# Opioid Crisis
# & Metabolism of Oxycodone

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CMSE 201-005

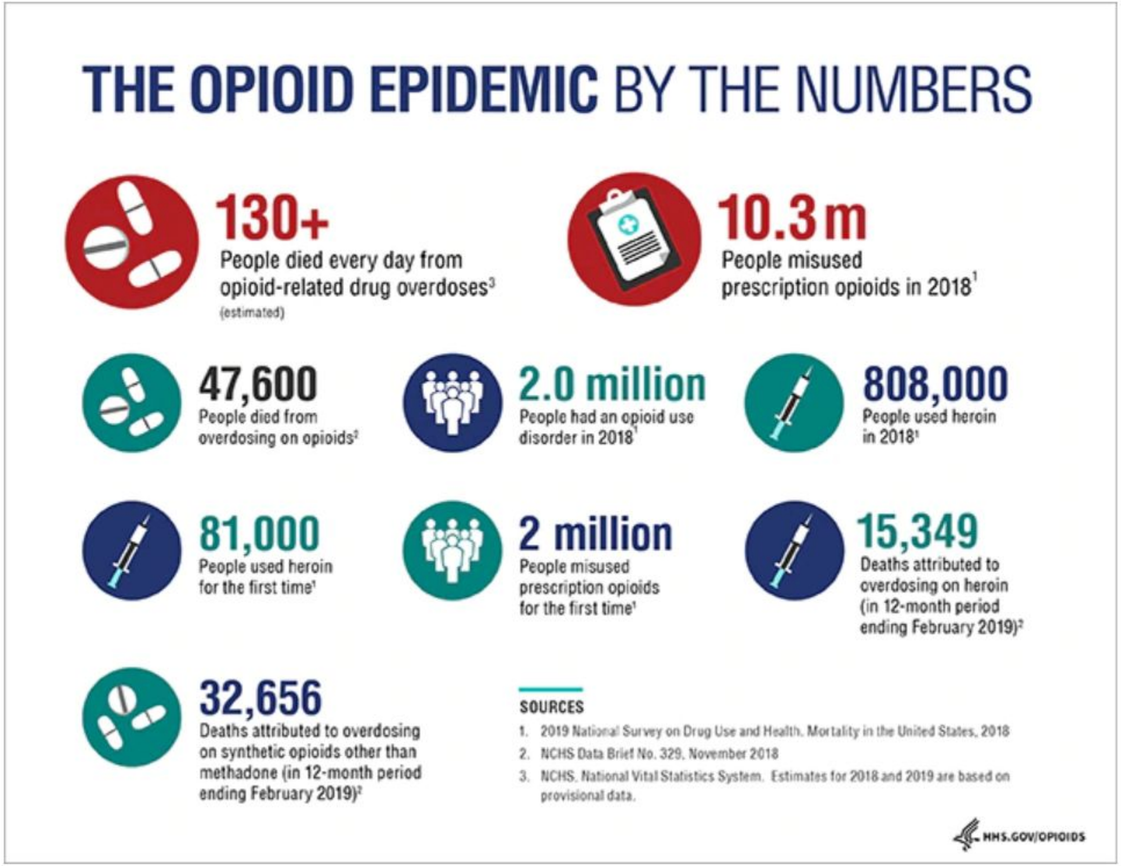
# Background & Motivation

# Questions

- Is the opioid crisis an issue and are there some parts of the country that are more impacted than others?
  - How has the fatality of opioids changed over the last two decades with respect to other closely associated drugs?
  - How has the sale of opioids changed in the last two decades?
- What can help explain the high rates of overdoses for opioids?
  - How does the presence of a CYP3A4 inhibitor affect the metabolism of oxycodone?
  - How does a competing substrate like alprazolam affect the metabolism of oxycodone and can this explain why more than 30 percent of overdoses involving opioids also involve benzodiazepines?

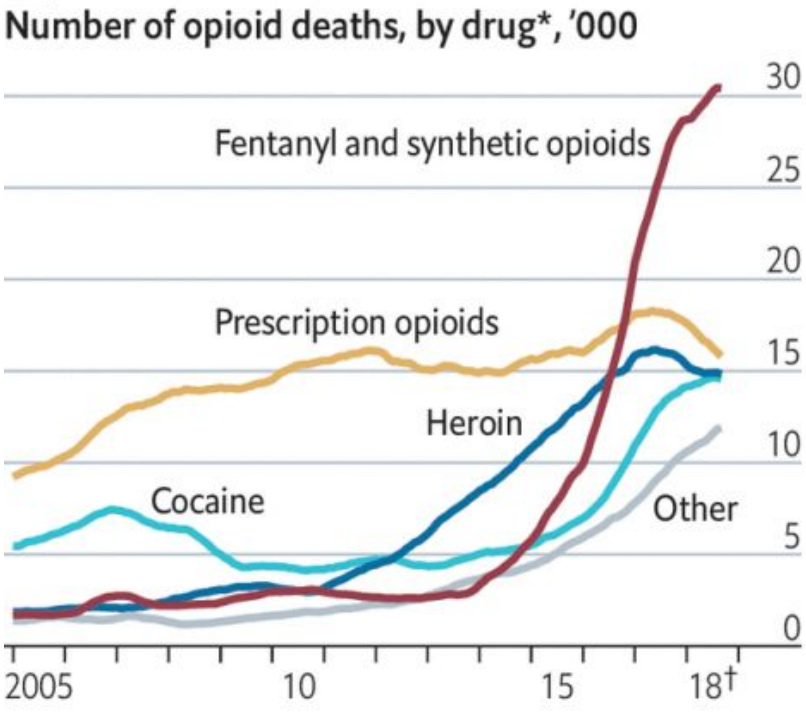
# Opioid Crisis

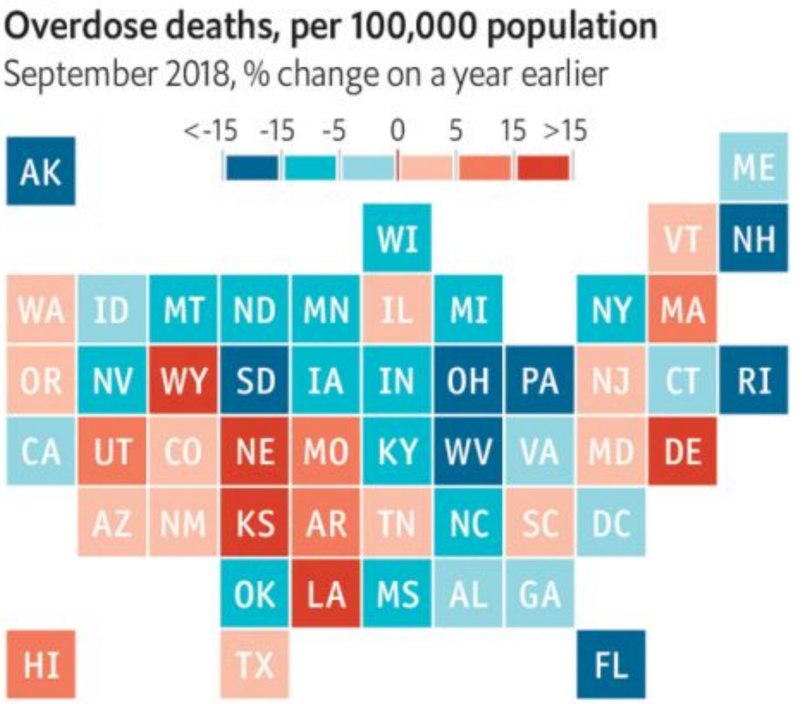
- Highly addictive and misused.
    - 21-29% of prescribed patients misuse opioids
    - 8-12% develop an addiction
    - 4-6% progress to heroin
    - 80% of heroin-users first started by misusing opioids



## The hope of the states

United States



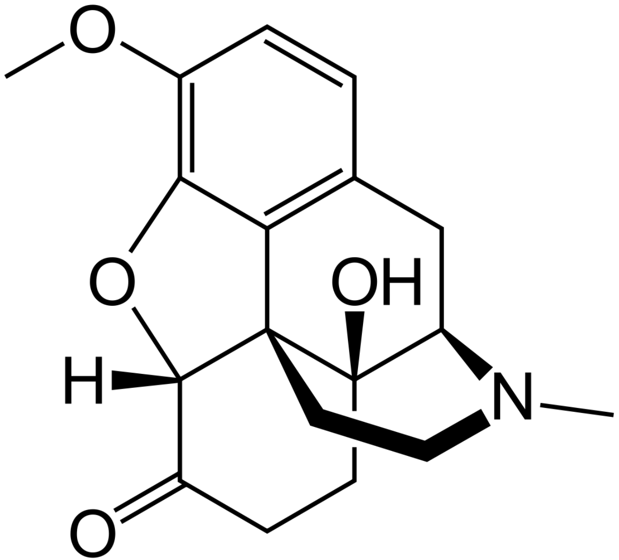

Source: Centres for Disease Control and Prevention

*Deaths involving multiple opioids counted in each category †To September

The Economist

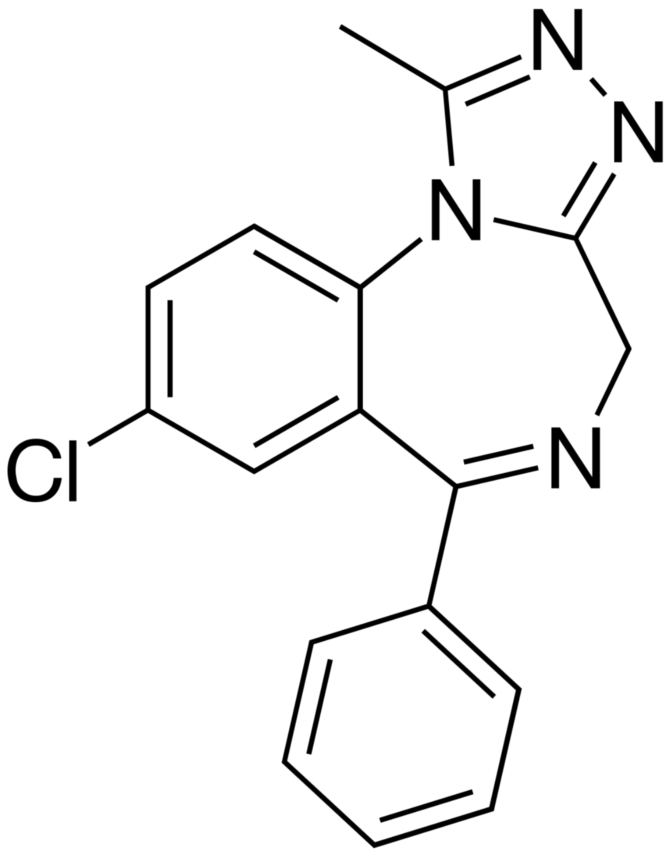
# Oxycodone

- Analgesic opioid used for the relief of moderate-to-severe pain.
- Approved by FDA in 1995 as OxyContin (Purdue Pharma)
- Best-selling narcotic pain reliever by 2001
- $2.5 billion in 2008
- Metabolized by p450 pathway
  - CYP3A4 & CYP2D6 enzymes
- Prone to pharmacokinetic drug interactions
  - >30% of opioid overdoses involve benzodiazepines



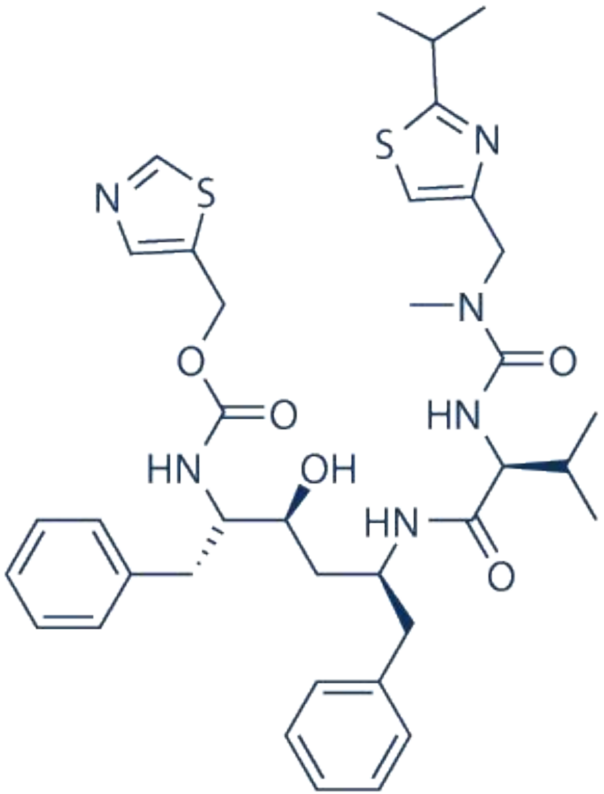
# Benzodiazepines

- Prescription sedatives for anxiety or insomnia
- One example is alprazolam (Xanax)
- Between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased from 8.1 million to 13.5 million.
- The quantity obtained increased from 1.1 kg to 3.6 kg per 100,000 adults.

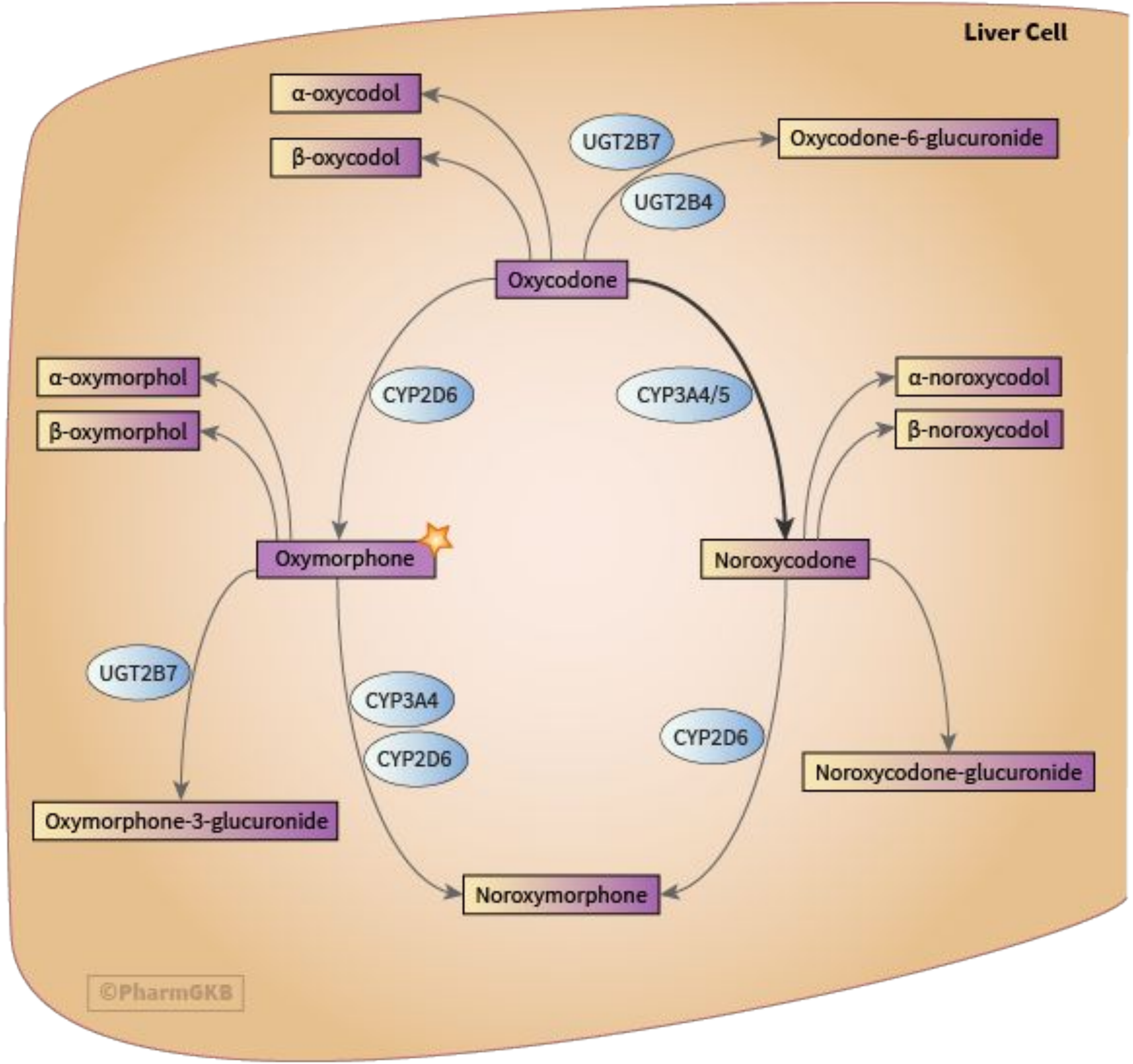


# Ritonavir

- Protease inhibitor used to treat HIV
- Potent inhibitor of CYP3A4

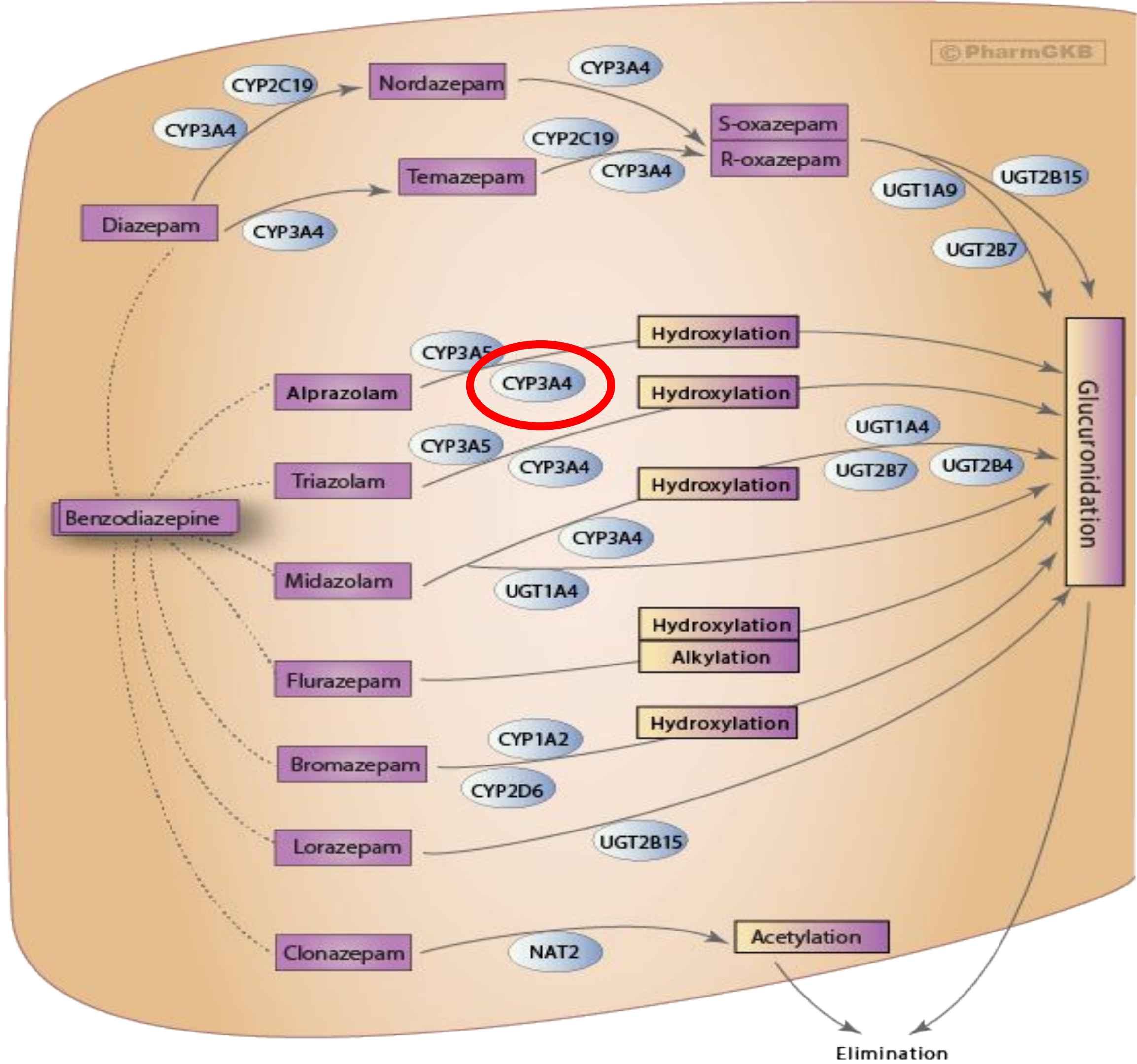


- 45% Metabolized by CYP3A4/5
- 19% Metabolized by CYP2D6
- CYP3A4/5 having a higher activity in females than males
- ~72% of an oxycodone dose is excreted in the urine




# Metabolism of Oxycodone

Alprazolam is also metabolized by CYP3A4




# Metabolism of Benzodiazepine

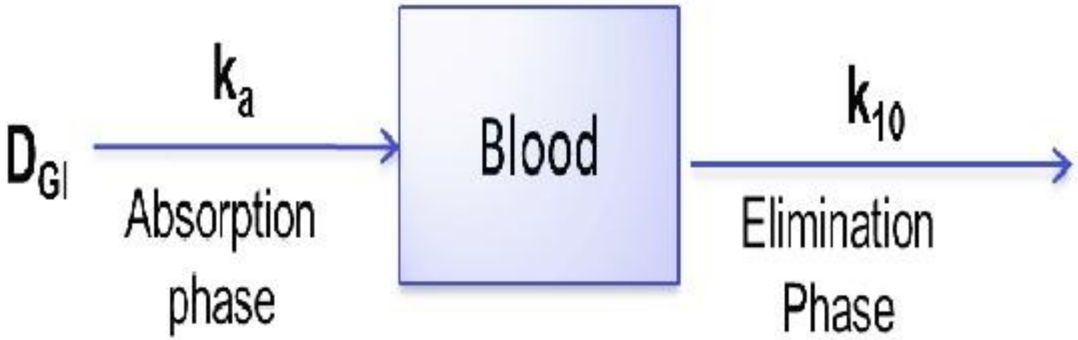
# Methodology

# Simple Oxycodone Model

Oxycodone Parameters

- $V_{ss}$ = 2.6 L/kg
- $Et_{1/2}$= 3.5 hr
- $At_{1/2}$ = 0.4 hr
- Dose: 10 mg every 12 hrs

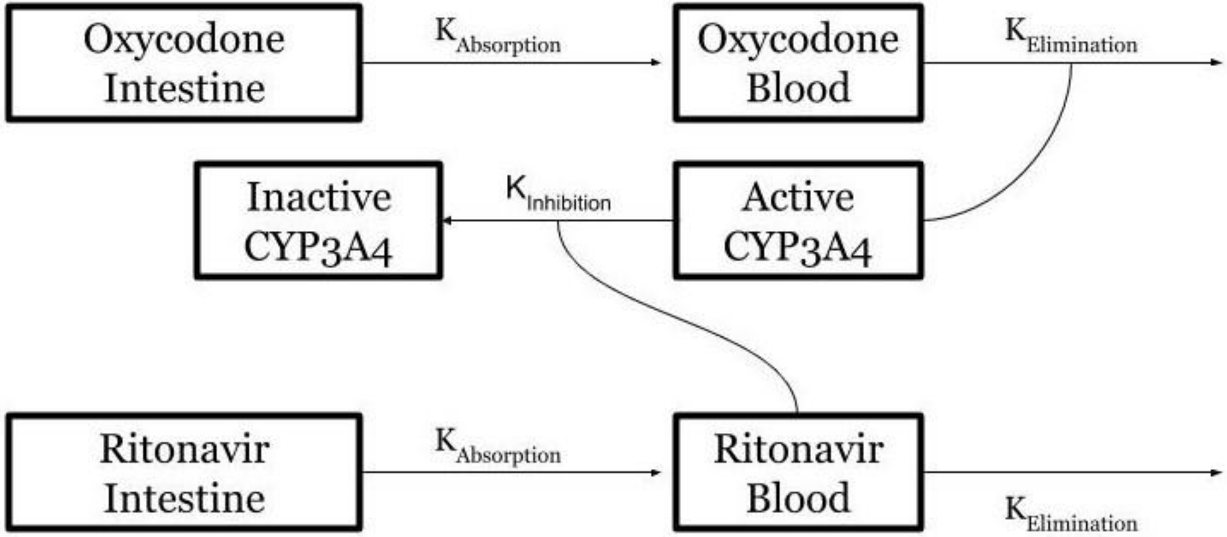
$$\frac{dg}{dt} = -Ag, \quad \frac{db}{dt} = Ag - Eb$$



# Ritonavir & Oxycodone Model

Ritonavir Parameters

- IC50 = 0.015 μM
- $V_{ss}$ = 0.41 L/kg
- $Et_{1/2}$= 4 hr
- $At_{1/2}$ = 0.4 hr
- Dose: 600 mg every 12 hrs

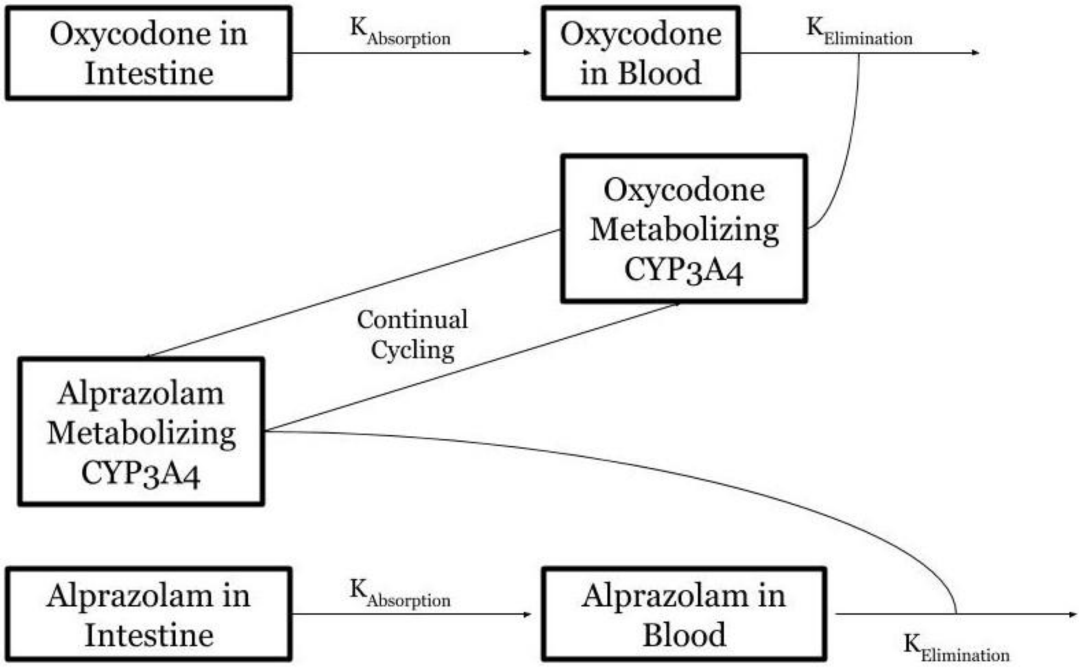



$$\frac{dOg}{dt} = -oAOg,\ \frac{dOb}{dt} = oAOg - oEObaC,\ \frac{dRg}{dt} = -rARg,\ \frac{dRb}{dt} = rARg - rERb - \frac{Ki\frac{daC}{dt}}{aC^2},\ \frac{daC}{dt} = \frac{-(aC^2)\frac{dRb}{dt}}{Ki},\ \frac{diC}{dt} = \frac{(aC^2)\frac{dRb}{dt}}{Ki}$$

# Alprazolam & Oxycodone Model

Alprazolam Parameters

- $V_{ss}$ = 0.84 L/kg
- $Et_{1/2}$= 11.2 hr
- $At_{1/2}$ = 0.2 hr
- Dose: 2 mg every 12 hrs




$$\frac{dOg}{dt} = -oAOg,\ \frac{dOb}{dt} = oAOg - oEObaC,\ \frac{dXg}{dt} = -xAXg,\ \frac{dXb}{dt} = xAXg - xEXbaC,\ \frac{daC}{dt} = -KiRbaC,\ \frac{diC}{dt} = KiRbaC$$

# Computational Techniques

Opioid Crisis:

- Used Pandas to read in .csv
- Masked out specific drugs and specific years and location.
- Used seaborn to graph plots
- Defined regions with a list.

Metabolism of Oxycodone:

- Used literature half-lives to get rate parameters: $k = \ln(2)/t_{1/2}$
- Used compartmental model to define derivs function
- Used odeint to get values in each compartment over a 24 hr period
- Used seaborn to plots.
- Used plt.arrow() to annotate

```python
# Read in the .csv data and skip the first 20 rows of text. Initially read in everything as 'str'
opioidperDT = pd.read_csv('Opioid-related and other drug poisoning deaths per 100,000 people, by drug type.csv',
                          skiprows = 20, dtype = 'str')
# Change the data type of some of the columns so that it will be easier to work with
opioidperDT = opioidperDT.astype({"TimeFrame": 'int',"Data": 'float',"MOE":'float'})
opioidperDT.head() # get a quick view of how the data looks
```

| | Fips | Location | Drug Type | TimeFrame | Data Type | Data | MOE |
|---|---|---|---|---|---|---|---|
| **0** | 01 | Alabama | Cocaine | 1999 | Rate per 100,000 | 0.51516 | 0.215516 |
| **1** | 02 | Alaska | Cocaine | 1999 | Rate per 100,000 | NaN | NaN |
| **2** | 04 | Arizona | Cocaine | 1999 | Rate per 100,000 | 2.75748 | 0.466495 |
| **3** | 05 | Arkansas | Cocaine | 1999 | Rate per 100,000 | NaN | NaN |
| **4** | 06 | California | Cocaine | 1999 | Rate per 100,000 | 1.21234 | 0.118646 |

```python
# Masks out the specific type of drug
CocaineMask = opioidperDT['Drug Type'] == 'Cocaine'
OpioidMask = opioidperDT['Drug Type'] == 'Natural and semi-synthetic opioids'
HeroinMask = opioidperDT['Drug Type'] == 'Heroin'
PsychoMask = opioidperDT['Drug Type'] == 'Psychostimulants'
SynOpioidMask = opioidperDT['Drug Type'] == 'Synthetic opioids'
# Masks out the specific year of the data (1999 is earliest time and 2017 is the newest data)
y99Mask = opioidperDT['TimeFrame'] == 1999
y17Mask = opioidperDT['TimeFrame'] == 2017
# Masks out the specific locations (Michigan and US)
US = opioidperDT['Location'] == 'United States'
Mich = opioidperDT['Location'] == 'Michigan'

# Regions According to the US Census Bureau
# Store each in lists so that they can be used to mask later
Northeast = ['Maine','New Hampshire','Vermont','Massachusetts','Rhode Island',
             'Connecticut','New York','New Jersey','Pennsylvania']
Midwest = ['Ohio','Michigan','Indiana','Wisconsin','Illinois','Minnesota','Iowa',
           'Missouri','North Dakota','South Dakota','Nebraska','Kansas']
South = ['Dist. of Columbia','Delaware','Maryland','Virginia','West Virginia','Kentucky','North Carolina','South Carolina',
         'Tennessee','Georgia','Florida','Alabama','Mississippi','Arkansas','Louisiana','Texas','Oklahoma']
West = ['Montana','Idaho','Wyoming','Colorado','New Mexico','Arizona','Utah',
        'Nevada','California','Oregon','Washington','Alaska','Hawaii']
# Masks out the data by location by whether or not the location of the data is in the above region lists.
NE = opioidperDT['Location'].isin(Northeast)
MW = opioidperDT['Location'].isin(Midwest)
ST = opioidperDT['Location'].isin(South)
WT = opioidperDT['Location'].isin(West)
```

```python
# Combines year and drug type masks to get specific drugs at specific times
opioid17 = opioidperDT[y17Mask & OpioidMask]
opioid99 = opioidperDT[y99Mask & OpioidMask]

# Combines region/location and drug type masks to get data frames of specific drugs at specific regions/locations
NEOpioids = opioidperDT[NE & OpioidMask]
MWOpioids = opioidperDT[MW & OpioidMask]
STOpioids = opioidperDT[ST & OpioidMask]
WTOpioids = opioidperDT[WT & OpioidMask]
```

```python
# Defined the derivative function for each compartment using the ODE's above
def CYP_derivs(y, t, oA, oE,rA,rE,Ki, lag, OV, RV):
    Og = y[0]
    Ob = y[1]
    Rg = y[2]
    Rb = y[3]
    aC = y[4]
    iC = y[5]
    dOgdt = 0
    dObdt = -(oE*Ob*aC)
    dRgdt = 0
    dRbdt = -(rE*Rb)
    daCdt = -(aC**2)*dRbdt/Ki # aC * Rb/iC = Ki, and aC +iC = 1, so differentiate respect to aC.
    diCdt = -daCdt
    dRbdt = -(rE*Rb)- daCdt*Ki/(aC**2)
    if t > lag:
        dOgdt = -oA * Og
        dObdt = (oA*Og/OV) - (oE*Ob*aC)
        dRgdt = -rA * Rg
        dRbdt = (rA * Rg/RV) - (rE*Rb)
        daCdt = -(aC**2)*dRbdt/Ki # aC * Rb/iC = Ki, and aC +iC = 1, so differentiate respect to aC.
        diCdt = -daCdt
        dRbdt = (rA * Rg/RV) - (rE*Rb) - daCdt*Ki/(aC**2)

    return [dOgdt,dObdt,dRgdt,dRbdt,daCdt,diCdt]
```

Ritonavir & Oxycodone Model

```python
# Defined the derivative function for each compartment using the ODE's above
def Benzo_derivs(y, t, oA, oE,xA,xE, lag, OV, XV):
    Og = y[0]
    Ob = y[1]
    Xg = y[2]
    Xb = y[3]
    oC = y[4]
    xC = y[5]
    dOgdt = 0
    dObdt = -(oE*Ob*oC)
    dXgdt = 0
    dXbdt = -(xE*Xb*xC)
    doCdt = np.cos(2*t)*0.5 # oC +xC =1.
    dxCdt = -doCdt
    if t > lag: # Accounts for lag in absorption
        dOgdt = -oA * Og
        dObdt = (oA*Og/OV) - (oE*Ob*oC)
        dXgdt = -xA * Xg
        dXbdt = (xA * Xg/XV) - (xE*Xb*xC)

    return [dOgdt,dObdt,dXgdt,dXbdt,doCdt,dxCdt]
```

Alprazolam & Oxycodone Model

```python
# Defined the derivative function for each compartment using the ODE's above
def simple_derivs(y, t, A, E, lag, V):
    g = y[0]
    b = y[1]
    dgdt = 0
    dbdt = -(E*b)
    if t > lag: # Accounts for lag in absorption
        dgdt = -A * g
        dbdt = (A*g/V) -(E*b)
    return [dgdt,dbdt]
```

Simple Oxycodone Model

```
simple_sol = odeint(simple_derivs, y0, time, args = (A,E,lag+tint, V)) # run odeint
g_simpleModel = simple_sol[:,0]/1e6 # Stores intestinal oxycodone in mg
b_simpleModel = simple_sol[:,1] # Stores blood oxycodone in ng/mL
```

Simple Oxycodone Model

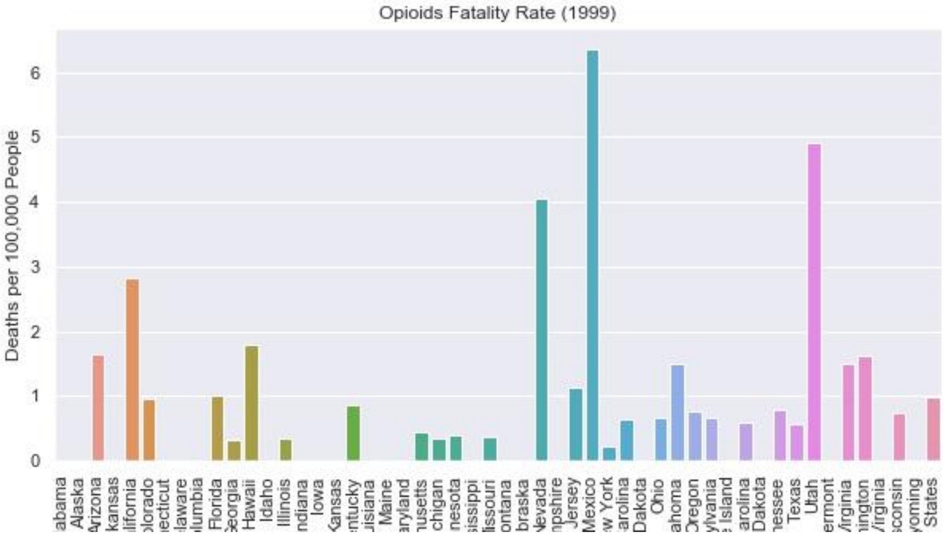
```
CYP_sol = odeint(CYP_derivs, y0, time, args = (oA, oE,rA,rE,Ki,lag+tint,OV,RV))
Og_CYPModel = CYP_sol[:,0]/1e6 # Stores intestinal oxycodone in mg
Ob_CYPModel = CYP_sol[:,1] # Stores blood oxycodone in ng/mL
Rg_CYPModel = CYP_sol[:,2]/1e6 # Stores intestinal ritonavir in mg
Rb_CYPModel = CYP_sol[:,3] # Stores blood ritonavir in ng/mL
aC_CYPModel = CYP_sol[:,4]*100 # Stores relative concentration of active CYP3A4
iC_CYPModel = CYP_sol[:,5]*100 # Stores relative concentration of inactive CYP3A4
```

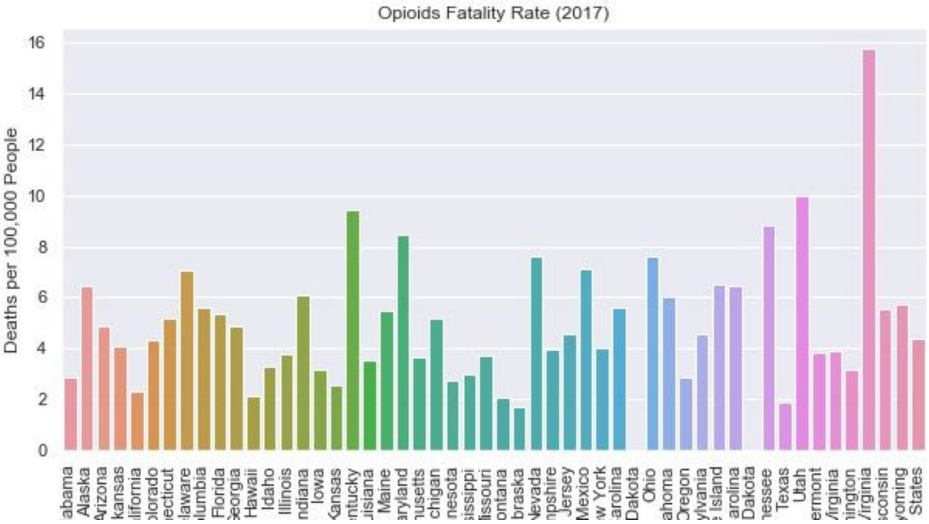
Ritonavir & Oxycodone Model

```
Benzo_sol = odeint(Benzo_derivs, y0, time, args = (oA,oE,xA,xE,lag+tint,OV,XV))
Og_BenzoModel = Benzo_sol[:,0]/1e6 # Stores intestinal oxycodone in mg
Ob_BenzoModel = Benzo_sol[:,1] # Stores blood oxycodone in ng/mL
Xg_BenzoModel = Benzo_sol[:,2]/1e6 # Stores intestinal alprazolam in mg
Xb_BenzoModel = Benzo_sol[:,3] # Stores blood alprazolam in ng/mL
oC_BenzoModel = Benzo_sol[:,4]*100 # Stores relative concentration of oxycodone-metabolizing CYP3A4
xC_BenzoModel = Benzo_sol[:,5]*100 # Stores relative concentration of alprazolam-metabolizing CYP3A4
```

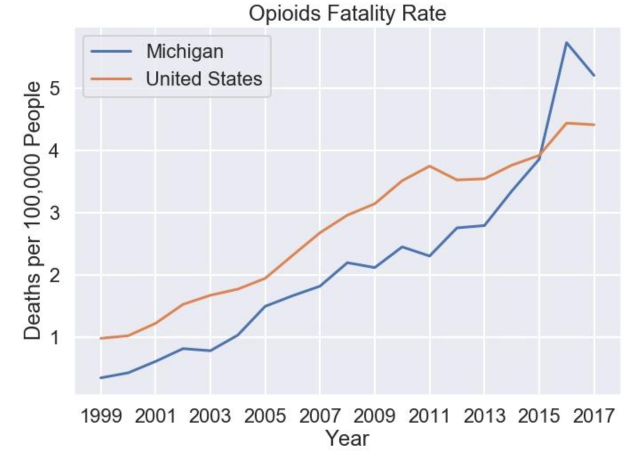
Alprazolam & Oxycodone Model

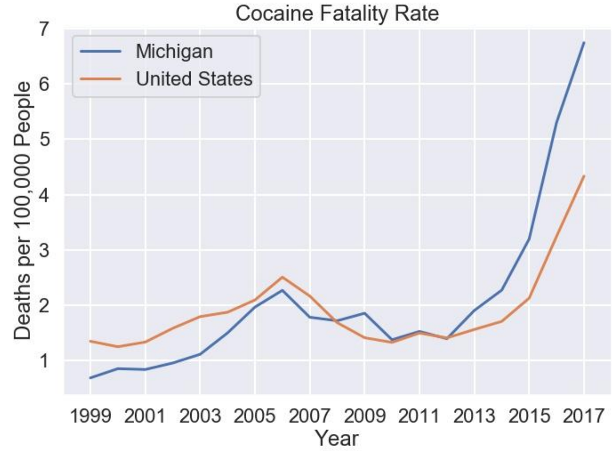
# Results



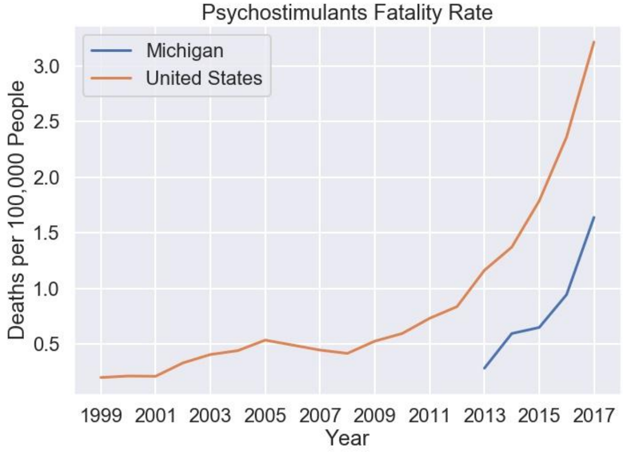



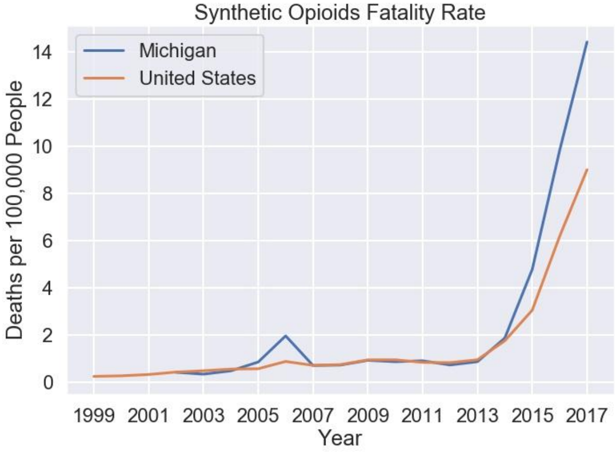

# Opioids’ Fatality Rate (1999 to 2017)

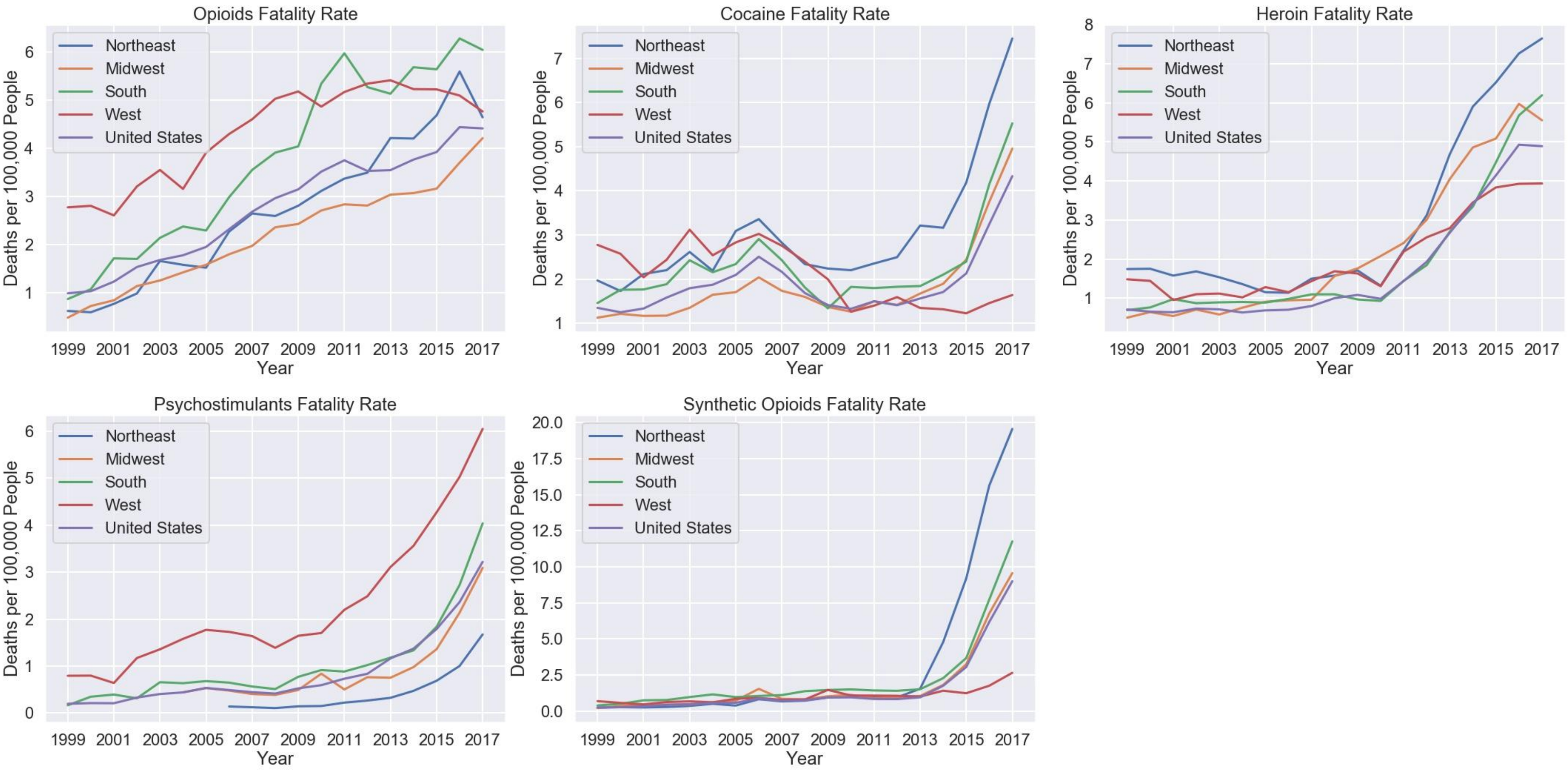

Opioids Fatality Rate
Michigan
United States
Deaths per 100,000 People
1
2
3
4
5
1999 2001 2003 2005 2007 2009 2011 2013 2015 2017
Year

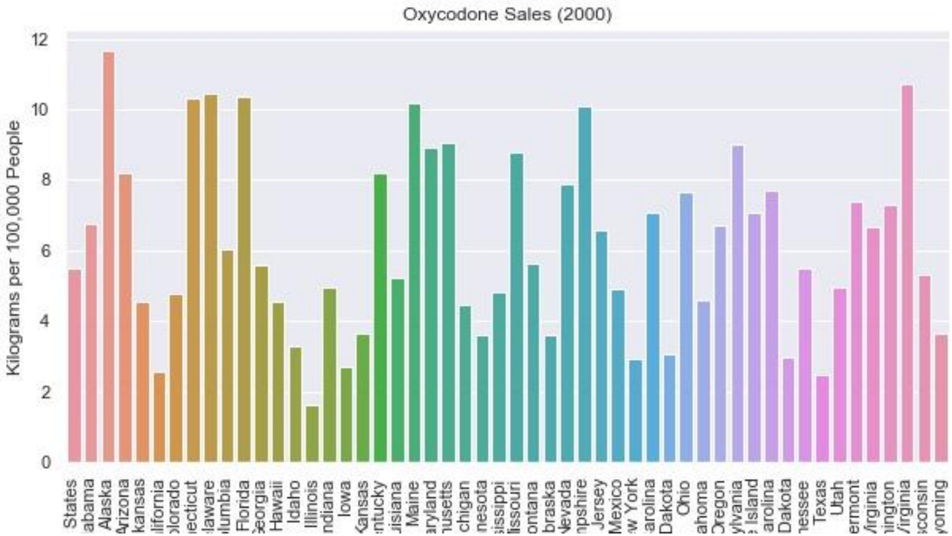

Cocaine Fatality Rate
Michigan
United States
Deaths per 100,000 People
1
2
3
4
5
6
7
1999 2001 2003 2005 2007 2009 2011 2013 2015 2017
Year

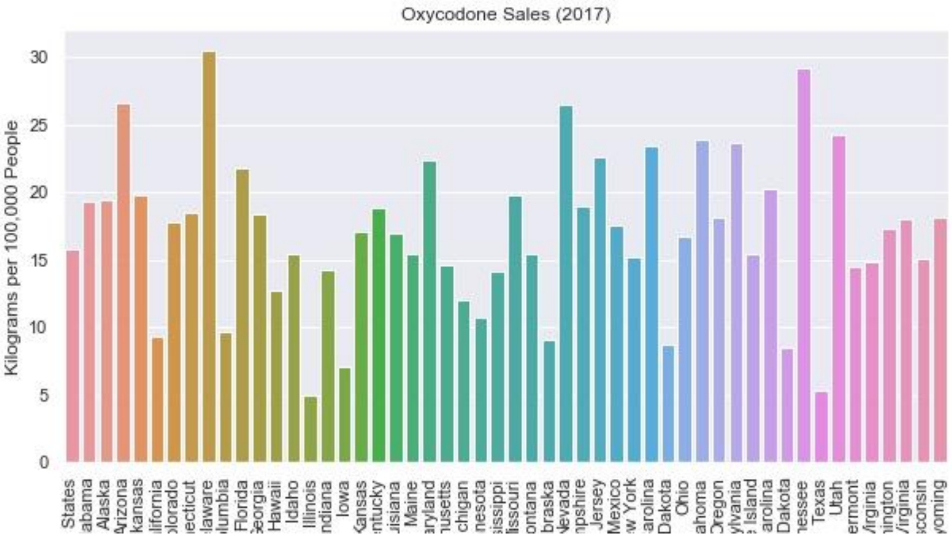

Heroin Fatality Rate
Michigan
United States
Deaths per 100,000 People
1
2
3
4
5
6
7
8
1999 2001 2003 2005 2007 2009 2011 2013 2015 2017
Year


Psychostimulants Fatality Rate
Michigan
United States
Deaths per 100,000 People
0.5
1.0
1.5
2.0
2.5
3.0
1999 2001 2003 2005 2007 2009 2011 2013 2015 2017
Year

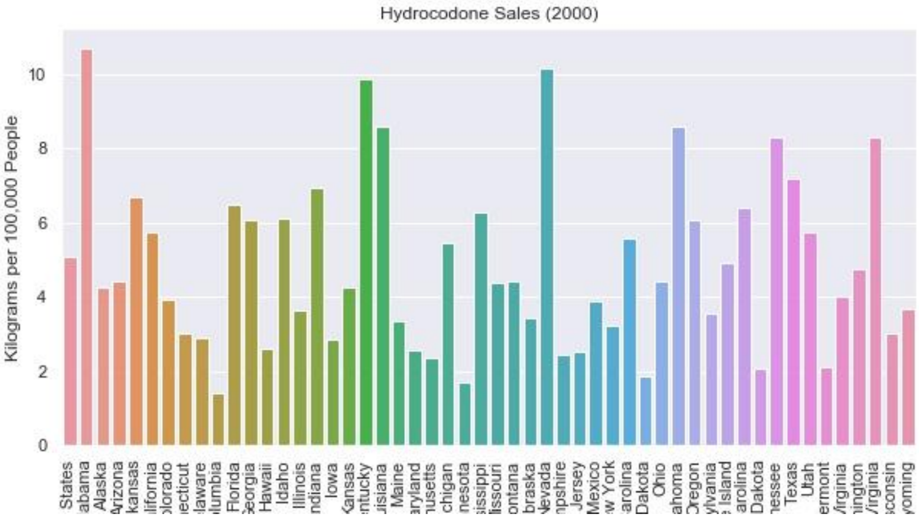

Synthetic Opioids Fatality Rate
Michigan
United States
Deaths per 100,000 People
0
2
4
6
8
10
12
14
1999 2001 2003 2005 2007 2009 2011 2013 2015 2017
Year

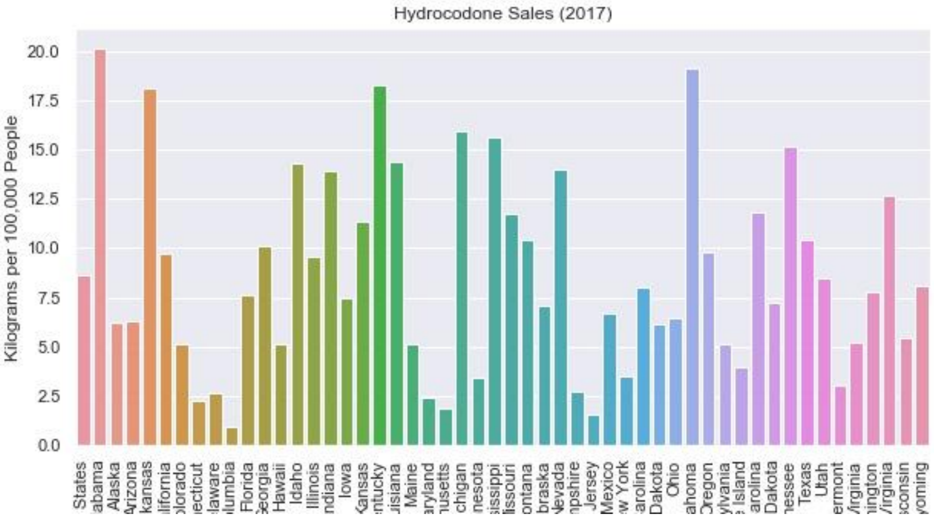

Opioids Fatality Rate
Cocaine Fatality Rate
Heroin Fatality Rate
Psychostimulants Fatality Rate
Synthetic Opioids Fatality Rate
Northeast
Midwest
South
West
United States
Deaths per 100,000 People
Year
1999 2001 2003 2005 2007 2009 2011 2013 2015 2017
0 1 2 3 4 5 6 7 8
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0



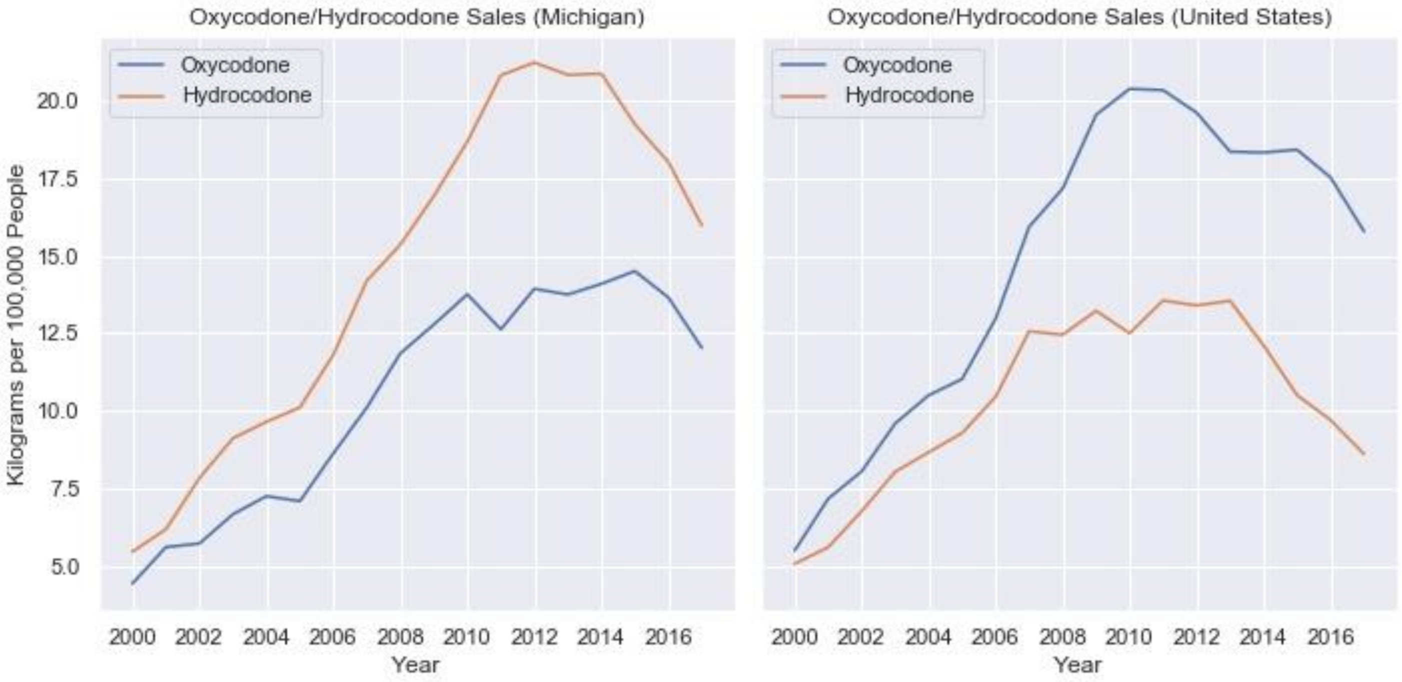




# Oxycodone Sales (2000 to 2017)

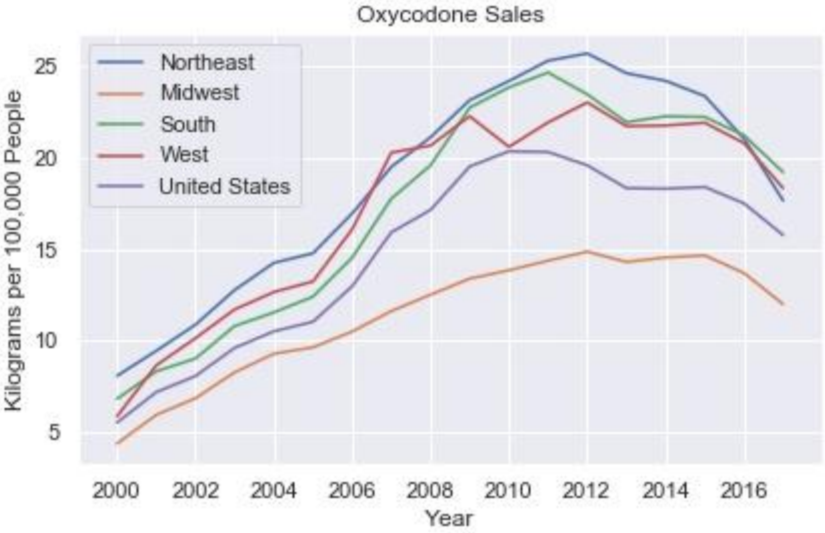


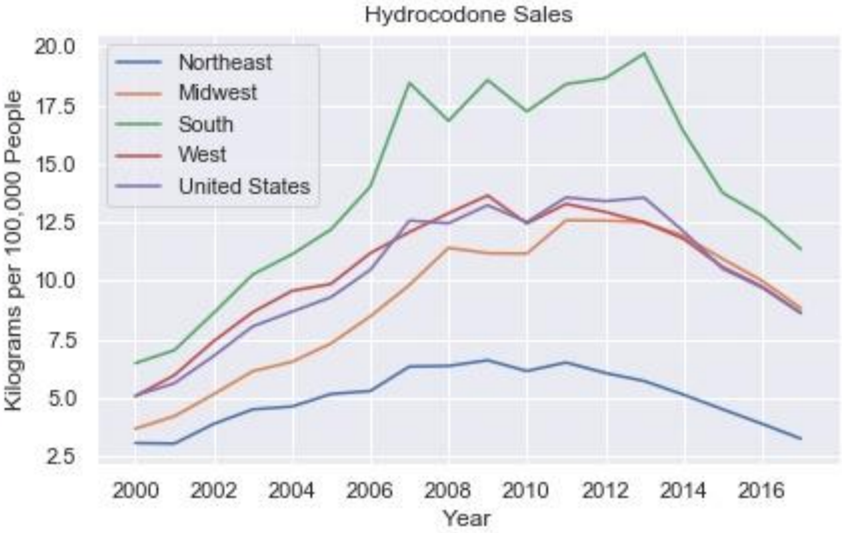



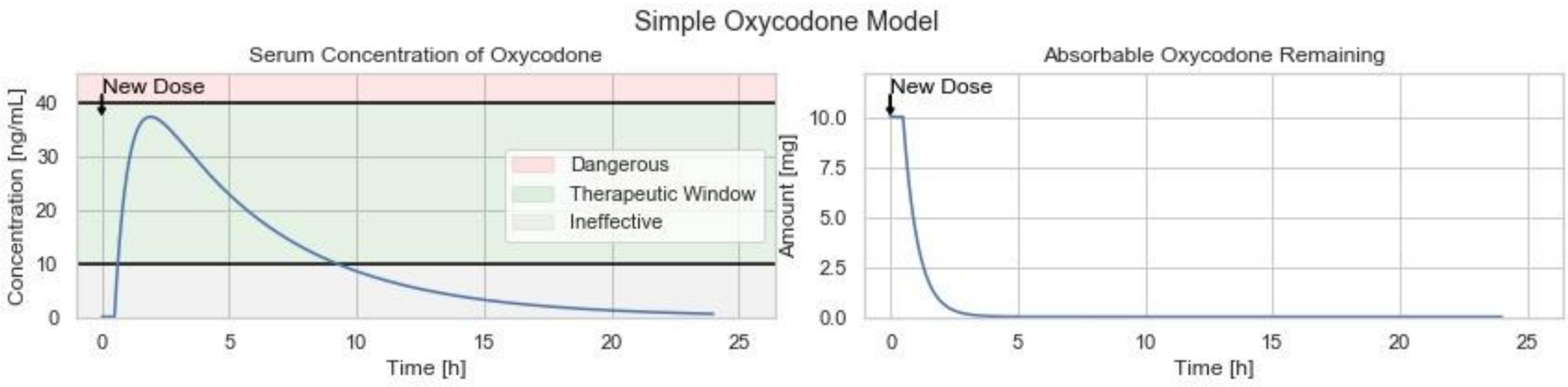

# Oxycodone Sales (2000 to 2017)



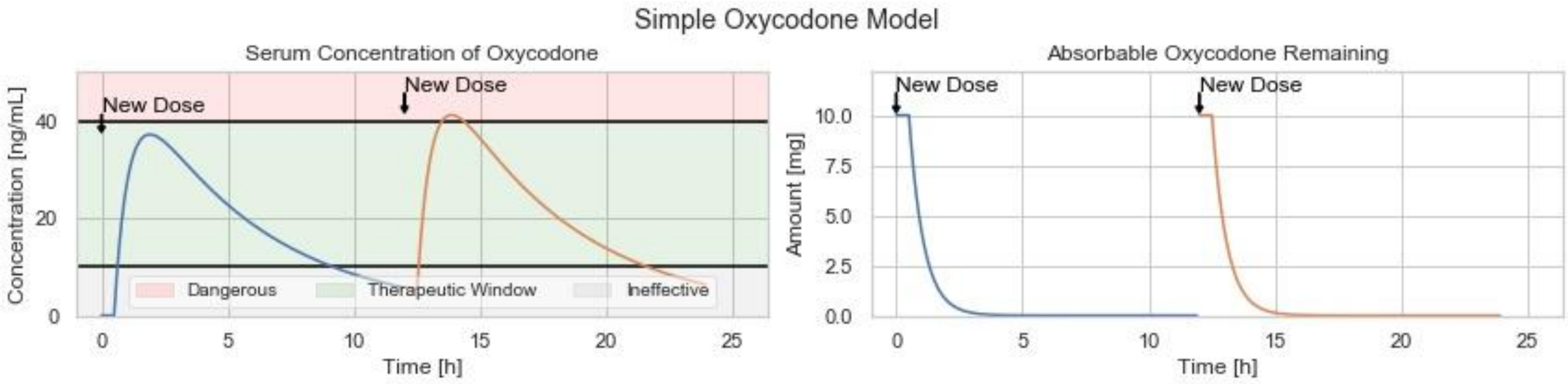
Oxycodone/Hydrocodone Sales (Michigan)
Oxycodone
Hydrocodone
Kilograms per 100,000 People
5.0
7.5
10.0
12.5
15.0
17.5
20.0
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year
Oxycodone/Hydrocodone Sales (United States)
Oxycodone
Hydrocodone
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year


Oxycodone Sales
Northeast
Midwest
South
West
United States
Kilograms per 100,000 People
25
20
15
10
5
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year


Hydrocodone Sales
Northeast
Midwest
South
West
United States
Kilograms per 100,000 People
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year



Simple Oxycodone Model
Serum Concentration of Oxycodone
Absorbable Oxycodone Remaining
New Dose
Dangerous
Therapeutic Window
Ineffective
Concentration [ng/mL]
Amount [mg]
Time [h]

Simple Oxycodone Model
Serum Concentration of Oxycodone
Absorbable Oxycodone Remaining
New Dose
New Dose
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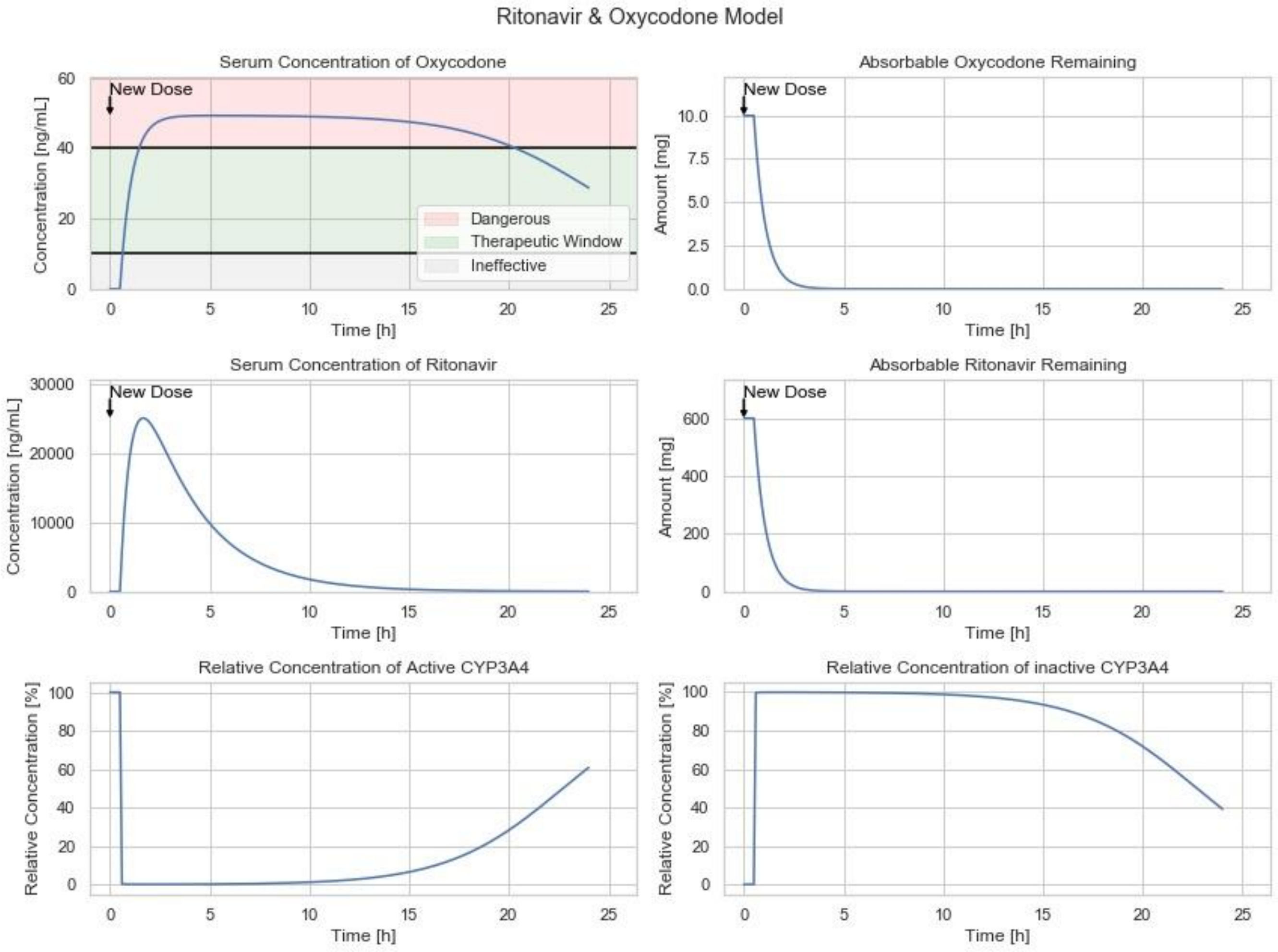
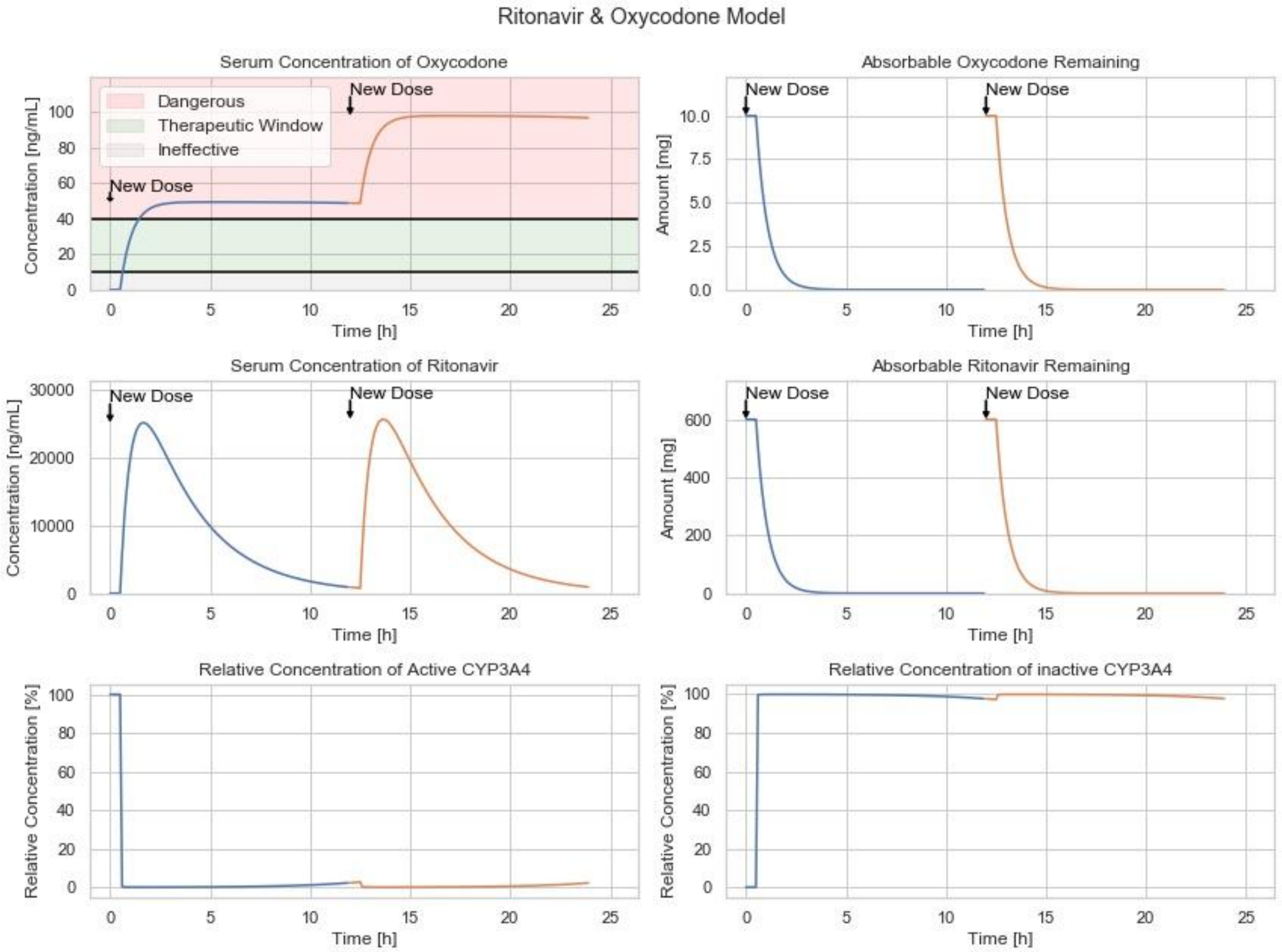
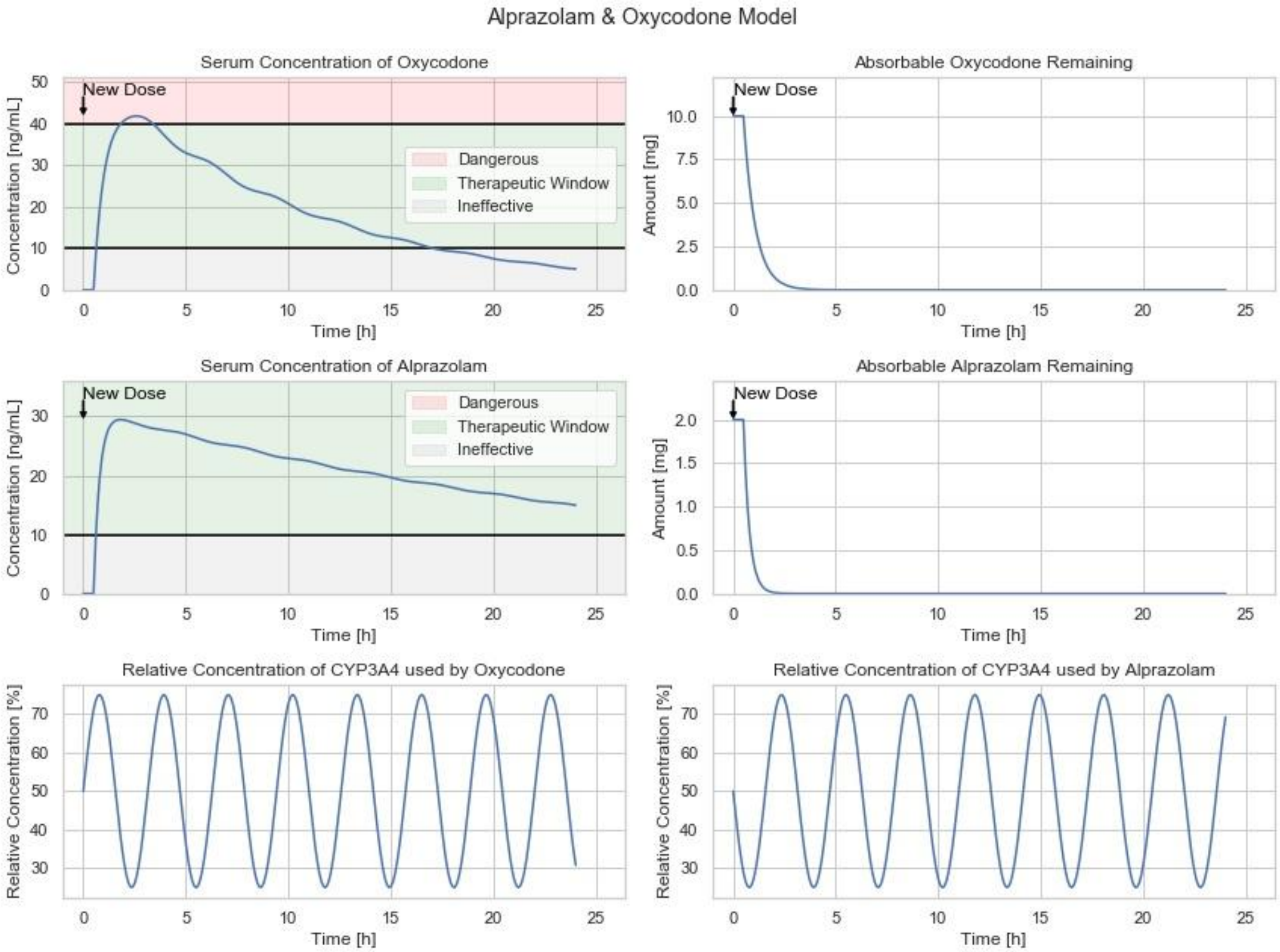
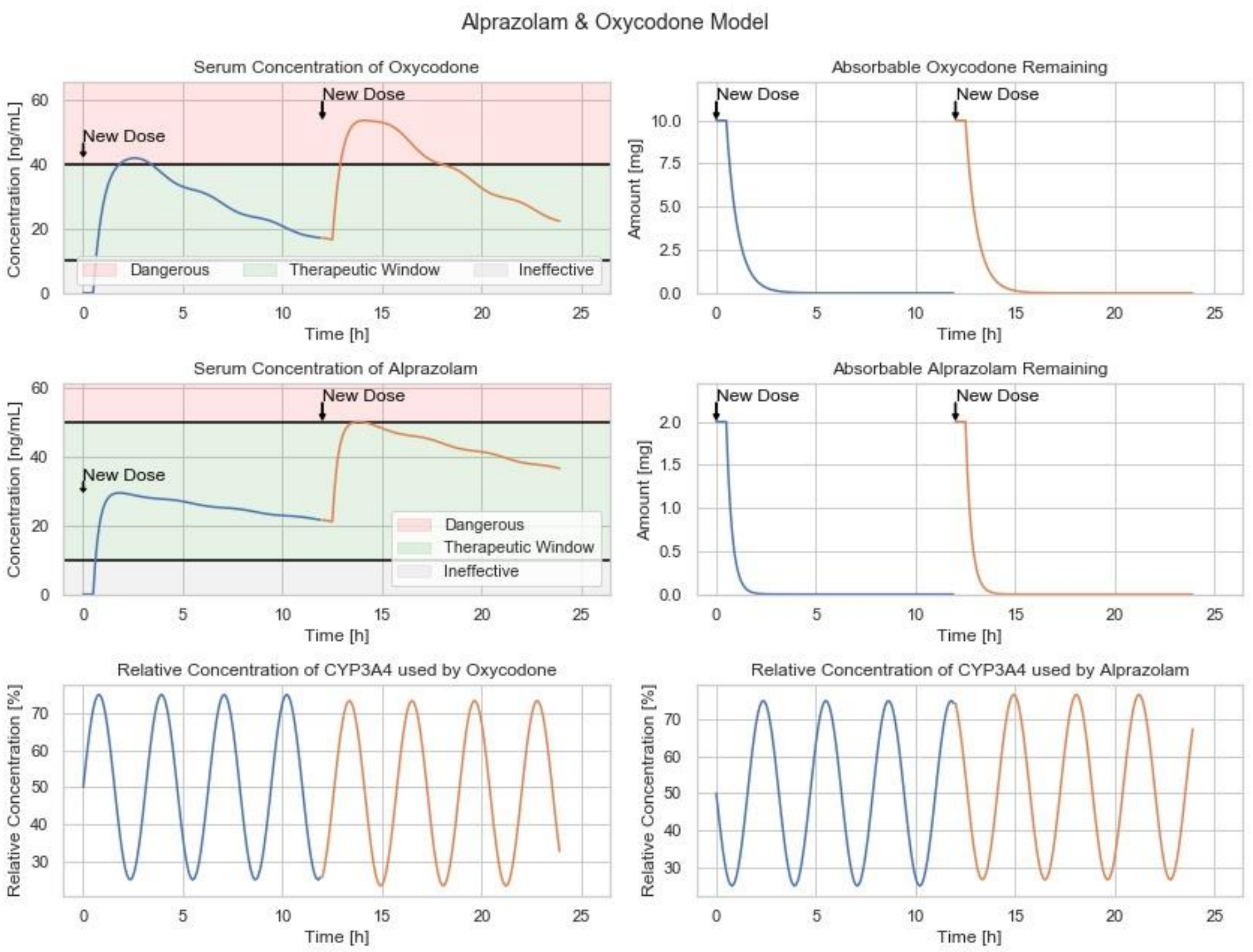
Therapeutic Window
Ineffective
Concentration [ng/mL]
Amount [mg]
Time [h]


Ritonavir & Oxycodone Model
Serum Concentration of Oxycodone
New Dose
Concentration [ng/mL]
Dangerous
Therapeutic Window
Ineffective
Time [h]
Absorbable Oxycodone Remaining
New Dose
Amount [mg]
Time [h]
Serum Concentration of Ritonavir
New Dose
Concentration [ng/mL]
Time [h]
Absorbable Ritonavir Remaining
New Dose
Amount [mg]
Time [h]
Relative Concentration of Active CYP3A4
Relative Concentration [%]
Time [h]
Relative Concentration of inactive CYP3A4
Relative Concentration [%]
Time [h]


Ritonavir & Oxycodone Model
Serum Concentration of Oxycodone
Dangerous
Therapeutic Window
Ineffective
New Dose
New Dose
Concentration [ng/mL]
Time [h]
Absorbable Oxycodone Remaining
New Dose
New Dose
Amount [mg]
Time [h]
Serum Concentration of Ritonavir
New Dose
New Dose
Concentration [ng/mL]
Time [h]
Absorbable Ritonavir Remaining
New Dose
New Dose
Amount [mg]
Time [h]
Relative Concentration of Active CYP3A4
Relative Concentration [%]
Time [h]
Relative Concentration of inactive CYP3A4
Relative Concentration [%]
Time [h]


Alprazolam & Oxycodone Model
Serum Concentration of Oxycodone
New Dose
Dangerous
Therapeutic Window
Ineffective
Concentration [ng/mL]
Time [h]
Absorbable Oxycodone Remaining
New Dose
Amount [mg]
Time [h]
Serum Concentration of Alprazolam
New Dose
Dangerous
Therapeutic Window
Ineffective
Concentration [ng/mL]
Time [h]
Absorbable Alprazolam Remaining
New Dose
Amount [mg]
Time [h]
Relative Concentration of CYP3A4 used by Oxycodone
Relative Concentration [%]
Time [h]
Relative Concentration of CYP3A4 used by Alprazolam
Relative Concentration [%]
Time [h]



Alprazolam & Oxycodone Model
Serum Concentration of Oxycodone
Absorbable Oxycodone Remaining
Serum Concentration of Alprazolam
Absorbable Alprazolam Remaining
Relative Concentration of CYP3A4 used by Oxycodone
Relative Concentration of CYP3A4 used by Alprazolam
New Dose
Dangerous
Therapeutic Window
Ineffective
Concentration [ng/mL]
Amount [mg]
Relative Concentration [%]
Time [h]

# Conclusion & Discussion

# Obstacles

- Modeling the concentrations of the active CYP3A4 and inactive CYP3A4 in my second odeint model
    - Rate of change was related to rate of change of Ritonavir
- Modeling competing substrates in third model

# Conclusion

1. The opioid crisis is real!
   a. The South and the West suffer from natural opioid overdoses
   b. Northeast suffers more with the synthetic opioids like fentanyl.
2. The decrease sales of oxycodone and hydrocodone since 2011 seem to be a contributing factor to decreasing rate of increase in fatality rates of opioids since 2011.
3. Narrow therapeutic range of oxycodone makes it a dangerous drug
   a. a slight deviation from dosage
   b. concurrent treatment with other inhibitors or competing substrates of the CYP3A4 enzyme will spike the blood concentrations of oxycodone and can have fatal consequences.