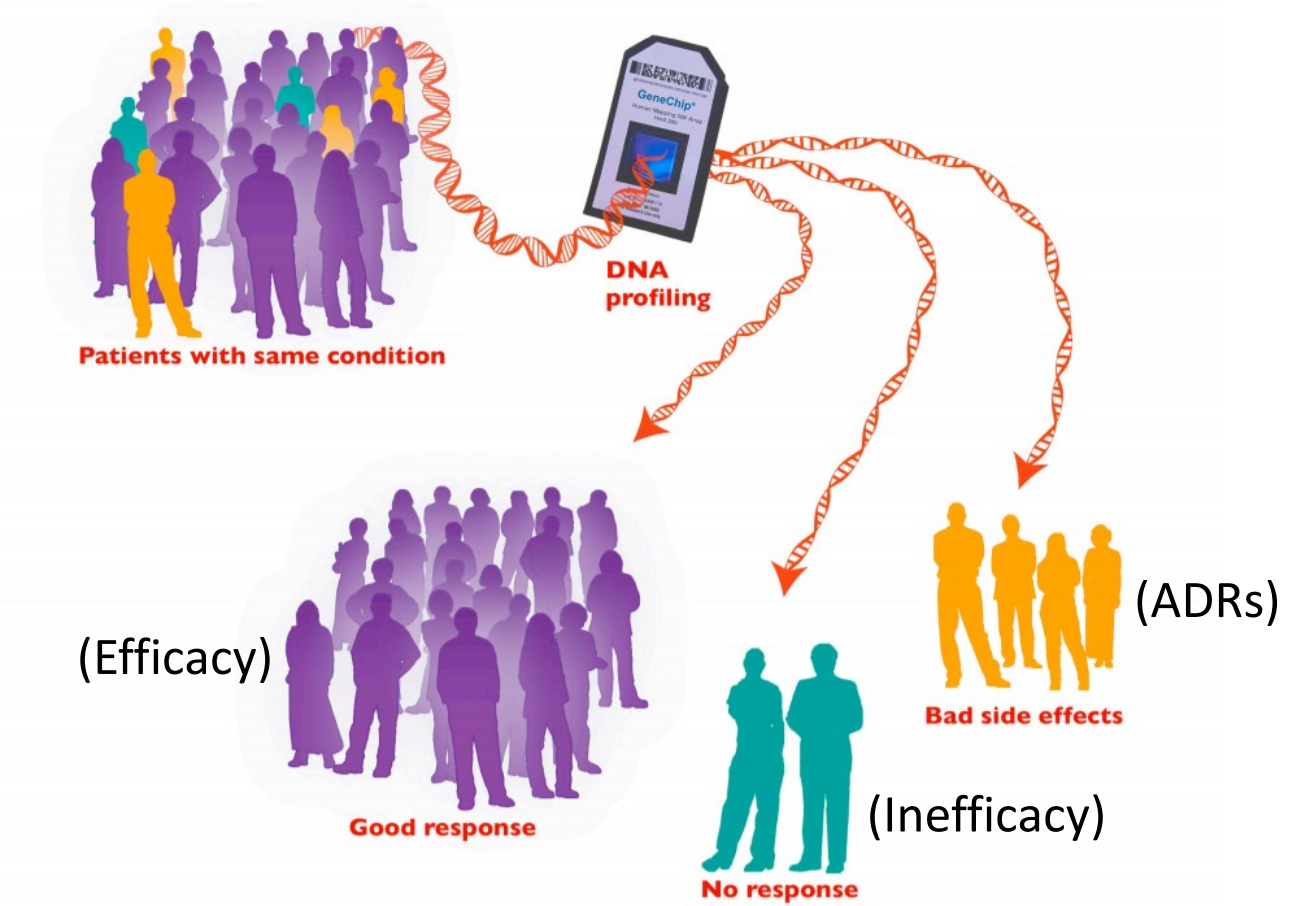
Influence expression:



Coding Polymorphisms Classifications

- Non-synonymous (missense)
  - ACG codes for threonine
  - CCG codes for proline
- Synonymous (sense)
  - ACG codes for threonine
  - ACA also codes for threonine
- Nonsense

PGx: Drug Efficacy • Adverse Drug Events



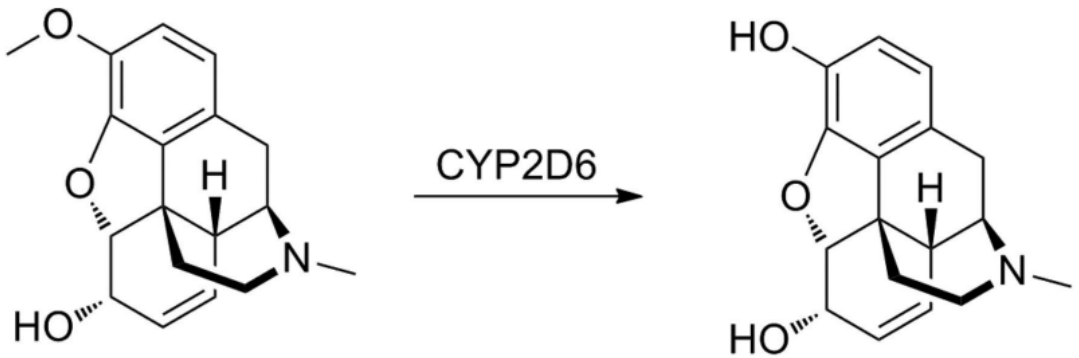
NIH, National Human Genome Research Institute. Available at www.genome.gov/27530645/faq-about-pharmacogenomics/. Accessed March 10, 2022

Adverse Drug Events: Example

Rani Jamieson (Ultra Rapid Metabolizer)

- Son Tariq was born April 18, 2005;
  - Episiotomy:
    - Received acetaminophen with codeine;

- 12 days later Tariq died.



Codeine Morphine

Owen Dyer. National Review of Medicine June 15, 2007.

Adverse Drug Events: Example

- Cause: morphine overdose
- Tariq not receiving morphine
  - Brain/nervous system depression
  - Slow breathing
  - Inactivity/inaction
  - Skin color
  - Poor feeding/failure to thrive

Gene Form	Drug (Std. Dose)	Response	Outcome
*CYP2D6**1/*2xN	Codeine	Morphine overdose	Adverse Drug Reaction - Death

http://babygooroo.com/2007/06/is-codeine-safe-for-breastfeeding-mothers-and-infants/

CPIC: *CYP2D6*-Codeine

Table 1 Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (*CYP2D6*) diplotypes

Likely phenotype[a]	Activity score	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (~1–2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	**1/*1xN, *1/*2xN*
Extensive metabolizer (~77–92% of patients)	1.0–2.0[b]	An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele	**1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *1/*10*
Intermediate metabolizer (~2–11% of patients)	0.5[b]	An individual carrying one reduced-function and one nonfunctional allele	**4/*10, *5/*41*
Poor metabolizer (~5–10% of patients)	0	An individual carrying no functional alleles	**4/*4, *4/*5, *5/*5, *4/*6*

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]

KR Crews KR, A Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. Clin Pharmacol Ther. 95(4):376-382.

The Ohio Opioid PGx Study

- Supported by the Ohio Attorney General's Office
- Collaboration with the Emergency Departments at the University of Cincinnati and The Ohio State University
- Sample size: 1300 patients
- PGx screening of 180 genes associated with opioid metabolism and pharmacodynamic response of the reward pathway

The Ohio Opioid PGx Study: Specific Aims

- *Aim 1:* Determine which genes are associated with development of opioid use disorder.

- *Aim 2*: Develop a Genomic Opioid Addiction Risk Score (G-OARs).

Ohio PGx Data Collected

- Genetic samples obtained for a cheek swab
  - Testing for 180 SNPs
- Blood drawn and banked for later testing
- DSM-5 screening for opioid use disorder
- Battery of questions
  - Mental health, prior trauma, prior drug use, environmental influences, risk taking behavior

Planned Analyses

Genetic contribution to opioid use disorder	• Which SNPs are associated with OUD
Machine learning	• Can risk be determined from questions alone?
Highlight prevalence of OUD	• 20% in our participants, despite only 4-5% of all ED visits coded with OUD diagnosis
Report reasons why people participate in research	• Much is known about why people DON'T participate • Does it differ in the OUD population

Sample Gene Targets

Pharmacokinetic

- ABCB1
- CYP2D6
- CYP2B6
- UGT2B7

Pharmacodynamic

- TH
- COMT
- OPRM1
- DRD2

General References

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- Volkow ND, Koob GF, McLellan AT. (2016): Neurobiologic advances from brain disease model of addiction. N. England J Med. 374:363-371.
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- U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, *Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health.* Washington, DC: HHS, November 2016.

Research Associates

- **Jamie Vieson**
- **Qizhen Lan**
- **Maggie McCorkle**
- **David Kisor**
- **Caroline Freiermuth**