

# 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 local, provincial death data should transform primary care prescribing practices.
- Investigate the role that polypharmacy plays in contribution to morbidity and mortality associated with poor prescribing practices.
- Recognized 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



# SLIDO QUESTIONS:

## DPIN:

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# 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 (Suboxone) deaths

# Chief Medical Examiners' Death Review

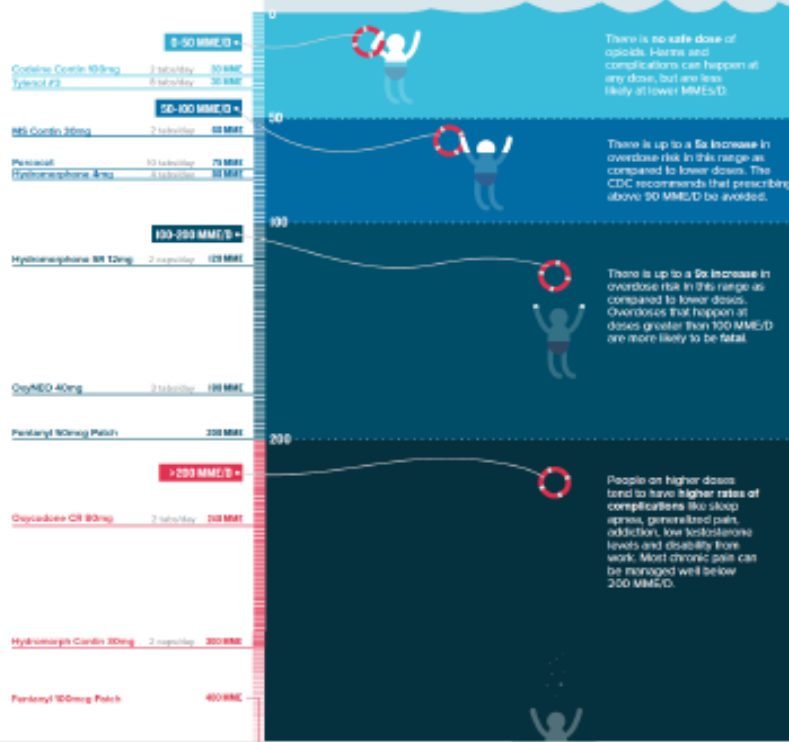
- ▶ Prescribers receive standard cover letter
- ▶ Plus summary of the ME report highlighting the manner of death, cause of death, notable circumstances of death, toxicology findings and summary of relevant DPIN data
- ▶ Feedback to prescribers in 3 categories:
  - FYI
  - Rx'bing falls outside of guidelines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



# NAVIGATING OPIOIDS FOR CHRONIC PAIN

Sometimes the best of intentions lead to devastating consequences. Canada and the U.S. are the two highest consumers of prescription opioids even though we don't have good evidence that they are effective for chronic pain. Since there are many different opioids used for the same purpose, we use **morphine equivalence** to compare how strong they are.

**AS THE NUMBER OF MORPHINE MILLIGRAM EQUIVALENTS PER DAY (MME/D) INCREASES, THE HARMS ASSOCIATED WITH OPIOID THERAPY ALSO INCREASE.**



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		% Var. # Unique Patients from Prev. Year	Q4 2016: Oct. 1 2016 to Dec. 31 2016	
	# Unique Patients	Proportion of Unique Patients		# Unique Patients	Proportion of Unique Patients
0 to 50	4,203	45.2%	↑ 1.8%	4,128	44.5%
50 to 90	2,385	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	9.8%
	<b>9,292</b>	<b>100.0%</b>	<b>↓ (2.5%)</b>	<b>9,274</b>	<b>100.0%</b>

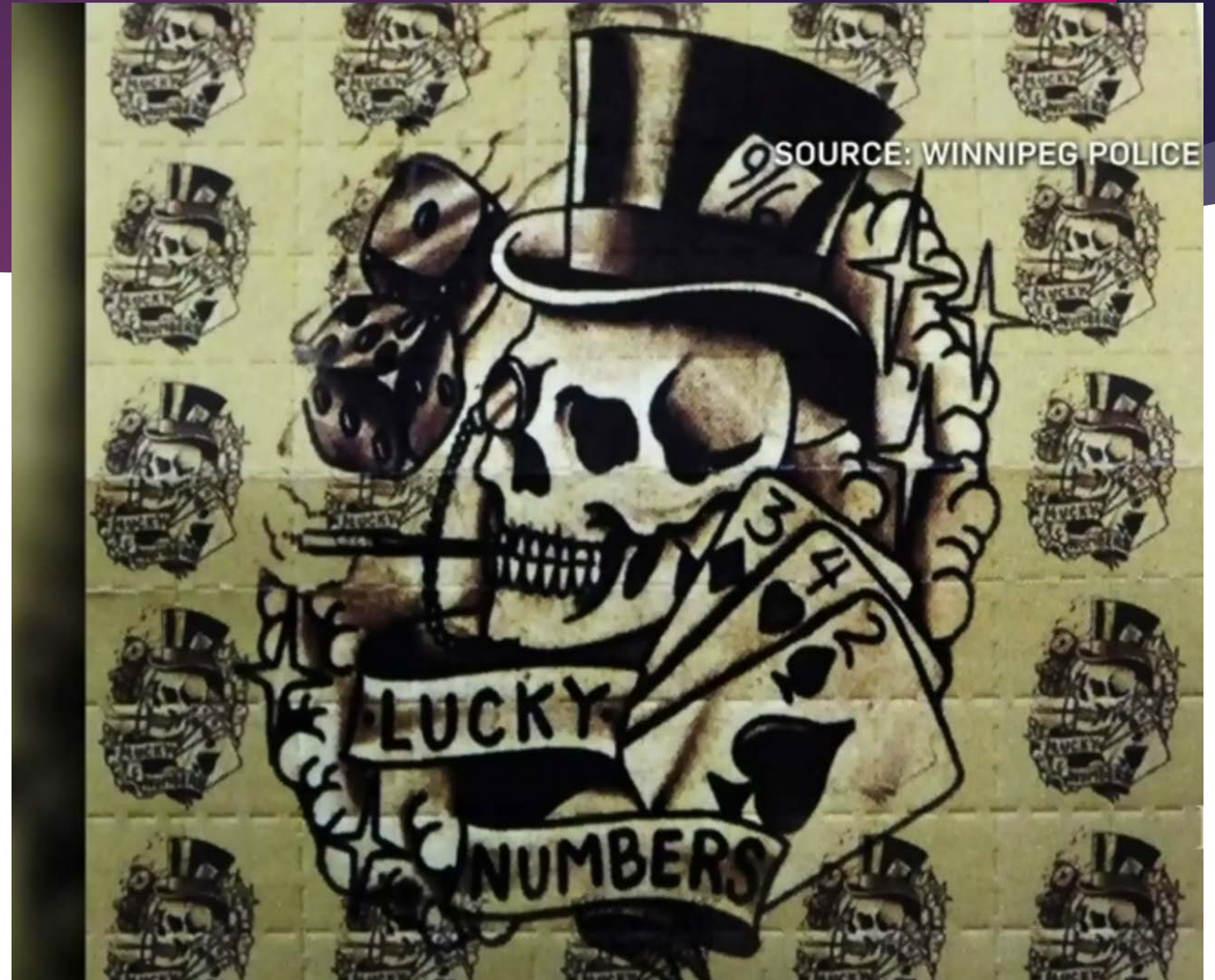
\*Data source is DPIN, excludes Long Term Care & Palliative Care clients; does not include drugs dispensed in hospital. Includes fentanyl.

\*\* 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

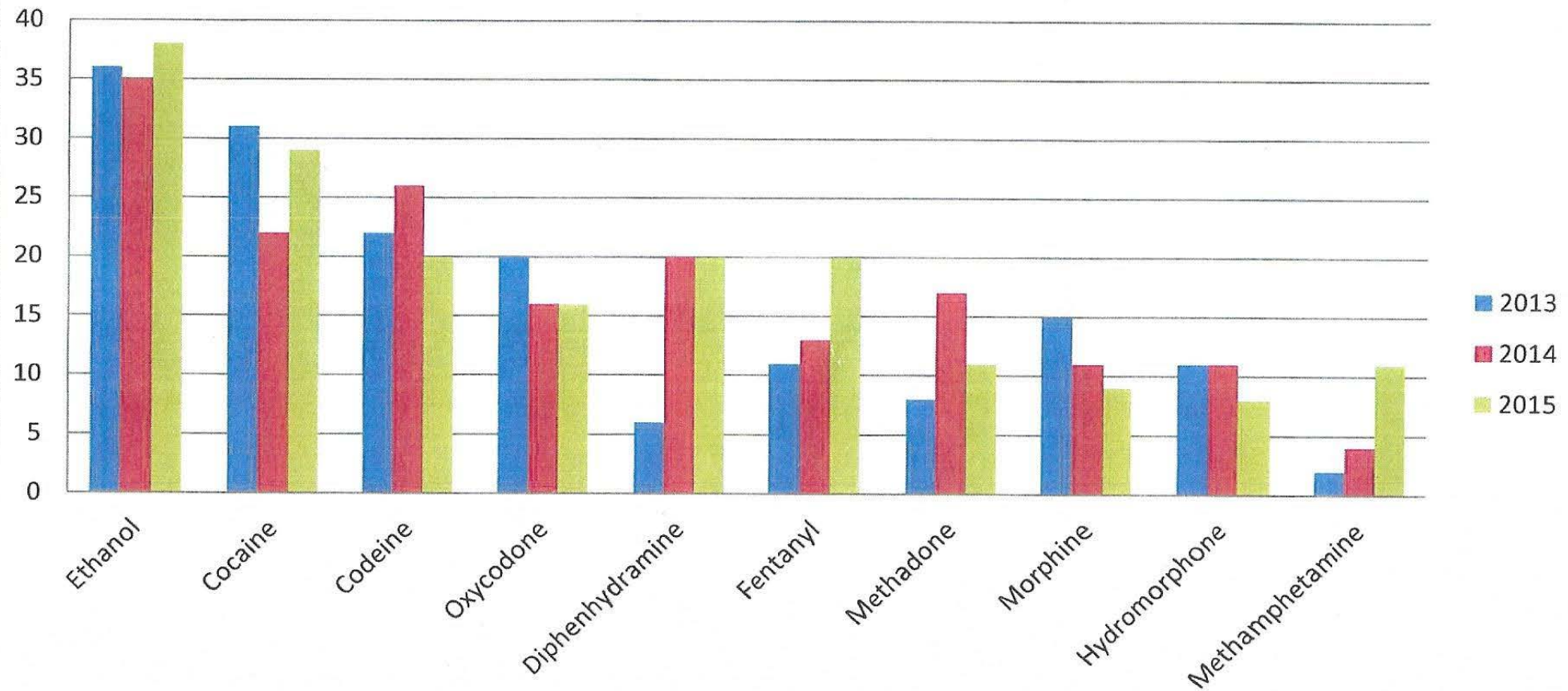
## -What's the connection?

- ❖ Jan 1<sup>st</sup> - April 4<sup>th</sup>, 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



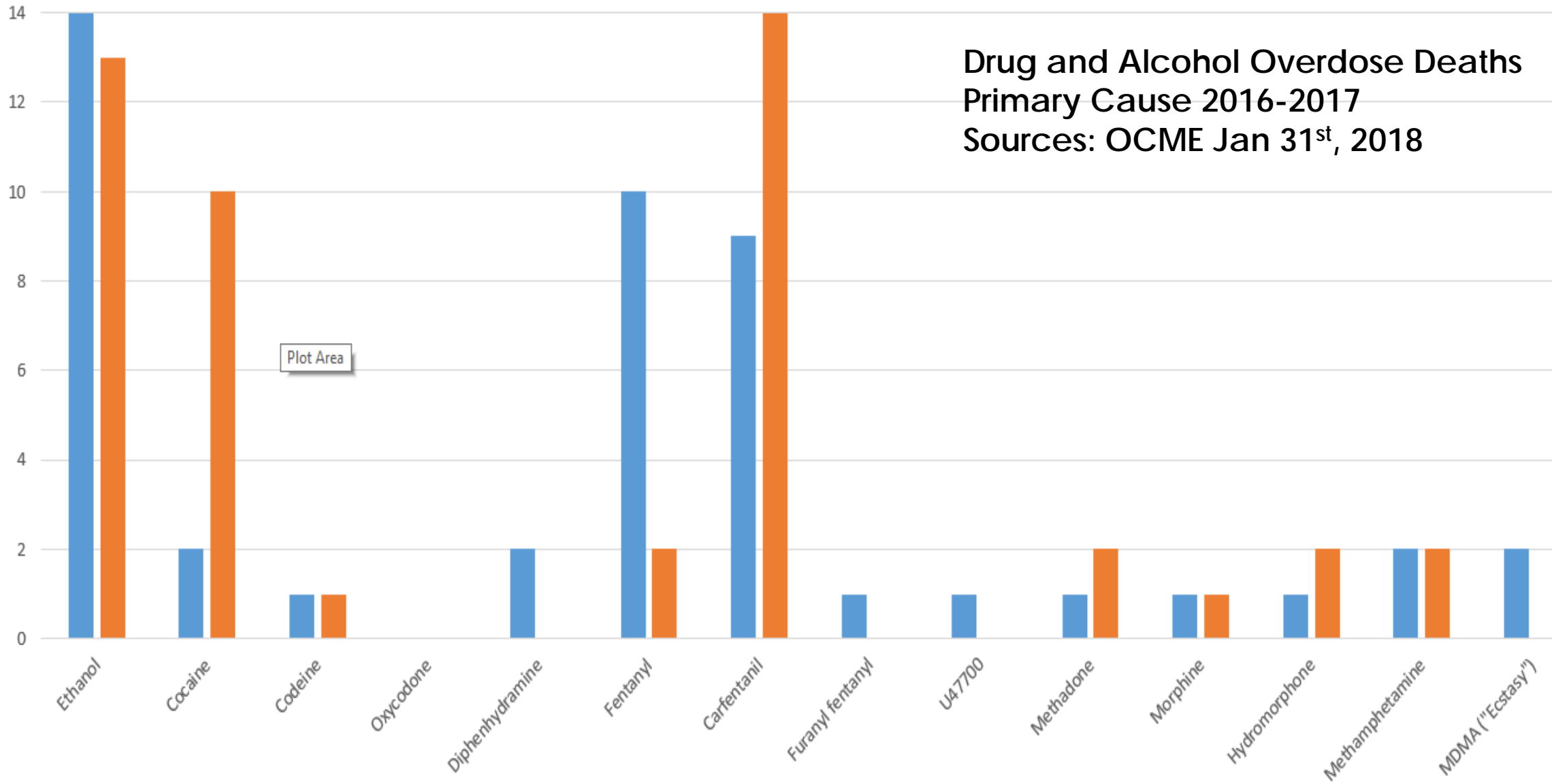
## Drug and Alcohol Overdose Deaths (primary or contributing cause) 2013-2015

source: OCME Nov 3, 2016



# Drug and Alcohol Overdose Deaths Primary Cause 2016-2017

Sources: OCME Jan 31<sup>st</sup>, 2018

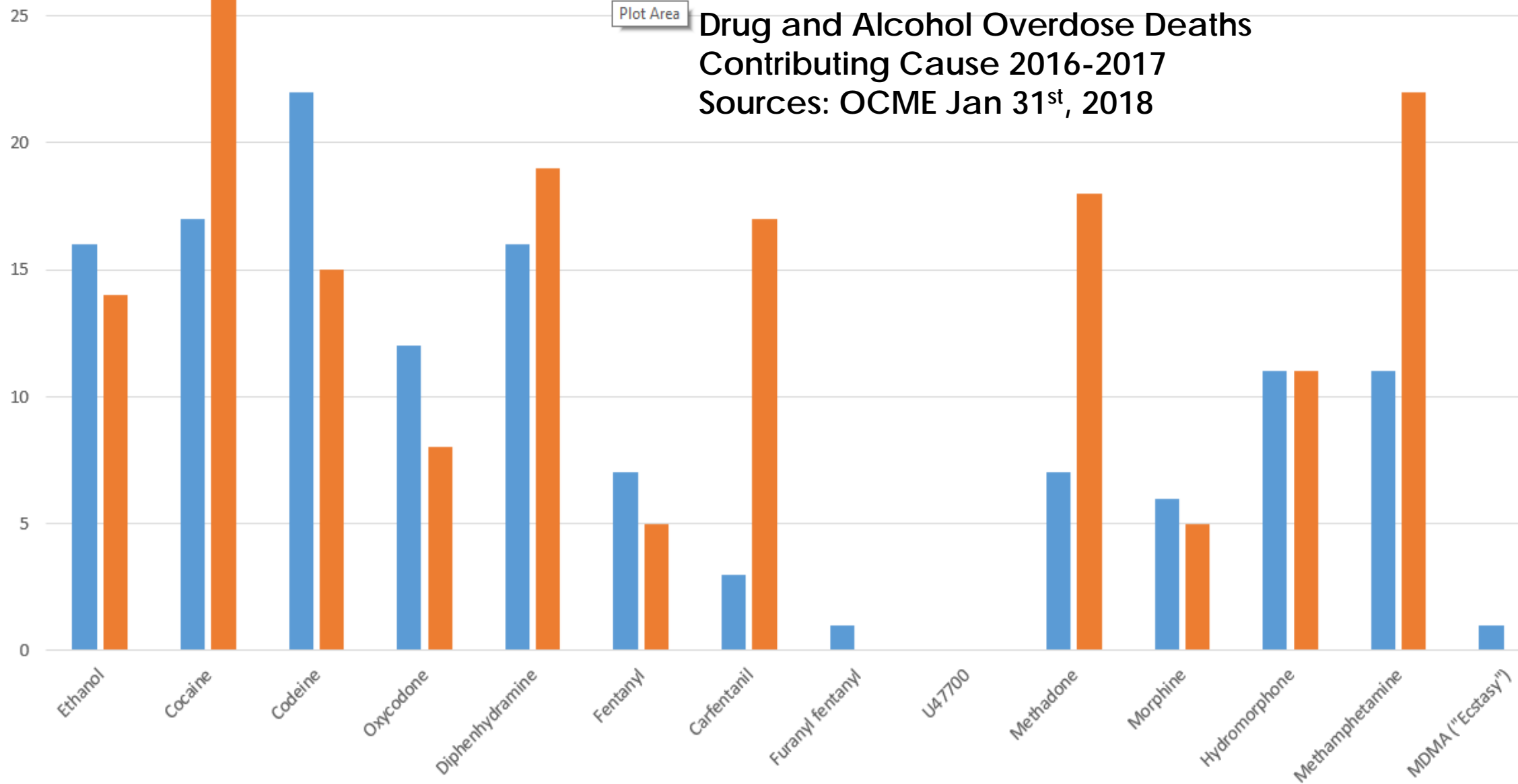




Plot Area

# Drug and Alcohol Overdose Deaths Contributing Cause 2016-2017

Sources: OCME Jan 31<sup>st</sup>, 2018



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!*

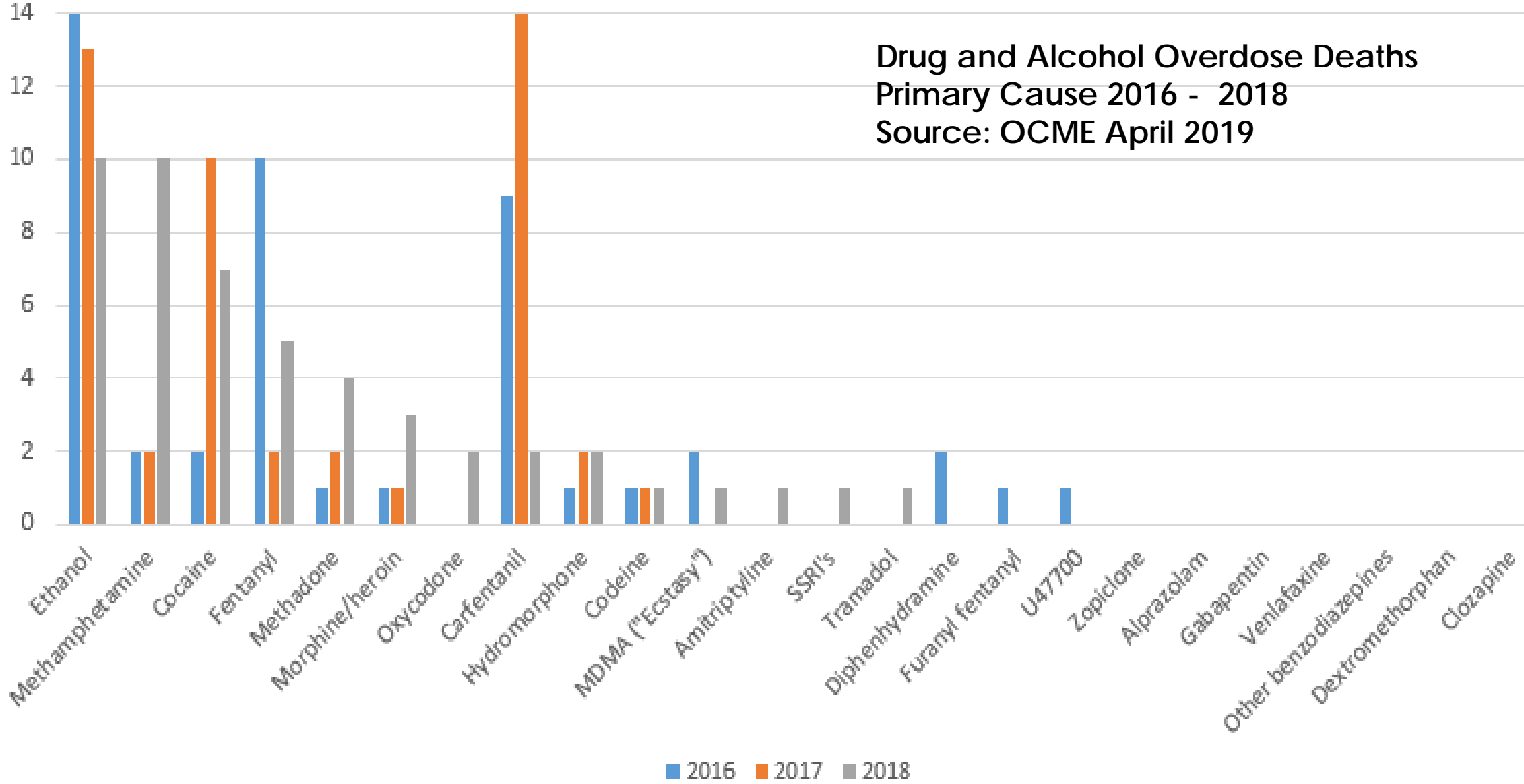
Patient safety is our priority



COLLEGE OF  
PHARMACISTS  
OF MANITOBA

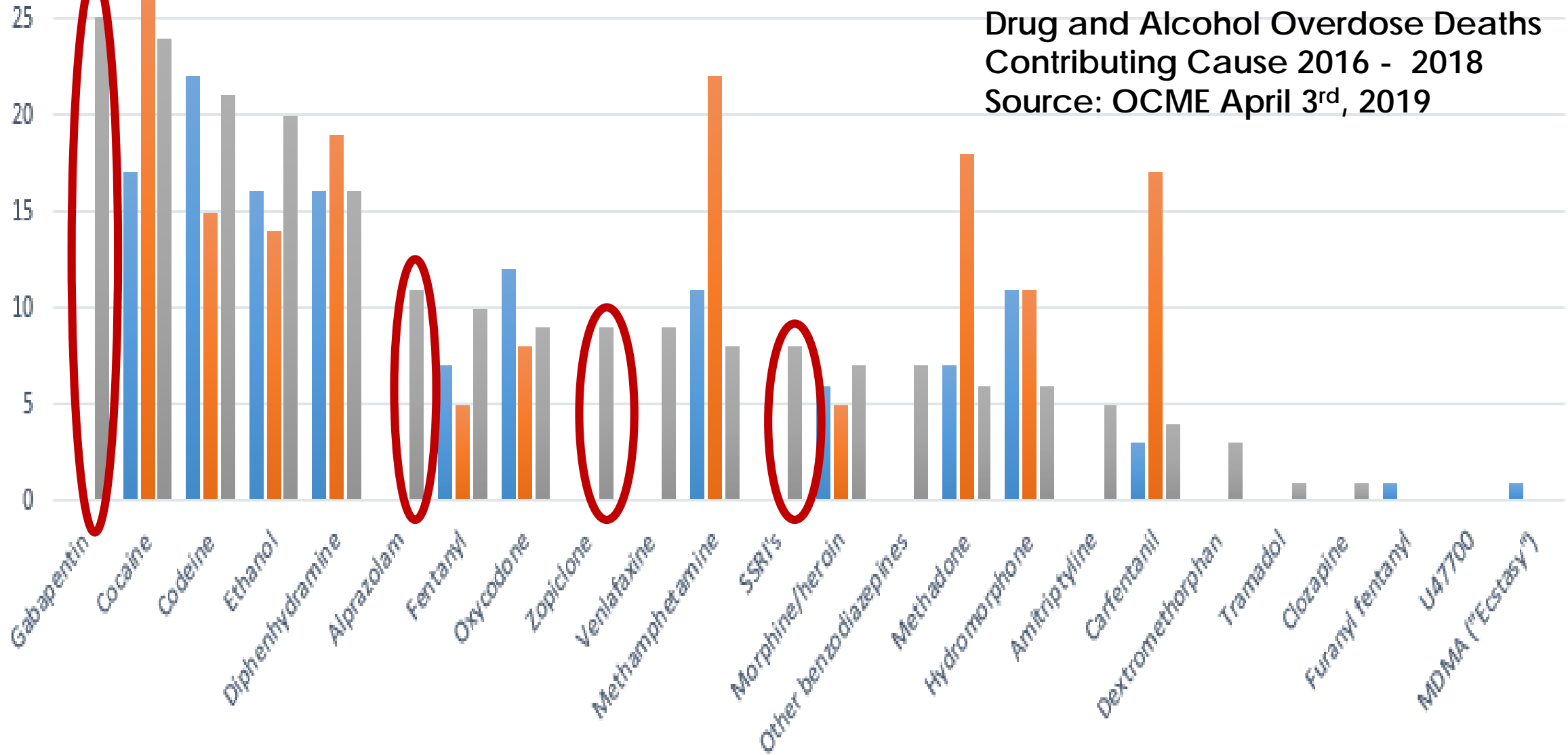
*LEARN MORE at [www.cphm.ca](http://www.cphm.ca)*

**Drug and Alcohol Overdose Deaths  
Primary Cause 2016 - 2018**  
Source: OCME April 2019



# Drug and Alcohol Overdose Deaths Contributing Cause 2016 - 2018

Source: OCME April 3<sup>rd</sup>, 2019





# 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.).

# CME Program Statistics

	<u>16/17</u>	<u>17/18</u>	<u>18/19</u> 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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→**The sleepier it gets - perhaps less is more!**

→Risk that increases over the counter.

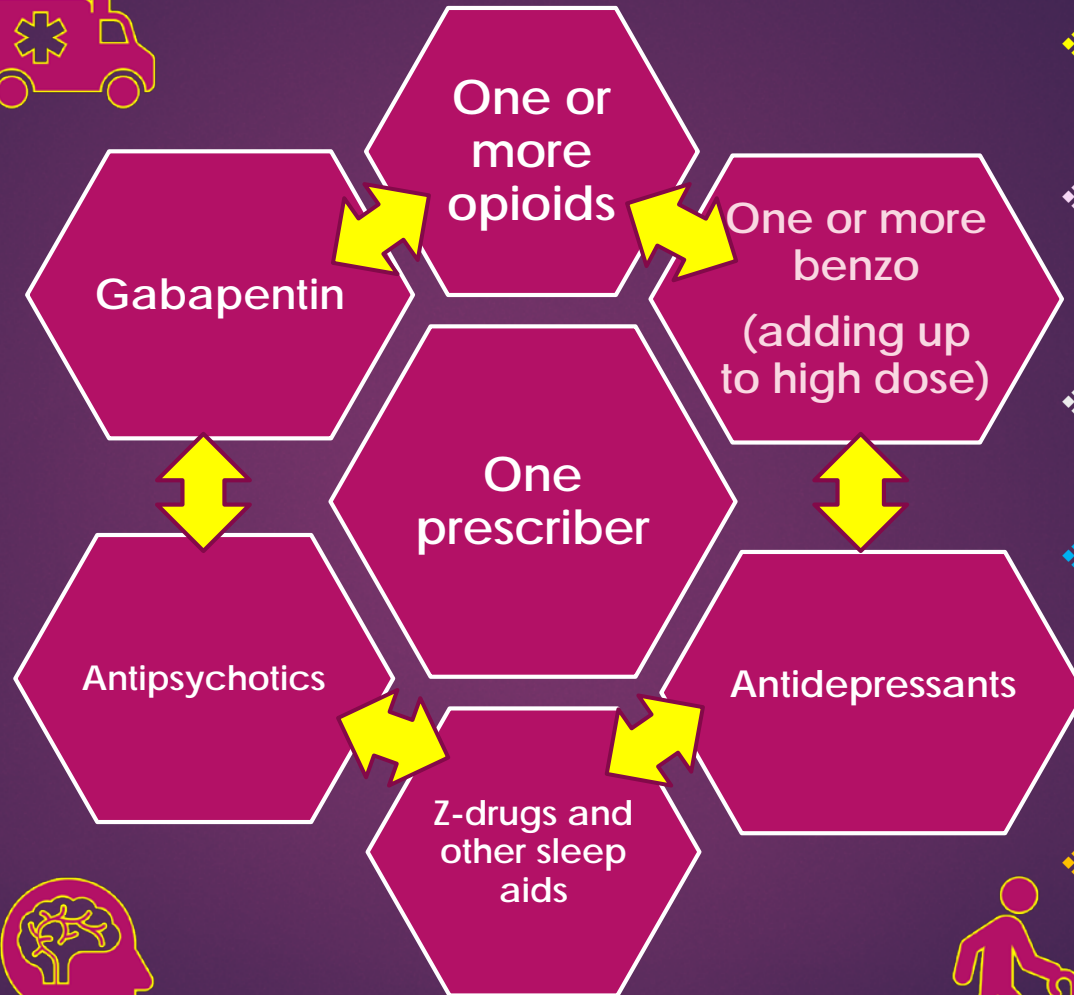
# What can we learn from local CME data?

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
- ▶ One at a time (if feasible)
- ▶ More frequent visits; increased supports; frequent safety messaging; enlist loved ones
- ▶ Be patient but persistent

# 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).



# 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?

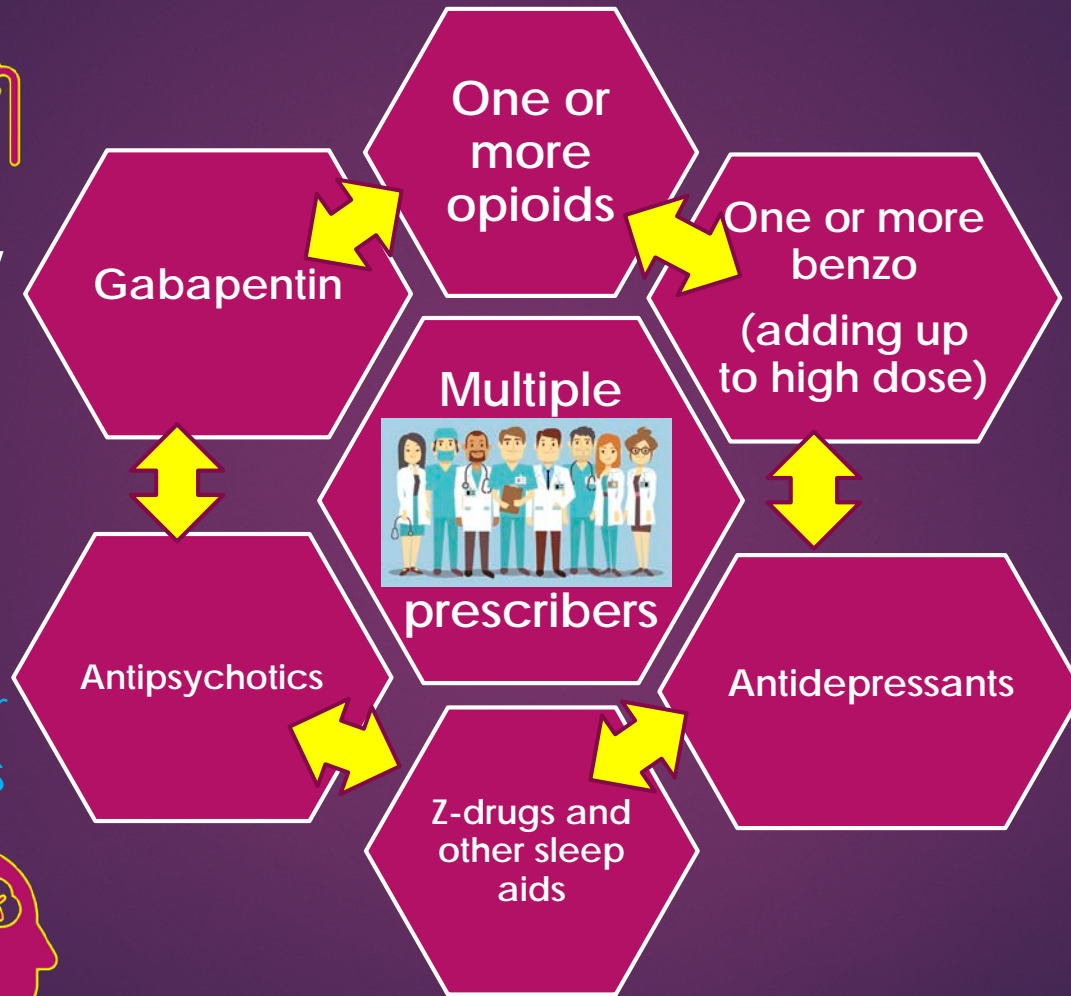
Deaths involving **multiple sedating medications** (often including an opioid and more than one benzodiazepine at a time) prescribed to the same patient by different physicians; filled at multiple different pharmacies.

❖ 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

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# What can we learn?

OTC medications used in combination with prescribed medications can significantly contribute to overdose risk.



# Deadly OTC in 2018

- ▶ Diphenhydramine (contributed to 16 deaths in 2018)
- ▶ It is a first generation H<sub>1</sub>-antihistamine and an anticholinergic
- ▶ Because of its sedative and anxiolytic properties, diphenhydramine is widely used in non-prescription sleep aids for insomnia.
- ▶ Diphenhydramine is 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!
- ▶ Educate!!
- ▶ Urine drug testing (UDT) may be useful **if concerning report, appearance, function or collateral information.**

**Comprehensive UDT preferred**

# 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



# 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.
- ▶ Chateau D, Enns M, Ekuma O, Koseva I, McDougall C, Kulbaba C, Allegro E. Evaluation of the Manitoba IMPROVE Program Winnipeg, MB. Manitoba Centre for Health Policy, January 2015.
- ▶ Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, NOUGG, April 3<sup>rd</sup>, 2010
- ▶ Clinical Guideline: Management of anxiety in adults. UK National Institute for Clinical Excellence. 2004;152. [http://www.nice.org.uk/pdf/CG02\\_2niceguideline.pdf](http://www.nice.org.uk/pdf/CG02_2niceguideline.pdf)
- ▶ Barbone F, McMahon AD, et al. Association of road-traffic accidents with benzodiazepine use. Lancet. 1998;352:1331-1336.

THANK YOU

