Polypharmacy and other *risky business*

→ The medical examiner weighs in
→ The sleepier it gets - perhaps less is more!
→ Risk that increases over the counter.

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Faculty/Presenter Disclosure

- **Faculty:** Marina Reinecke
- **Relationships with commercial interests:** None
- Medical consultant for CPSM (employee) and MB Health (MMDRC and other committees)

Learning Objectives

- **At the conclusion of this activity, participants will be able to:**
- Propose how lessons learned from Manitoba's provincial death data should transform local prescribing and dispensing practices.
- Investigate the role that polypharmacy plays in morbidity and mortality associated with poor prescribing/dispensing practices.
- Recognize that certain combinations of prescription medications significantly increases overdose risk.
- Propose an approach to managing concurrent over-the-counter medication use in patients who are at risk for multidrug toxicity.

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Glen

- 44 y/o male
- Working full time as a project manager for a construction company.
- History of hypertension, GERD, heavy smoking and prescription drug abuse in his 20's. He was successfully treated for Hepatitis C in his early 30's.
- Non drinker.
- Known to have had an argument with his common law partner the night before..
- Found unresponsive face up on his bed the following morning.
- No threats of suicide or suicide note

Case discussion - Glen

- DPIN:
- Tylenol #3 240 tabs q 60 days
- Alprazolam 1mg 180 tabs q 60 days
- Temazepam 30mgs 60 tabs q 60 days
- Cyclobenzaprine 10mgs 180 tabs q 60 days
- Quetiapine 200mgs 120 tabs q 60 days
- Enalapril, HCTz, esomeprazole and ferrous gluconate
- ……..last delivered 9 days prior to death

ME's report:

- **COD:** Acute multidrug toxicity
- **Manner of death:** Undetermined
- **Toxicology:** codeine (free) 2310 ng/ml (10 - 100)
  morphine (free) 22 ng/ml
  temazepam 3180 ng/ml (600 - 900)
  ethanol 0 mg/dl
  cyclobenzaprine 510 ng/ml (3-23)
  norcyclobenzaprine 120 ng/ml

Polling Questions

Polling Questions:

1. Between 2013-2018 in Manitoba, which opioid is responsible for the largest number of overdose deaths, either as primary cause or as a major contributing factor?

a) Fentanyl
b) Carfentanil
c) Codeine
d) Tramadol
e) Oxycodone

Polling Questions:

2. In 2018 in Manitoba, which benzodiazepine contributed to the largest number of overdose deaths?

a) Alprazolam
b) Diazepam
c) Temazapam
d) Bromazepam
e) Lorazepam

Polling Questions:

3. In Manitoba, most opioid overdose deaths can be attributed to:

a) A single prescribed opioid
b) Multiple prescribed opioids
c) A single illicit opioid
d) One or more opioids combined with multiple other drugs
e) Opioids in combination with alcohol

Polling Questions:

4. In Manitoba between 2014-2017, which two drug classes were the top contributors to opioid overdoses?

a) Alcohol and benzodiazepines
b) Antipsychotics and antidepressants
c) Benzodiazepines and antidepressants
d) Statins and antihypertensives
e) Benzodiazepines and Z-drugs

Polling Questions:

5. In Manitoba in 2018, which two over-the-counter ingredients contributed to the largest number of deaths?

a) Acetaminophen and ASA
b) Acetaminophen and pseudoephedrine
c) Diphenhydramine and dextromethorphan
d) Dextromethorphan and acetaminophen
e) Ibuprophen and desloratadine

Chief Medical Examiners' Death Review

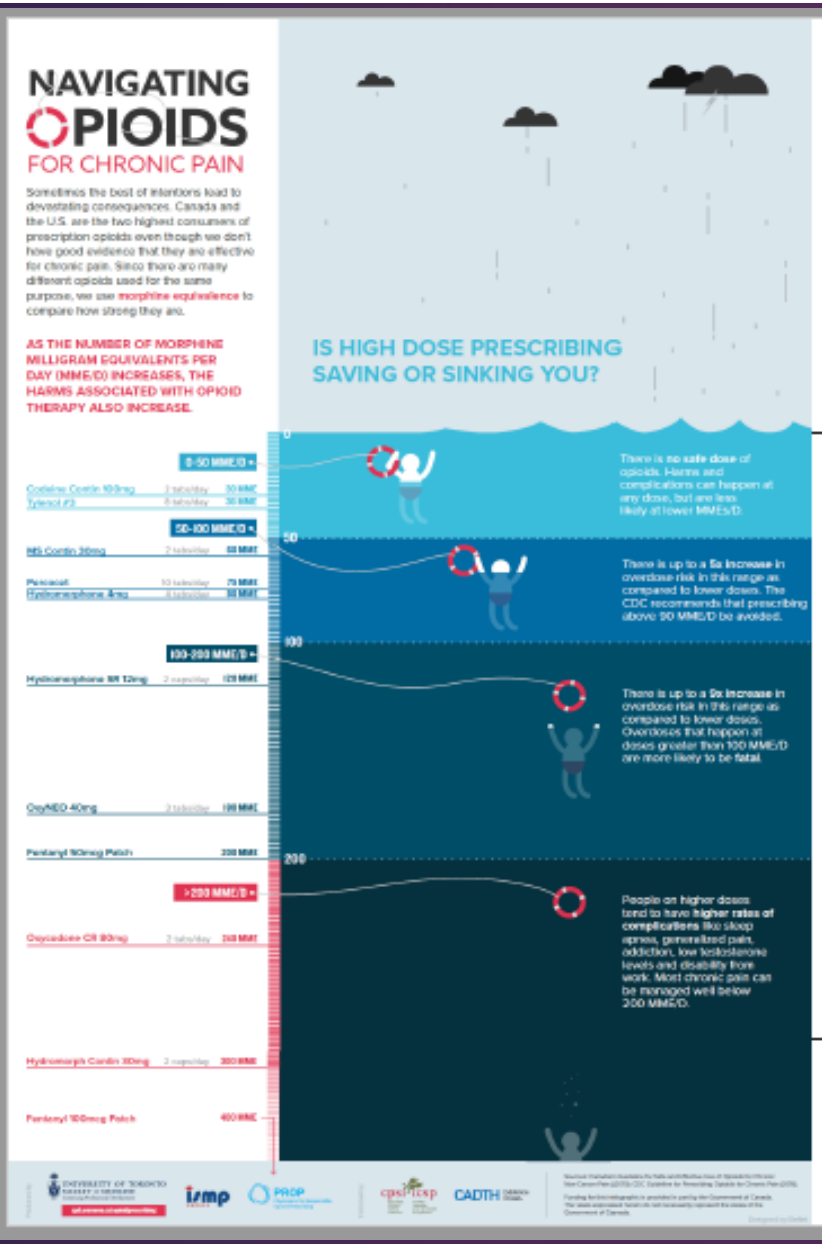
A component of the CPSM Prescribing Practices Program

Chief Medical Examiners' Death Review

- Relationship initiated by the previous ME who was concerned regarding the number of prescription drug related deaths
- Reviewers: 2 medical consultants with extensive primary care experience in the management of pain, addiction and mental health concerns.
- **Adult Inquest Review Committee**
- All deaths involving prescription medications undergo detailed review
- No chart information unless we ask for it (high volume and educational process and meant to prompt self-reflection)
- Methadone; buprenorphine/naloxone deaths

Chief Medical Examiners' Death Review

- Prescribers receive standard cover letter
- Plus summary of the ME report highlighting the manner of death, cause of death, notable circumstances of death, toxicology findings and summary of relevant DPIN data
- Feedback to prescribers in 3 categories:
  - FYI
  - Rx'bing falls outside of guidelines (standardized evidence-based quality indicators, e.g. concomitant opioids and benzo's); includes resources
  - Significant concerns (rare)



Updated March 1, 2018

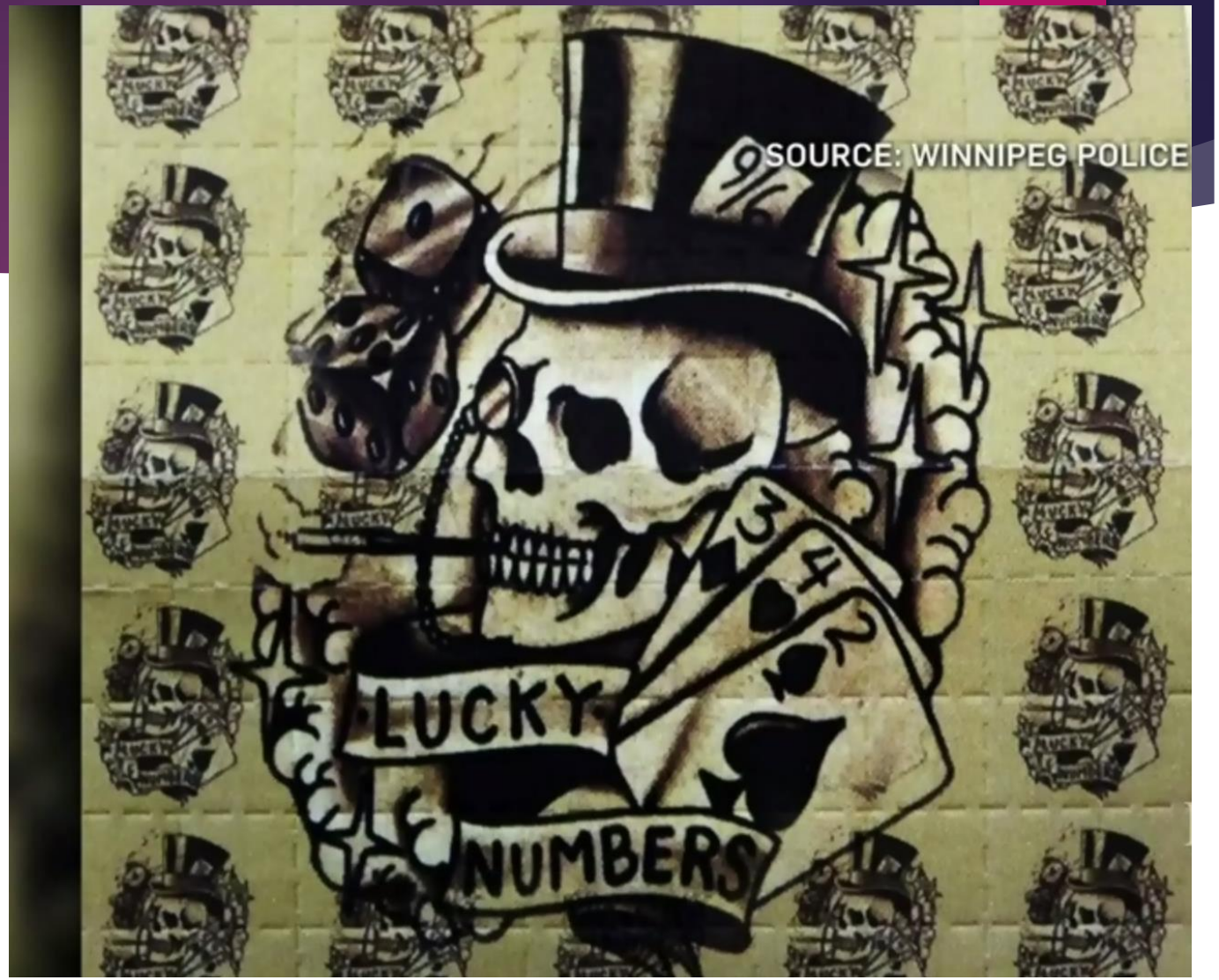
Number* of Unique Patients in Manitoba with "Average Morphine Equivalence Per Day"**

Ave. MME Per Day	Q4 2017: Oct. 1 2017 to Dec. 31, 2017 # Unique Patients	Q4 2017: Oct. 1 2017 to Dec. 31, 2017 Proportion of Unique Patients	% Var. # Unique Patients from Prev. Year	Q4 2016: Oct. 1 2016 to Dec. 31 2016 # Unique Patients	Q4 2016: Oct. 1 2016 to Dec. 31 2016 Proportion of Unique Patients
0 to 50	4,203	45.2%	↑ 1.8%	4,128	44.5%
50 to 90	2,365	25.5%	↑ 4.0%	2,273	24.5%
90 to 200	1,937	20.8%	↓ (0.7%)	1,951	21.0%
>200	787	8.5%	↓ (14.6%)	922	9.9%
	9,292	**100.0%**	**↓ (2.5%)**	**9,274**	**100.0%**

*Data source is DPIN, excludes Long Term Care & Palliative Care clients; does not include drugs dispensed in hospital. Includes fentanyl.
** MME Per Day Calculated by taking Total MME divided by Days Supply

Non prescription Fentanyl

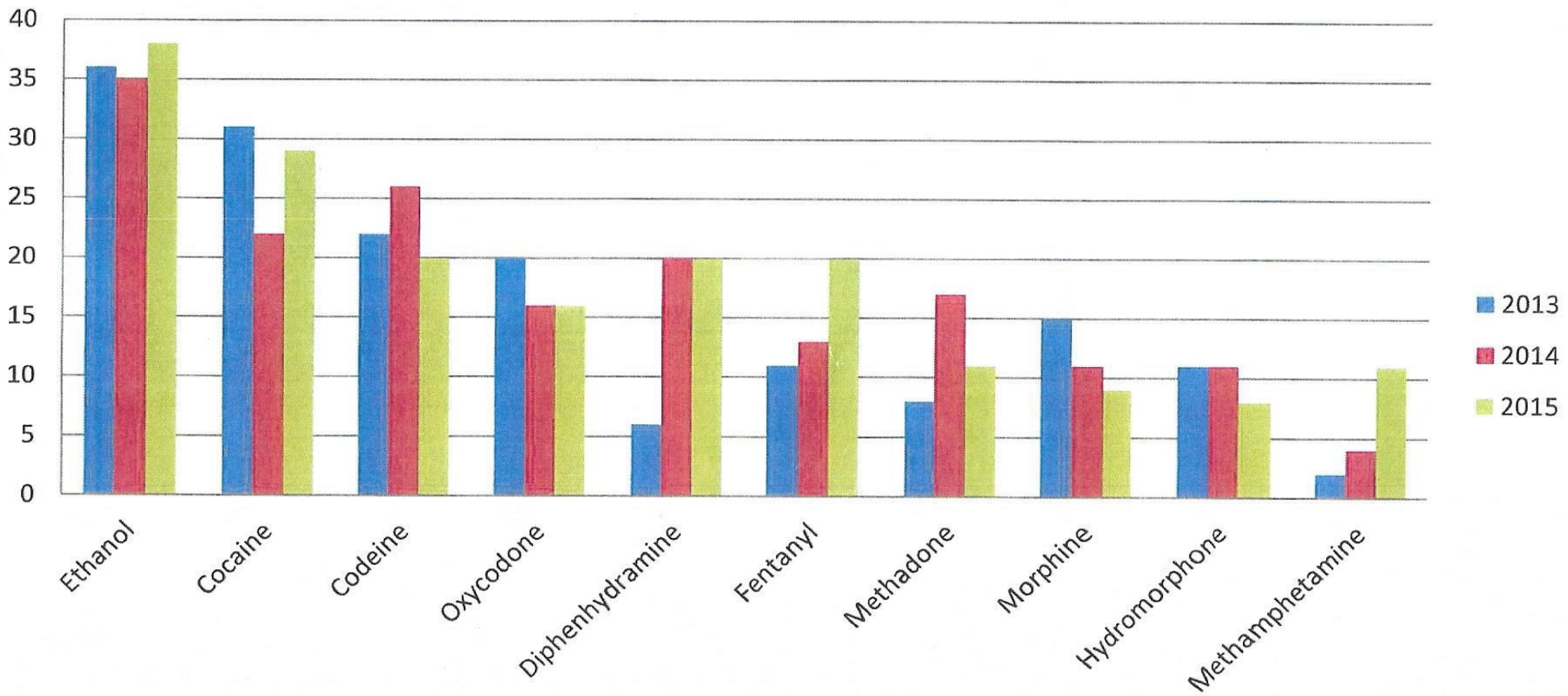
- Fentanyl smuggled in from China on west coast. Available through internet pharmacies
- Different formulations of fentanyl with varying strengths (carfentanil)
- Attainable from internet pharmacies – 1 kg goes a long way (100K street value)
- Adulterated into other drugs:
  - West coast heroin 70%
  - Local – adulterated into powdered cocaine, crystal meth, fake oxys.
  - Blotter tabs

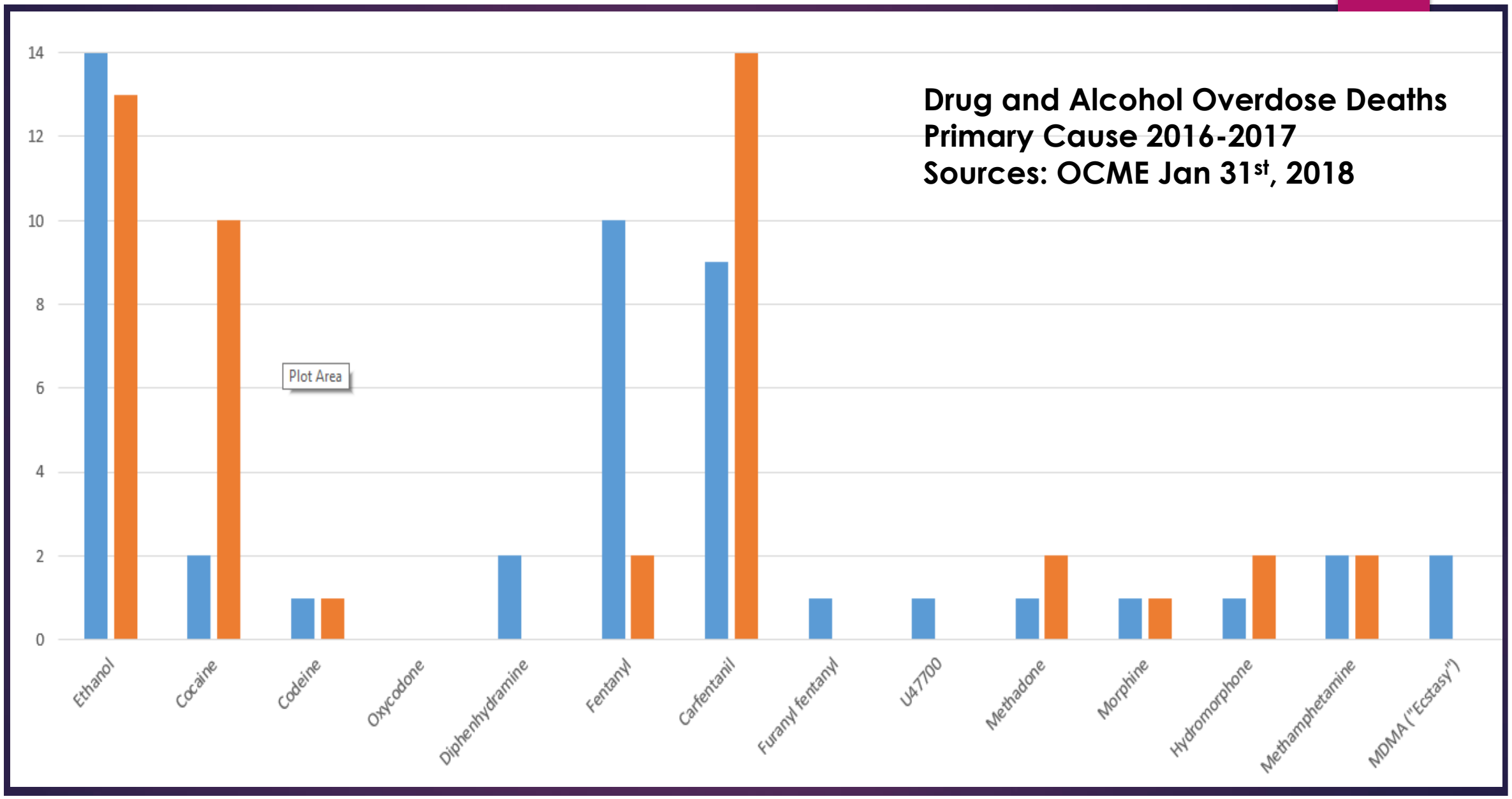


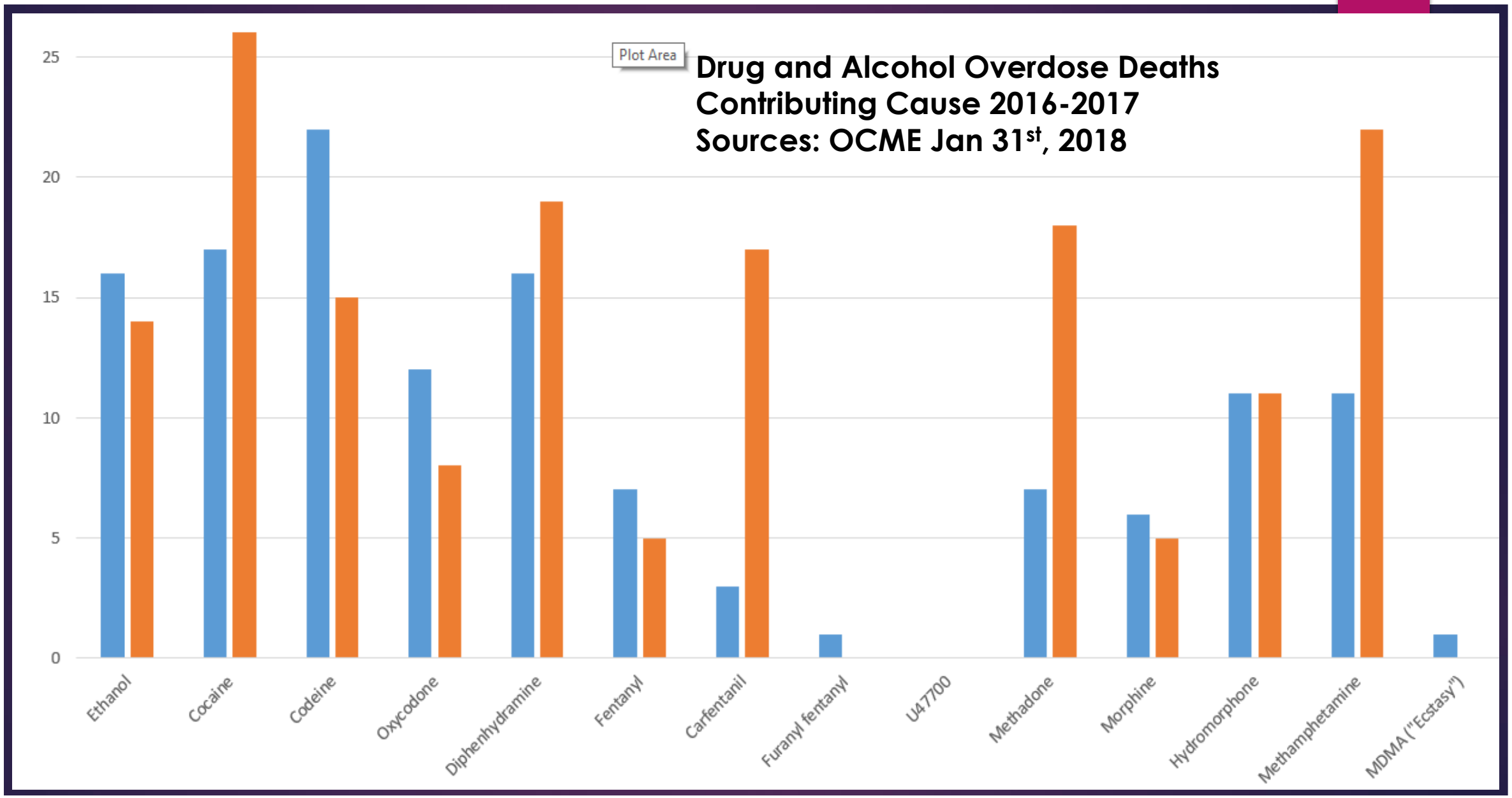
Illicit fentanyl and prescribed opioids -What's the connection?

- Jan 1st - April 4th, 2017: 20 deaths with positive screens for fentanyl analogs
- 75% positive for carfentanyl (15), Furanyl Fentanyl (2), U47700 (3), 2 unknown
- 60% of individuals who died during this period had a recent opioid prescription on DPIN
- Frequently negative toxicology for prescribed opioid in illicit opioid deaths

Drug and Alcohol Overdose Deaths (primary or contributing cause) 2013-2015 source: OCME Nov 3, 2016




Drug and Alcohol Overdose Deaths
Primary Cause 2016-2017
Sources: OCME Jan 31st, 2018
Plot Area
14
12
10
8
6
4
2
0
Ethanol
Cocaine
Codeine
Oxycodone
Diphenhydramine
Fentanyl
Carfentanil
Furanyl fentanyl
U47700
Methadone
Morphine
Hydromorphone
Methamphetamine
MDMA ("Ecstasy")


Plot Area
Drug and Alcohol Overdose Deaths
Contributing Cause 2016-2017
Sources: OCME Jan 31st, 2018
25
20
15
10
5
0
Ethanol
Cocaine
Codeine
Oxycodone
Diphenhydramine
Fentanyl
Carfentanil
Furanyl fentanyl
U47700
Methadone
Morphine
Hydromorphone
Methamphetamine
MDMA ("Ecstasy")

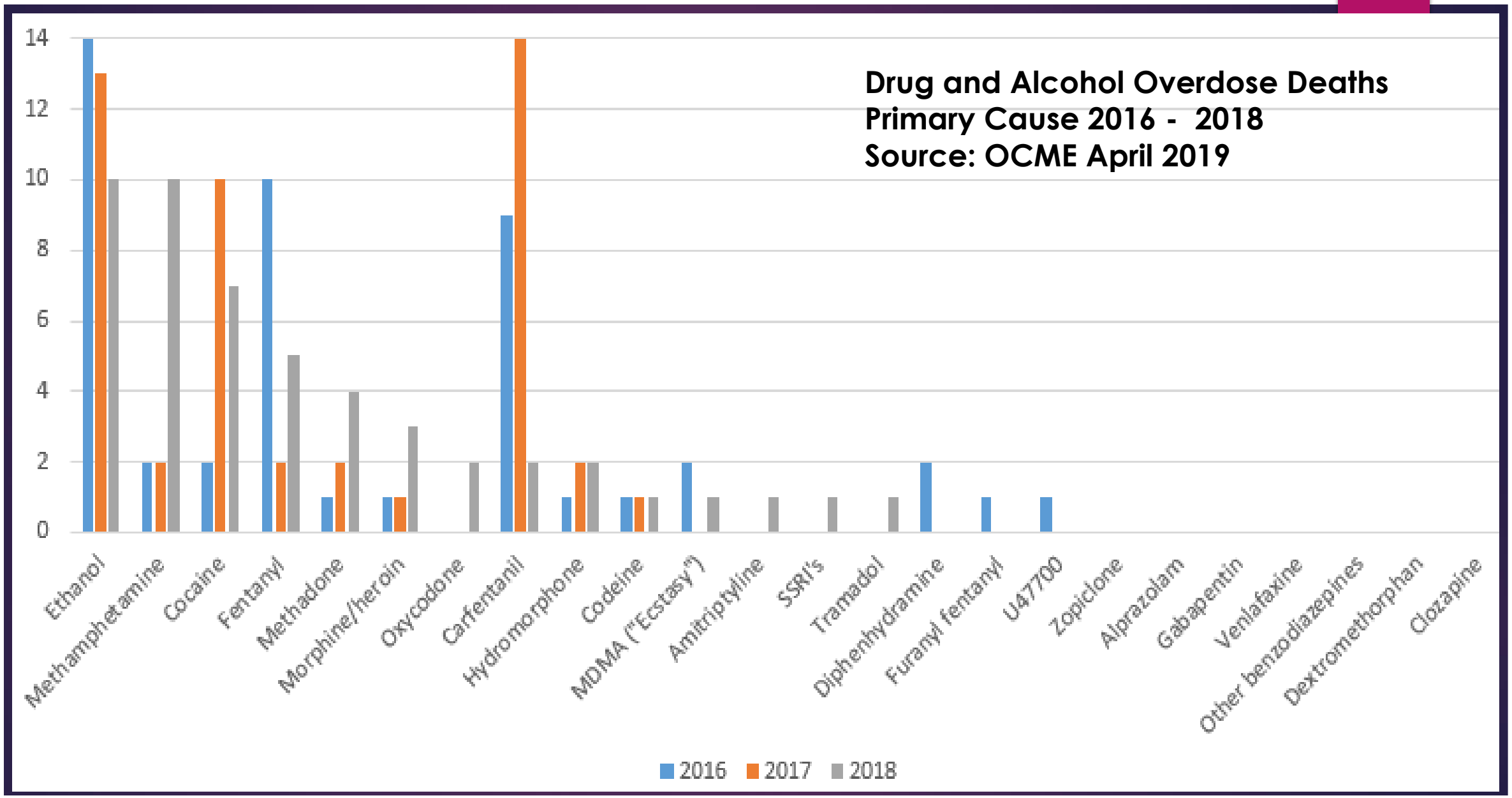
Effective February 1, 2016,
ALL CODEINE PRODUCTS
will require a prescription

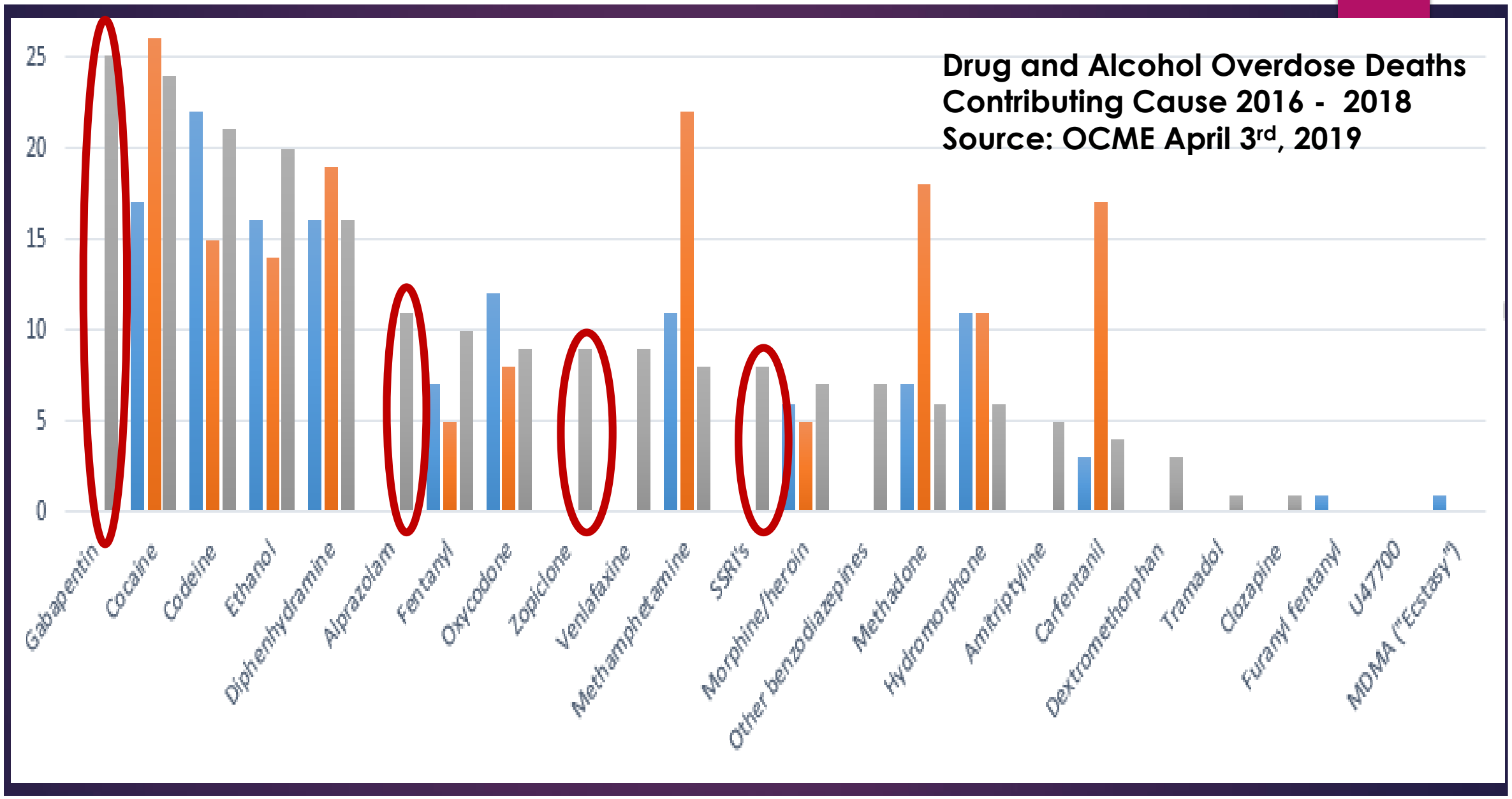
Ask your pharmacist
or another healthcare prescriber
about a prescription for
EXEMPTED CODEINE PRODUCTS...
It's all about your safety!

Patient safety is our priority

COLLEGE OF PHARMACISTS OF MANITOBA

LEARN MORE at www.cphm.ca


Drug and Alcohol Overdose Deaths
Primary Cause 2016 - 2018
Source: OCME April 2019
14
12
10
8
6
4
2
0
Ethanol
Methamphetamine
Cocaine
Fentanyl
Methadone
Morphine/heroin
Oxycodone
Carfentanil
Hydromorphone
Codeine
MDMA ("Ecstasy")
Amitriptyline
SSRI's
Tramadol
Diphenhydramine
Furanyl fentanyl
U47700
Zopiclone
Alprazolam
Gabapentin
Venlafaxine
Other benzodiazepines
Dextromethorphan
Clozapine
2016
2017
2018


Drug and Alcohol Overdose Deaths
Contributing Cause 2016 - 2018
Source: OCME April 3rd, 2019
25
20
15
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5
0
Gabapentin
Cocaine
Codeine
Ethanol
Diphenhydramine
Alprazolam
Fentanyl
Oxycodone
Zopiclone
Venlafaxine
Methamphetamine
SSRI's
Morphine/heroin
Other benzodiazepines
Methadone
Hydromorphone
Amitriptyline
Carfentanil
Dextromethorphan
Tramadol
Clozapine
Furanyl fentanyl
U47700
MDMA ("Ecstasy")

Important changes in 2018

- Opioid deaths have leveled off.
- **Stimulant-related deaths are climbing rapidly. Alprazolam** and **gabapentin**, as well as **diphenhydramine**, have become significant drugs of abuse.

- Note that more than one drug is often involved in a given death where a drug is given as a "contributing" cause.
- Overall, **138 drug-related deaths have been tabulated for 2018** so far. This does not include deaths where drug intoxication led to death by other means (MVAs, suicides, homicides, etc.), or where death occurred due to the effects of chronic drug use (cirrhosis, etc.).

CPSM CME Program Statistics

	16/17	17/18	18/19 to Date
Total Deaths From Overdose	73	128	47 (48 pending)
Prescribing Deemed Appropriate	34	30	43
Prescribing Fall Outside Guidelines	79	95	27
Referred to Other Colleges	0	3	0

- *Numbers don't add up because in some cases letters to multiple physicians were generated from the same death

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What can we learn from local CME data?

Three themes:

Largest category: Deaths involving sedating polypharmacy where all prescriptions were written by a single physician.

- Drug interactions
- Additive ADVERSE EFFECTS
- Often mimics symptoms of the condition being treated
- Memory impairment, falls, confusion, sedation and additive respiratory depression
- Often leads to high doses increases risk of DM, metabolic syndrome, cognitive impairment

- Incomplete tapers or switches
- Poor adherence (looks like partial response)
- No Longer clinically relevant
- No evidence that combining agents from same class increases efficacy (**benzodiazepines** hypnotics, SSRI's)
- Simplifying therapy without clinical deterioration is possible with medical supervision

An APPROACH to polypharmacy

- Set the stage
- Get a detailed history of every drug
- Reformulate list of active problems (acute or in remission)
- Discontinue what is not indicated, not being taken, diverted, or reduced dose if appropriate
- Taper what can't be discontinued abruptly

An APPROACH to polypharmacy

- One at a time (if feasible)
- More frequent visits; increased supports; frequent safety messaging; enlist loved ones
- Be patient but persistent
- **Listen to and actively collaborate with community/hospital pharmacist!**

The evidence: Opioids and benzodiazepines

Benzodiazepines increase opioid toxicity and risk of overdose.

- The **serum concentration of opioids is lower in mixed overdoses** than in pure overdoses, suggesting that other drugs significantly lower the lethal opioid dose (Cone 2004).

- Most **opioid overdoses involve multiple drugs in addition to opioids.** Overall, the top two other substances contributing to deaths between 2014 and 2017 were **benzodiazepines** and antidepressants.

Government of Manitoba, Manitoba Health, Seniors and Active Living, Epidemiology and Surveillance. (2018). Surveillance of Opioid Misuse and Overdose in Manitoba: October 1 – December 31, 2017.

The evidence: Opioids and benzodiazepines

There is evidence that benzodiazepines can be successfully tapered in a primary-care setting, with improved health outcomes.

- Several controlled trials have demonstrated that benzodiazepine tapering can be done in a primary-care setting.

- R06 For patients taking benzodiazepines, particularly for elderly patients, consider a trial of tapering (Grade B). If a trial of tapering is not indicated or is unsuccessful, opioids should be titrated more slowly and at lower doses. (Grade C).

Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, NOUGG, April 3rd, 2010

The evidence: benzodiazepines

- **Multiple benzodiazepines** prescribed concurrently is a **major concern** in the context of prescribing safety.
- **High doses** (single or combined benzo's) compounds the risks
- **No evidence** that combining these agents increases efficacy
- ? Are you attempting to treat insomnia, anxiety/panic with different agents…They have common causes
- **Increased** confusion, falls, MVA, episodic memory impairment and abuse/addiction

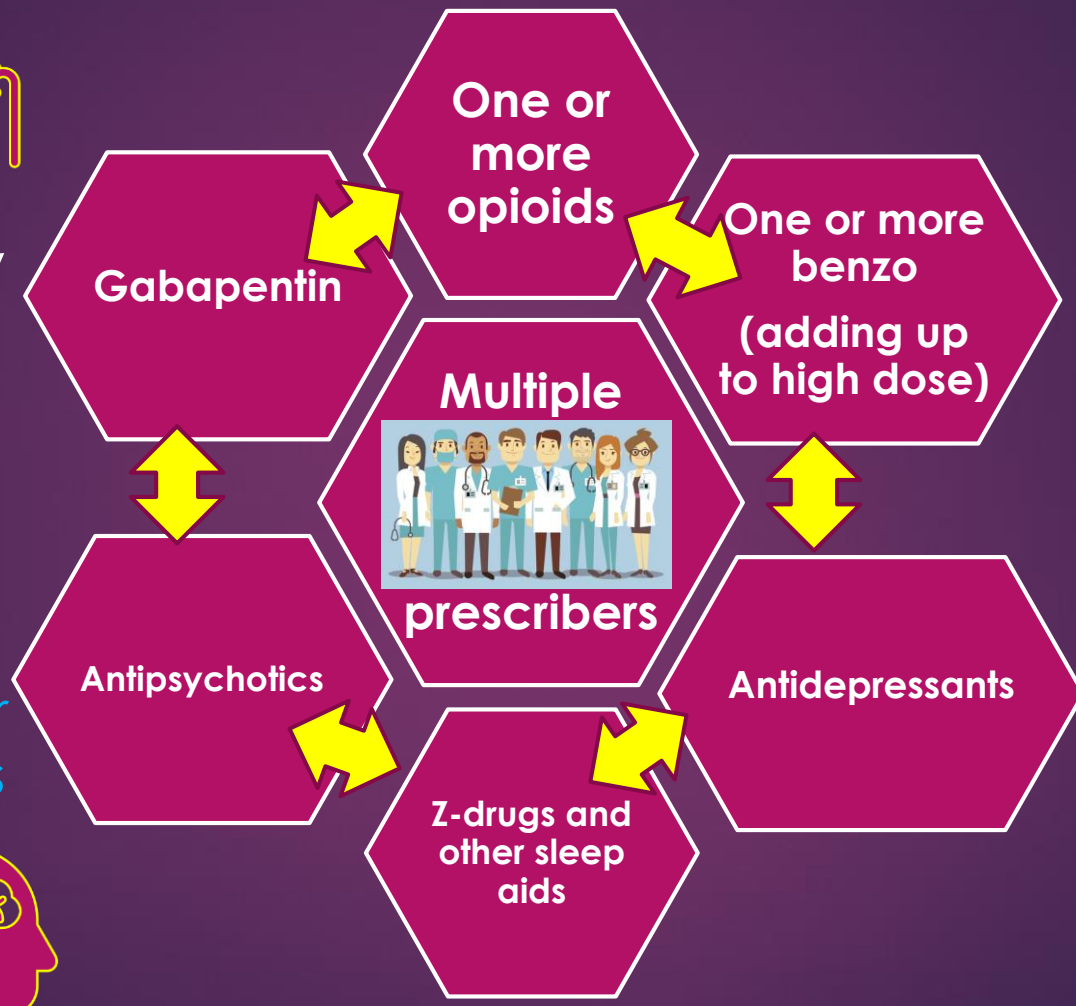
Key message

- Keep the overall picture in mind: The overall risk may outweigh the benefit from individual medications

What can we learn?

Deaths involving multiple sedating medications (often including an opioid and more than one benzodiazepine at a time) prescribed to the same patient by different physicians; filled at multiple different pharmacies.

- Frequently prescribers not aware of Rx history or each other?
- Increases risk of adverse events even further…
- CPSM Standard for prescribing opioids requires DPIN review



- Cross-over or consultative collaborative care?
- Who takes the lead on different aspects of care?
- DPIN not universally available
- e-Chart
- Collaboration with community pharmacist key!

Key messages

- All prescribers are encouraged to utilize DPIN or e-Chart (ungrouped) to improve patient safety.
- Clear treatment agreement and one primary responsible physician for monitored drugs may be helpful
- Listen to and actively collaborate with community/hospital pharmacist!

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What can we learn?

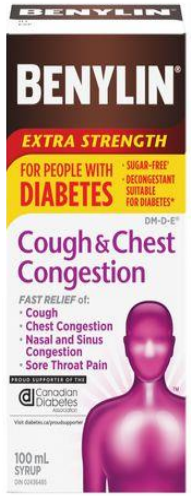
- OTC medications used in combined with prescribed medications can significantly contribute to overdose risk.
- Pharmacists can provide valuable collateral information – listen to and actively collaborate with community pharmacist!

Deadly OTC's in 2018

- **Diphenhydramine (contributed to 16 deaths in 2018)**
- **It is a first generation H_1-antihistamine and an anticholinergic**
- **Because of its sedative and anxiolytic properties, diphenhydramine is widely used in non-prescription sleep aids for insomnia.**
- **Diphenhydramine i**s the primary constituent of **dimenhydrinate** and dictates the primary effect. The main difference relative to pure diphenhydramine is a lower potency due to being combined with 8-chlorotheophylline

Others to watch…

- Dextromethorphan (contributed to 3 deaths in 2018)
- Dextromethorphan acts as a dissociative anesthetic in doses exceeding recommended ranges.
- DXM and its major metabolite, dextrorphan, also act as an NMDA receptor antagonist at high doses, which produces effects similar to, yet distinct from, the dissociative states created by other dissociative anesthetics such as ketamine and phencyclidine.



Increase screening!!!

- Ask your patient in a non-judgemental way!!
- Pay attention to collateral - "family" and pharmacists!!
- Educate!!
- Urine drug testing (UDT) may be useful **if concerning report, appearance, function or collateral information.**

  Comprehensive UDT preferred
- **Policy?? More risky meds behind the counter or a Rx??**

Types of Urine Drug Testing (UDT)

- **Point-of-care Testing**

For point-of-care (POC) testing: urine sample collected and test interpreted at the physician's office/clinic. POC test kits are available for purchase; Cups or dips; Results are immediate, but it tends to be less sensitive and specific than laboratory tests.

- **Laboratory Testing**

For laboratory testing: urine sample collected at physician's office/clinic and sent to a laboratory for testing.

Two types of laboratory tests: **immunoassay** and **chromatography**

Provincial health plans pays for immunoassays for **classes of drugs** (opioids, cocaine, benzodiazepines, cannabis), but **does not distinguish between different types of opioids** and often misses semi-synthetic or synthetic opioids such as oxycodone or meperidine.

Chromatography is more expensive and **requires specification of the drug(s) to be identified** e.g., oxycodone, morphine, codeine, hydromorphone (alternatively can indicate: "full screen" or "broad spectrum screen").

Key messages

- Smaller dispensed quantities
- Consider past hx of substance/medication abuse
- Ask re OTC meds and screen utilizing comprehensive UDS's if concerning appearance, function or collateral reports
- Listen to and actively collaborate with community pharmacist!

References

I wish to recognize the following excellent sources:

- Government of Manitoba, Manitoba Health, Seniors and Active Living, Epidemiology and Surveillance. (2018). Surveillance of Opioid Misuse and Overdose in Manitoba: October 1 – December 31, 2017.
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THANK YOU