



# **Thinking Outside the Opioid Box: Non-Opioid Pharmaceutical Abuse**

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# Roadmap

- Why nonopioid prescription drug misuse and abuse is increasingly common
- Framework for identifying nonopioid drug misuse and abuse
- Highlights of drug classes
- Gaps in knowledge

Why is nonopioid  
prescription drug misuse  
and abuse increasingly  
common?



# Non-Opioid Prescription Drugs

- Potentiate effects of opioids
- “Smooth out” effects of other drugs
- Used as substitution or replacement when drug of choice not available

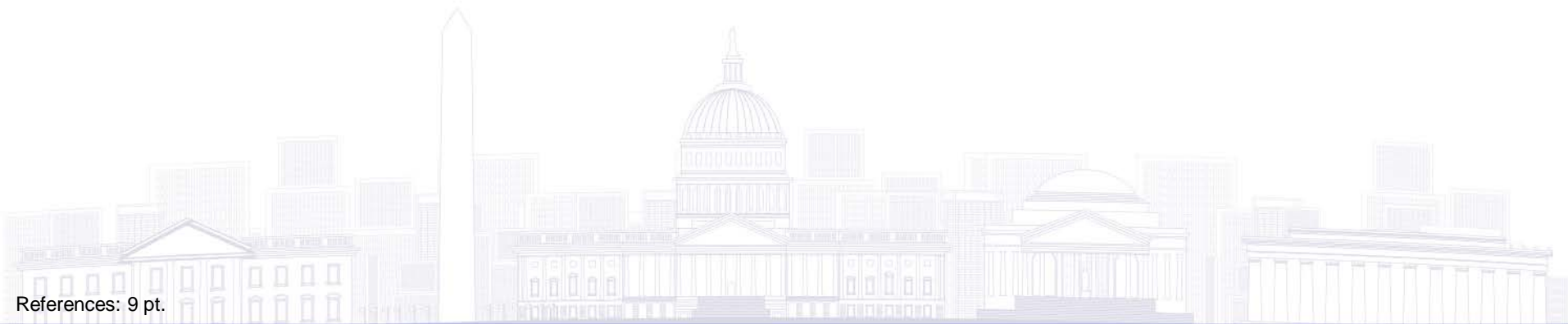


# Framework for Identifying Non-Opioid Drug Misuse and Abuse



# Surveillance Data

- National Poison Data System (NPDS)



# NPDS Intentional Abuse Rates

Generic Code	Intentional Abuse	Single Substance
Benzodiazepines	51275	15895
Dextromethorphan	18182	12852
Amphetamines	13833	7402
Carisoprodol	8633	3375
Atypical Antipsychotics	8556	2982
Other Sedative/Hypnotic/Anti-Anxiety or Anti-Psychotic	8150	3700
Diphenhydramine	5927	3163
Other SSRI	5185	1329
Other Antihistamines	5155	2208
Other Anticonvulsant (Excluding Barbiturates)	3931	1371
Methylphenidate	3662	2116
Other Antidepressant	3173	1133
Trazodone	3124	868
Ibuprofen	3017	1057
Other Muscle Relaxant	2989	1257
Cyclobenzaprine	2948	853
Gabapentin	1373	379
Phenothiazines	1288	642
Amitriptyline	1271	365
Clonidine	1159	389

# NPDS

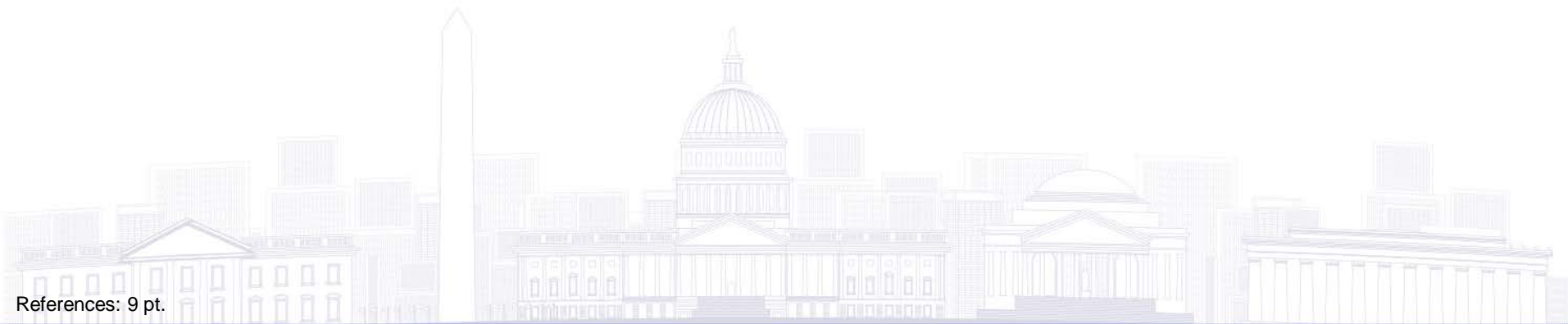
- Approaches to interpreting the data
  - Signal detection
    - » Increased mentions
    - » Increased single substance cases
    - » Shift from intentional to unintentional
    - » Increased cases in teenagers/young adults



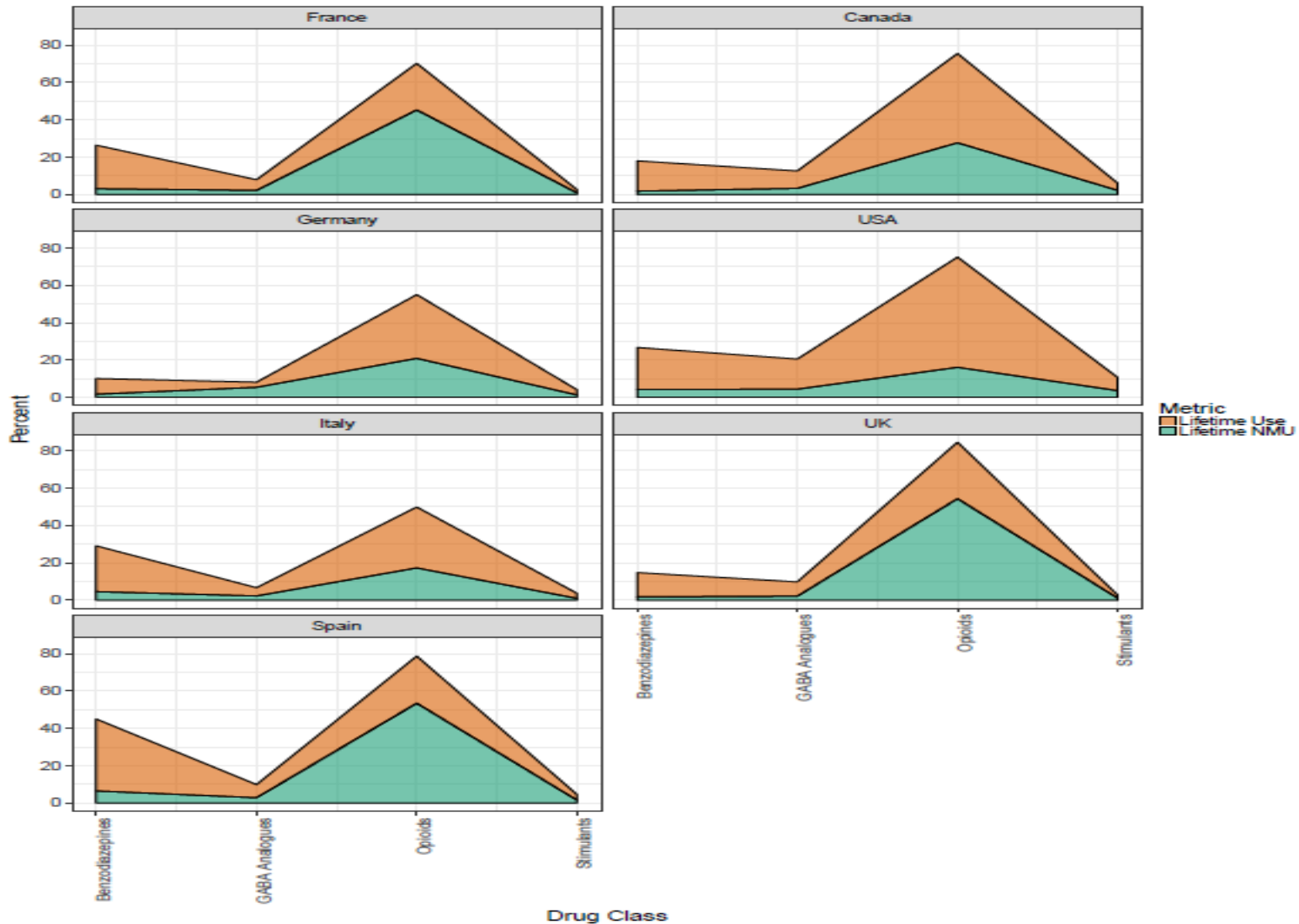


# Surveillance Data

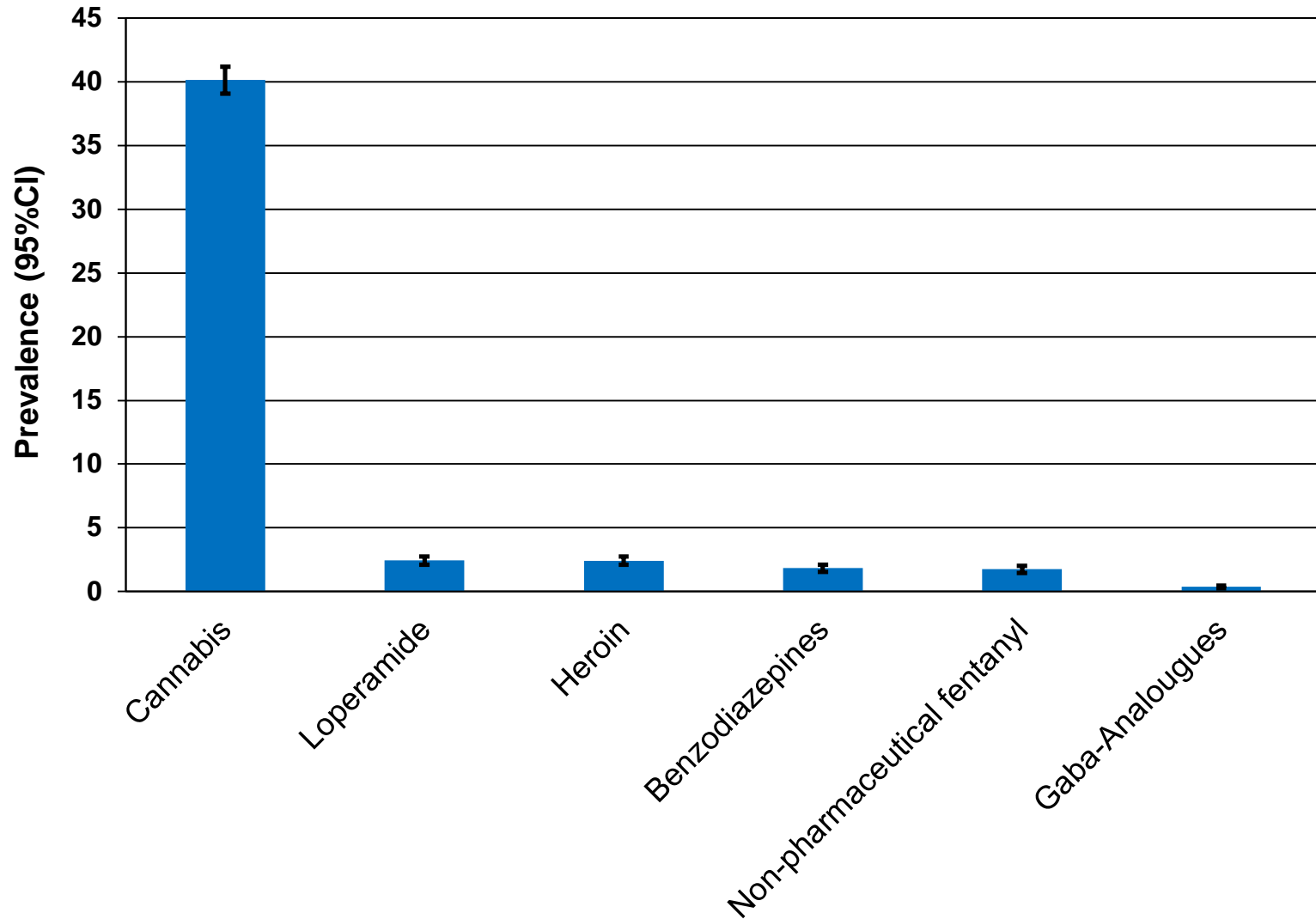
- National Poison Data System (NPDS)
- General population surveys
  - Survey of Nonmedical Use of Prescription Drugs (NMURx)



# Lifetime Use and Nonmedical Use

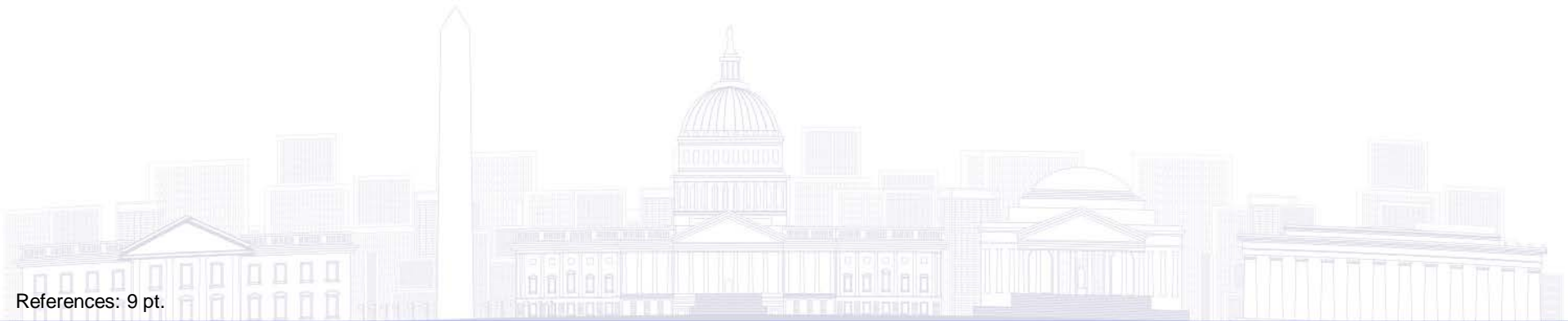


# Lifetime Nonmedical Use



# Surveillance Data

- High risk groups
  - Department of Corrections, jails
  - Teenagers and young adults
  - Substance abuse treatment programs
  - Diversion

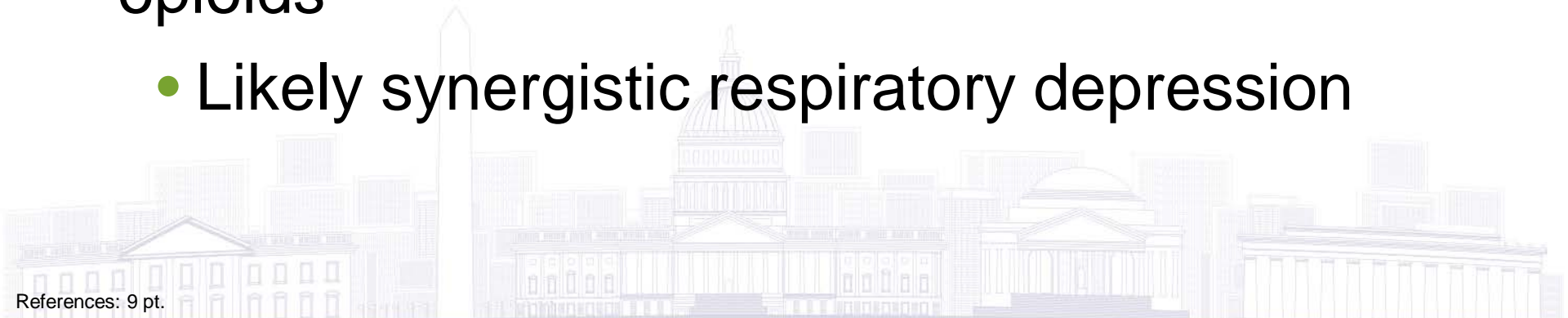


# Highlights of Commonly Abused Non-Opioid Pharmaceuticals



# GABA Analogs (Gabapentinoids)

- Gabapentin, pregabalin
- 10-15% prescribed opioids also prescribed gabapentin
- Misuse common in opioid use disorders (15-28%)
- Increased mortality when combined with opioids
  - Likely synergistic respiratory depression

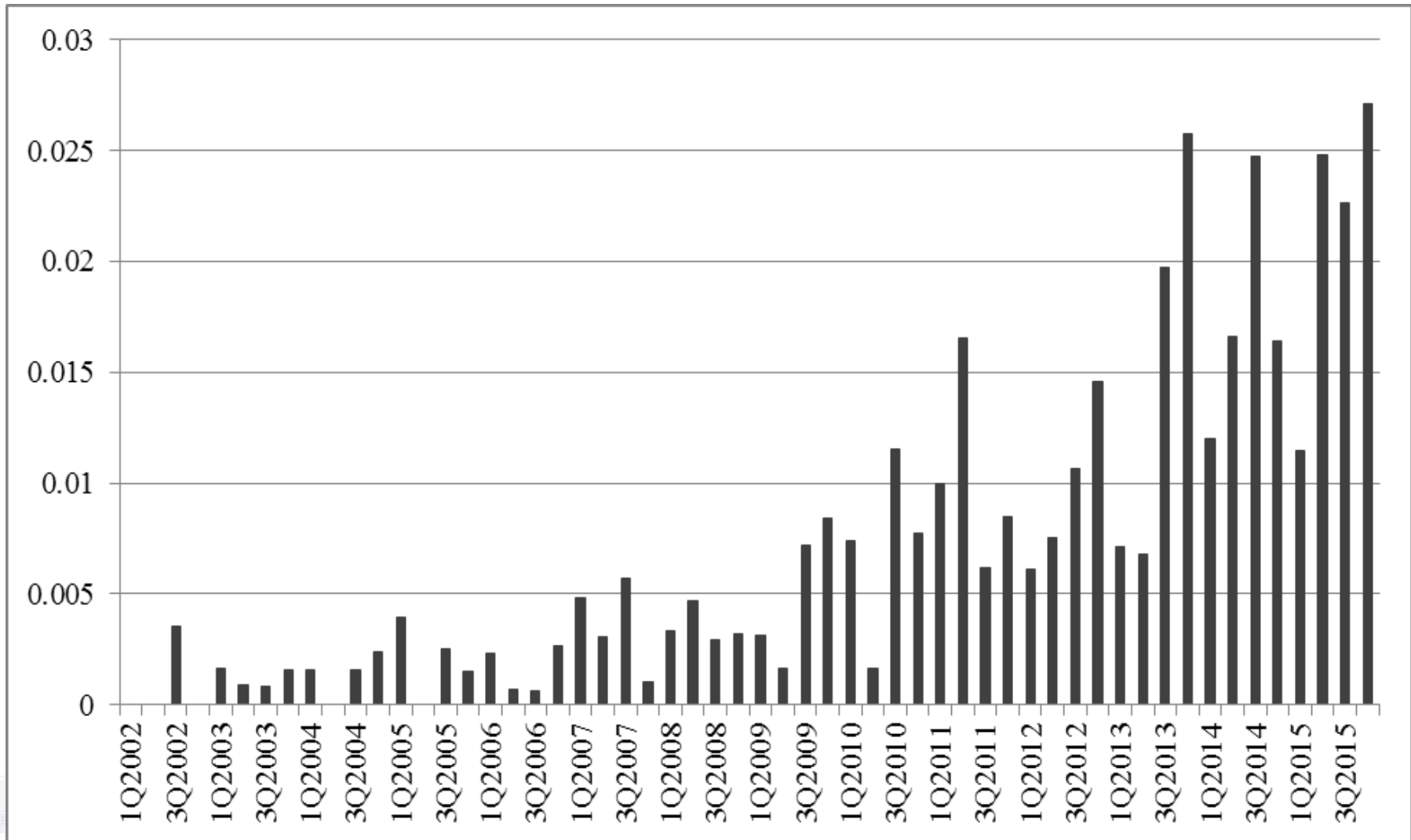


# Gabapentin – NPDS 2011-2017

- Increased ratio of mentions to single exposure calls
  - Polysubstance cases on the rise
- Slight increase in proportion of intentional exposures
- Increased use in teenAGERS

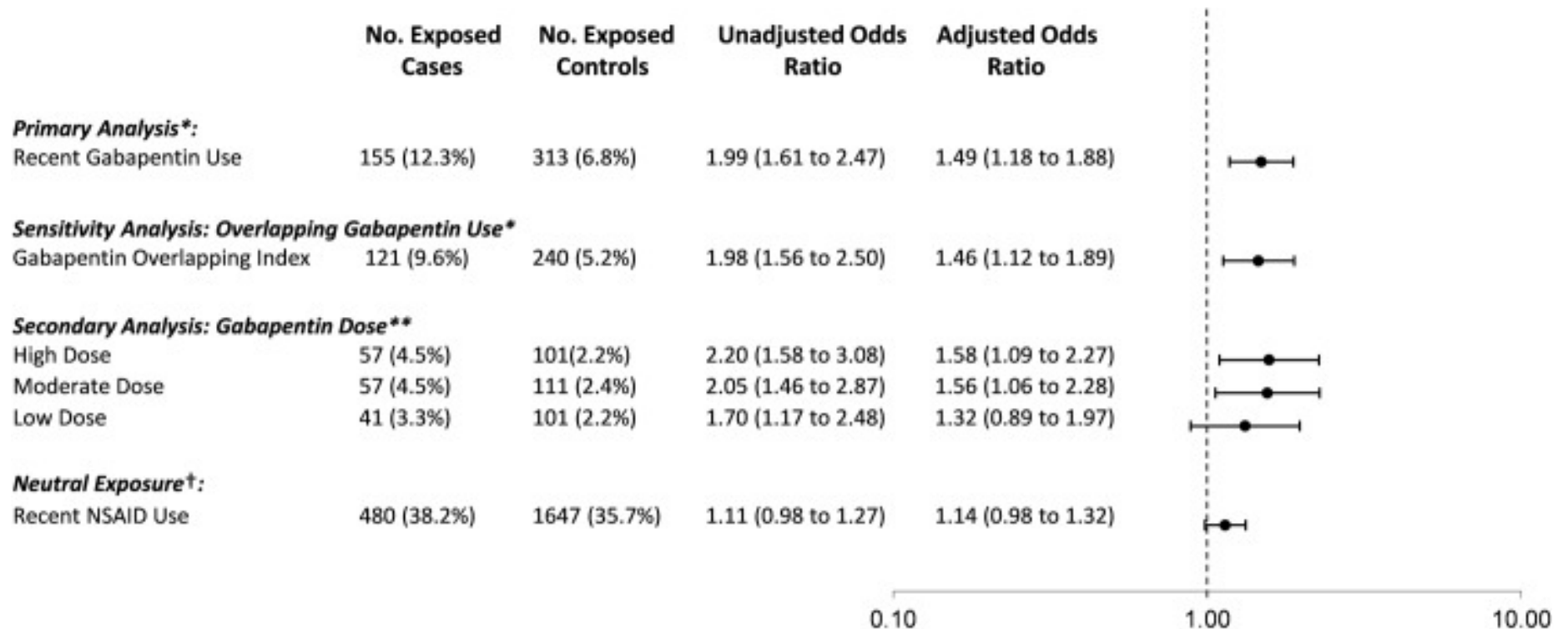


# Diversion of GABA Analogs





# Gabapentin and Mortality



\*1,256 cases and 4,619 controls; Reference Group: no gabapentin use

\*\* Low dose: <900mg/day; moderate dose: 900-1799mg/day; high dose: ≥1800mg/day; Reference Group: no gabapentin use

† Reference Group: no NSAID use

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# Loperamide

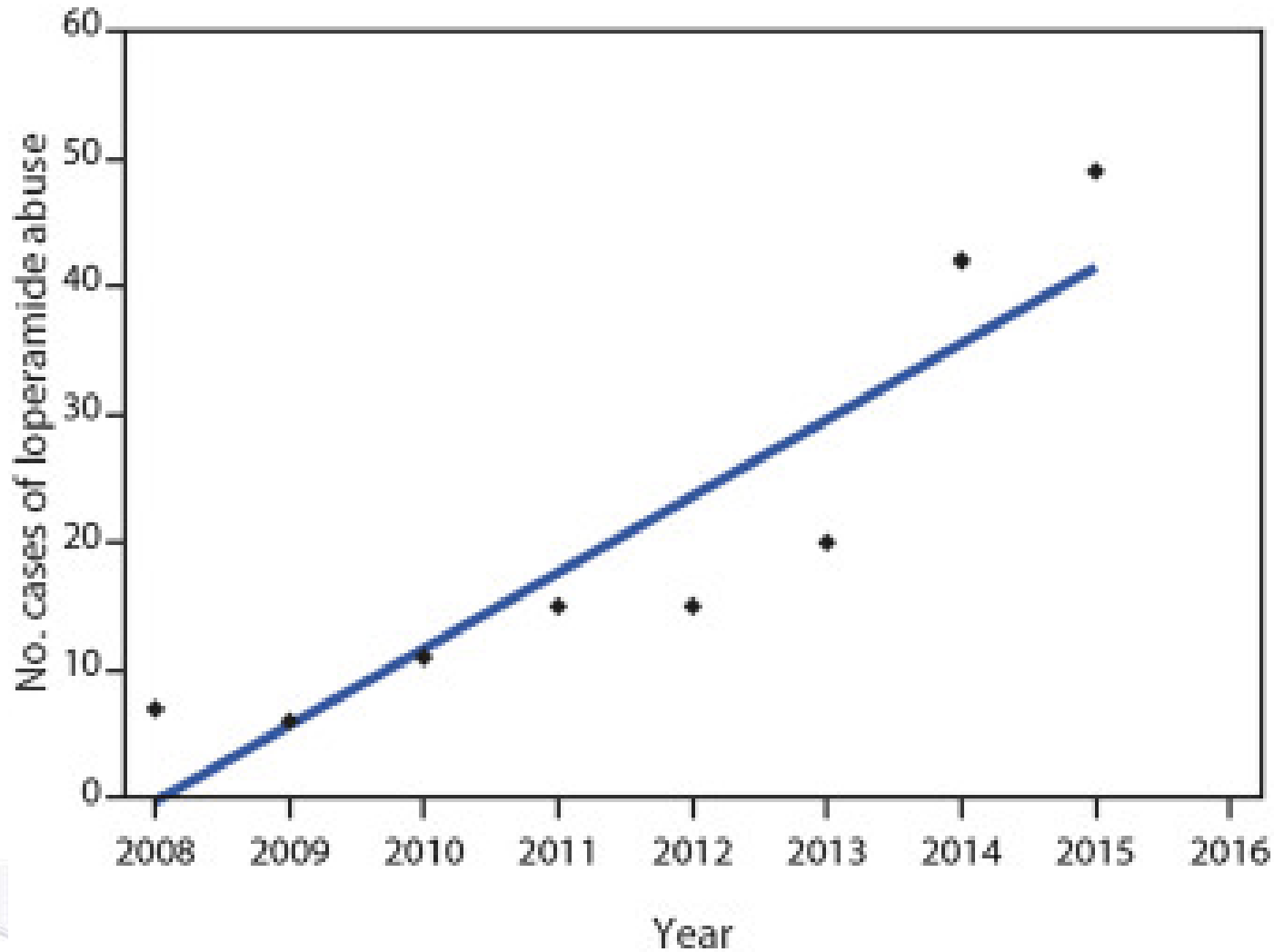
- Antidiarrheal
- Prescription and OTC
- Intestinal mu agonist
- Poor systemic absorption due to p-glycoprotein
  - BUT often co-used with inhibitors
- Abused alone or in combination with opioids



# Loperamide – NPDS 2010-2017

- Ratio of mentions to single substance cases unchanged
- Increased proportion of intentional abuse cases
  - 8% -> 34%
- No significant change in rate of exposures, but behavior and reasons are changing

# Loperamide Abuse



# Loperamide Abuse

## Reported Toxicities by Organ System

<u>Organ System</u>	<u>1985-2013</u> (n = 21)	<u>2014-2016</u> (n = 33)	<u>Total, 1985-2016</u> (n = 54)
Gastrointestinal	6	1	7
Cardiovascular	4	15	19
Respiratory	2	2	4
Neurological	4	5	9
Death	10	17	27

# Antidepressants

- Reports of abuse of all classes
- May have higher rates with SNRI
  - Stimulant effects due to norepinephrine reuptake inhibition
  - When used with opioids, pharmaceutical “speedball” effect
- Adverse effects include seizures and dysrhythmias

# Bupropion – NPDS 2012-2017

- Increased single substance exposures compared to total mentions
  - Used as a primary drug
- Increased proportion of intentional exposures
- Markedly increased use in teenage population



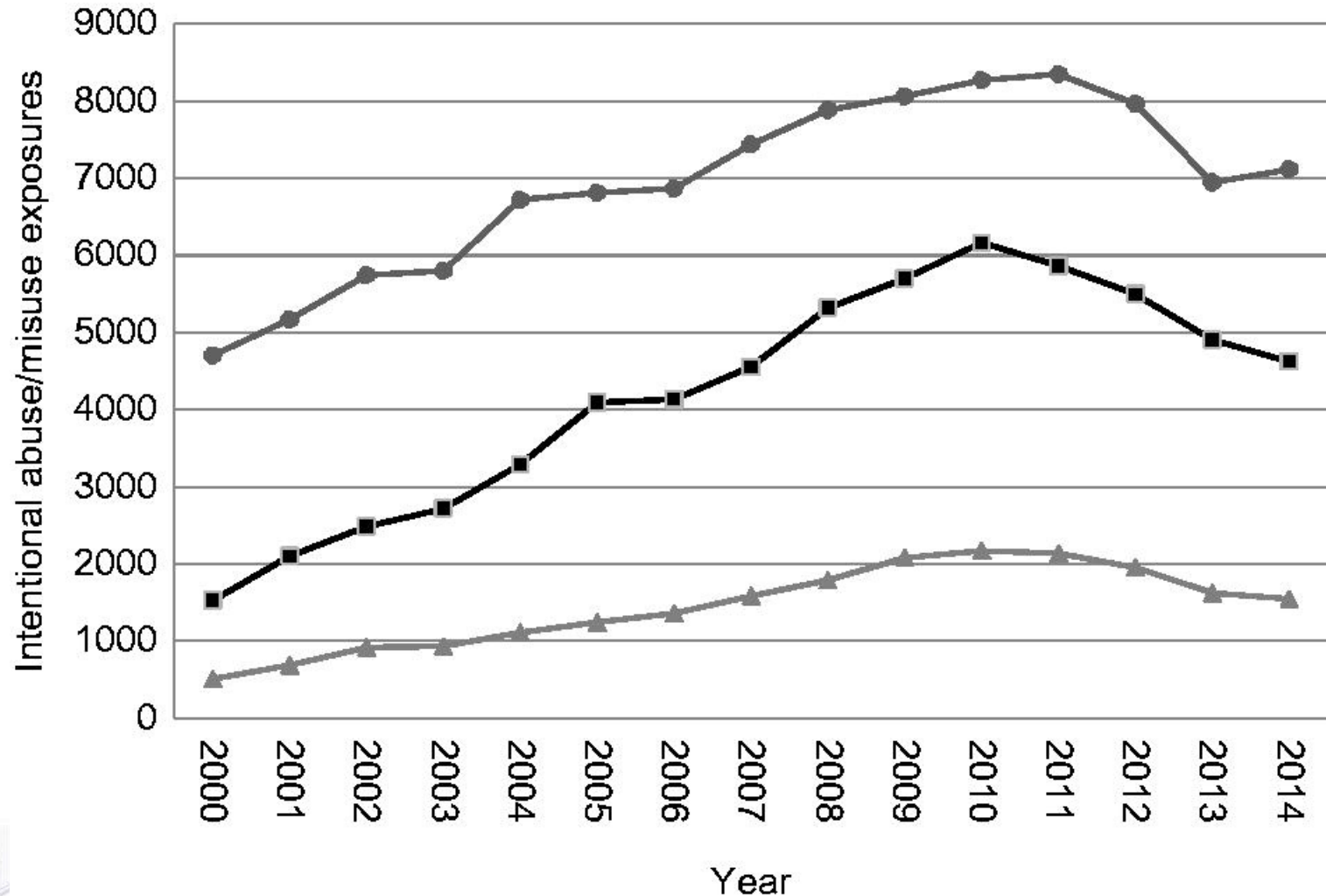
# Benzodiazepines

- GABA-A agonists
- Single agent and polysubstance exposures
- CNS depression
  - Can be synergistic with EtOH and opioids
- Respiratory depression rare with isolated oral exposure BUT also synergistic





# Benzodiazepines and Opioids, NPDS 2000-2014



# Benzodiazepines and Opioids, NPDS 2000-2014

**Table 2.** Odds of death among people who were exposed to opioid analgesics compared to people who were exposed to benzodiazepines and/or opioid analgesics.

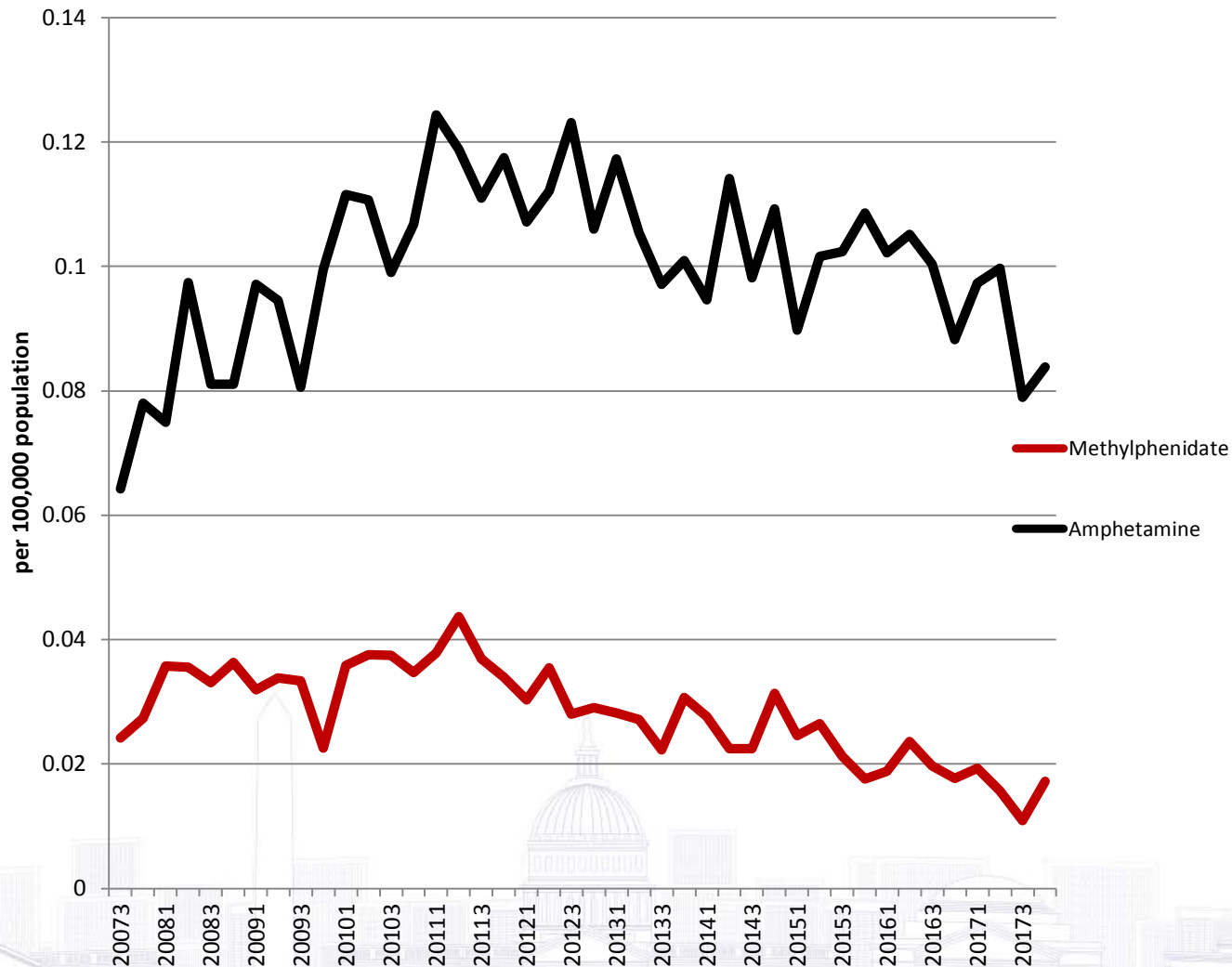
Variables	Deaths/exposures (% resulting in death)	Unadjusted OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>
<b>Drug of misuse or abuse</b>			
Benzodiazepines + opioid analgesics	28/5342 (0.52%)	1.53 (1.00–2.34) <sup>b</sup>	1.55 (1.01–2.37) <sup>b</sup>
Benzodiazepines	3/35,665 (0.01%)	0.02 (0.01–0.08) <sup>d</sup>	0.03 (0.01–0.08) <sup>d</sup>
Opioid analgesics	93/27,125 (0.34%)	Reference	Reference
<b>Gender</b>			
Male	85/36,210 (0.23%)	Reference	Reference
Female	39/31,922 (0.12%)	0.52 (0.36–0.76) <sup>c</sup>	0.51 (0.35–0.74) <sup>c</sup>
Age (in increasing ten years increments)	N/A	1.05 (0.93–1.18)	1.08 (0.96–1.21)

# Stimulants

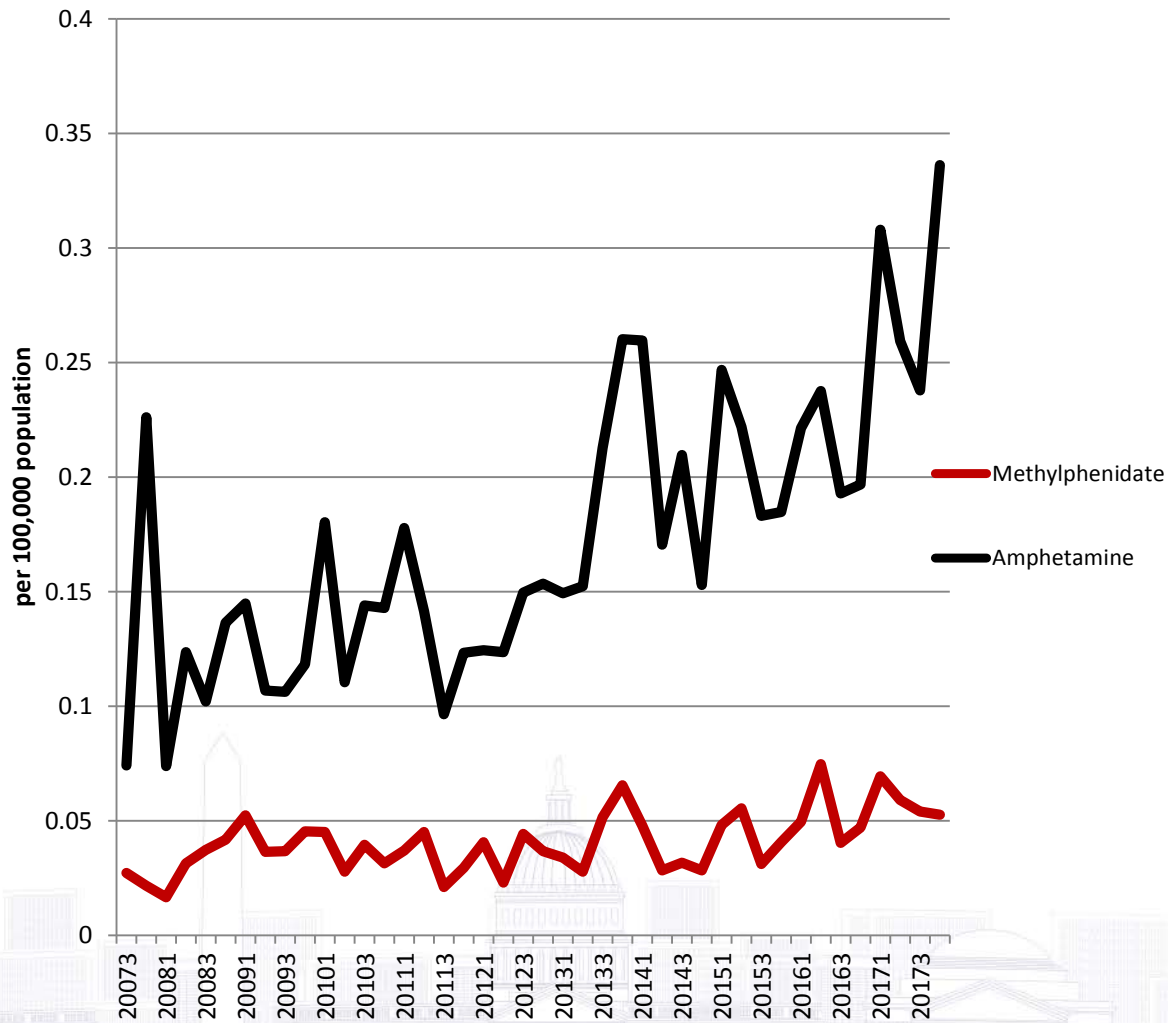
- Used as single substance or polysubstance
  - Pharmaceutical "speedball" effect
- Highest rates in teenage and young adult population
- Rates of intentional abuse stable, but diversion increasing



# Stimulants, Poison Centers



# Stimulants, Drug Diversion



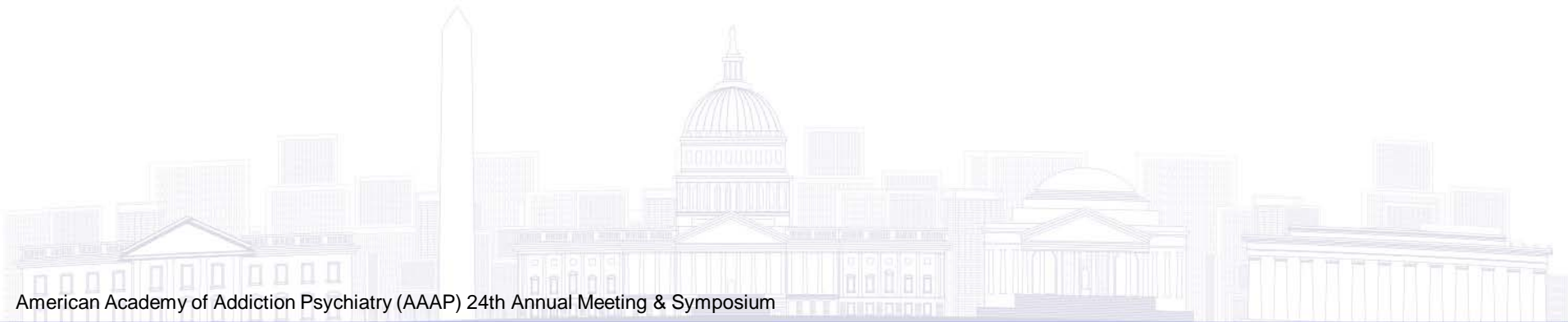
# Antipsychotics

- Atypical antipsychotics commonly abused both alone and in combination with other drugs
- Especially popular in incarcerated population
- Quetiapine often drug of choice



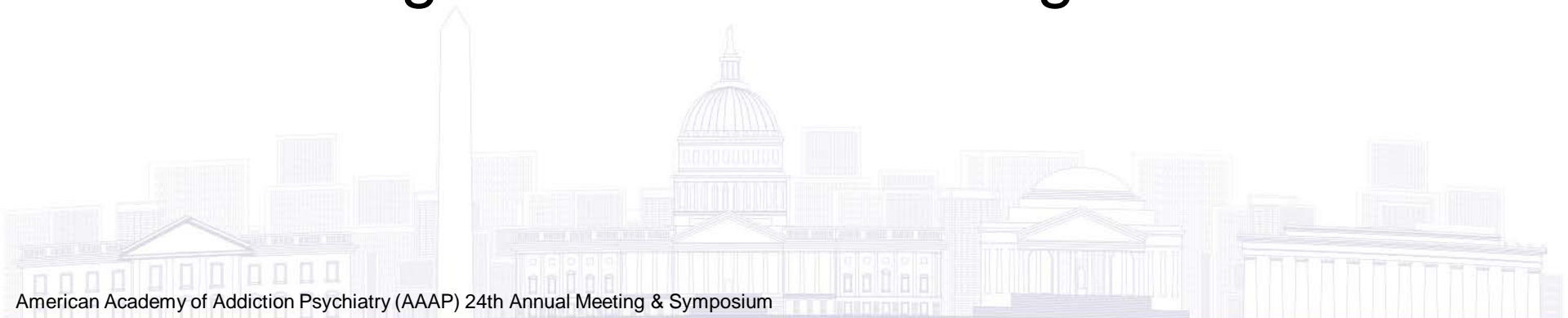
# Antipsychotic Abuse

- 429 patients from detox and rehab units
- 73 (17%) abuse atypical antipsychotics with other substances
  - Alcohol, opioids, cocaine/crack, methamphetamine, cannabis



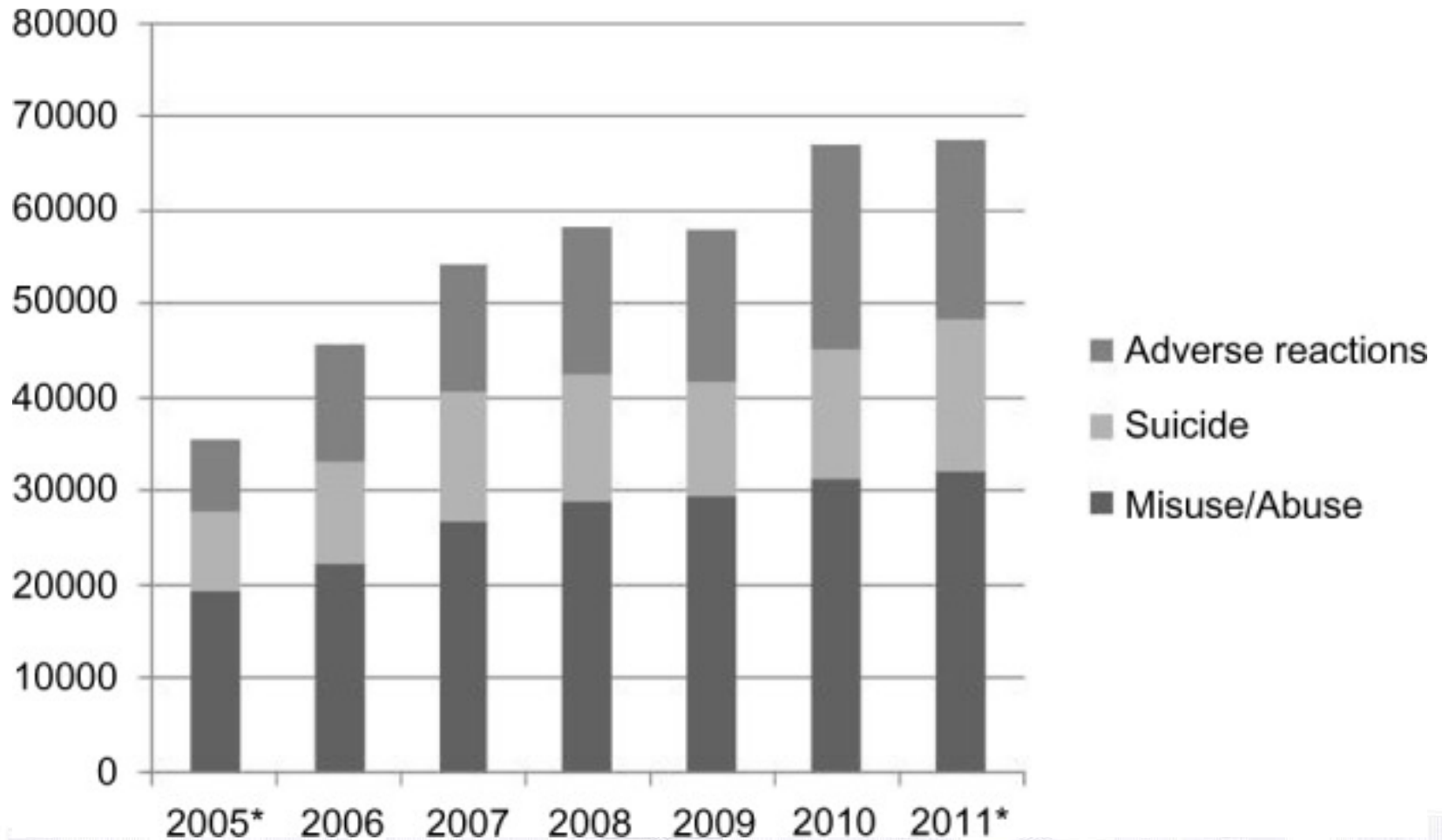
# Antipsychotic Abuse

- Quetiapine most common (84.9%)
  - Olanzapine (17.8%), risperidone (24.7%), aripiprazole (20.5%), ziprasidone (8.1%), asenapine (2.9%)
- Goals: "getting mellow", "slowing down", or enhancing effects of other drugs





# Quetiapine DAWN ED Visits



# Cyclobenzaprine

- Reported via NPDS
- Few studies of misuse/abuse
- Anticholinergic effects
- Structural similarity to tricyclic antidepressants
- Anticipate synergistic CNS and respiratory depression with opioids



# Other Antiepileptics

- Nearly all have been reported both in single substance and polysubstance abuse cases
- Levitiracetam may be on the horizon
- Synergistic CNS depression with opioids
- Cardiac effects also possible



# Gaps in Knowledge

- What interventions are needed to decrease polysubstance abuse?
- Is postmarketing surveillance needed for nonopioid drugs?
- What education should be given to prescribers regarding risks?



# Summary

- Nonopioid pharmaceutical drug abuse is becoming more common
- Many likely to be co-abused with opioids
- Synergistic CNS and respiratory depression most common interaction
- Need methods for surveillance and early warning
  - NPDS and NMURx may provide ideas

# Questions?

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