



*Opioid Agonist Therapy 101:
An Introduction to Clinical Practice Workshop*

**Polypharmacy and OTC medication use
in the context of opioid agonist therapy**

MARINA REINECKE MBCHB, CCFP (AM), ISAM

Disclosure of Commercial Support

- ▶ This program has received financial support from *The College of Physicians and Surgeons of Manitoba* in the form of *funding for payment of presenters and organizers*.
- ▶ This program has received in-kind support from *The College of Physicians and Surgeons of Manitoba* in the form of *logistical support*.
- ▶ Potential for conflict(s) of interest:
 - ▶ None identified

Faculty/Presenter Disclosure

- ▶ **Faculty:** Marina Reinecke
- ▶ **Relationships with commercial interests:** None

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 OAT prescribing and dispensing practices.
- Investigate the role that polypharmacy plays in morbidity and mortality in the context of poor prescribing practices.
- Recognize that certain combinations of prescription medications significantly increases overdose risk in OAT patients.
- Propose an approach to managing polypharmacy and concurrent over-the-counter medication use in OAT patients who are at risk for multidrug toxicity.

Glen

- ▶ Glen; 42 years old
- ▶ Working full time as a project manager for a construction company.
- ▶ History of hypertension, GERD, cigarette smoker and prescription drug abuse since his 20's. Non Drinker.
- ▶ Diagnosed with OUD and started on methadone 8 days ago.
- ▶ 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:
- Methadone 20mgs per day for 5 days, then 30mgs per day for 3 days; no missed doses; last dose taken day he died; all witnessed
- Alprazolam 0.5mg 90 tabs q 30 days; last filled on day 2 of methadone induction
- Gabapentin 600mgs 90 tabs last filled day 5 of methadone induction
- Citalopram 20mgs 30 tabs started 3 days prior to methadone induction
- Dimenhydrinate 50mgs 30 tabs; last filled 3 days prior to methadone start
- Mirtazapine 30mgs 30 tabs; last filled 3 days prior to methadone start
- Tylenol # 1 100 tabs at a time; multiple docs; last filled 20 days prior to methadone start
- Enalapril, HCTz, and omeprazole

ME's report:

- ▶ **COD:** Mixed drug toxicity
- ▶ **Manner of death:** Accidental
- ▶ **Toxicology:** all alcohols negative
 - codeine, diazepam, clonazepam, diphenhydramine, mirtazapine present; not quantifiable
 - alprazolam 279 ng/ml (therapeutic 22 - 55)
 - citalopram 468 ng/ml (therapeutic 20 - 200)
 - gabapentin 66 ug/ml (therapeutic 2 - 20)
 - methadone 608 ng/ml (therapeutic 100 - 400)
 - EDDP 233 ng/ml

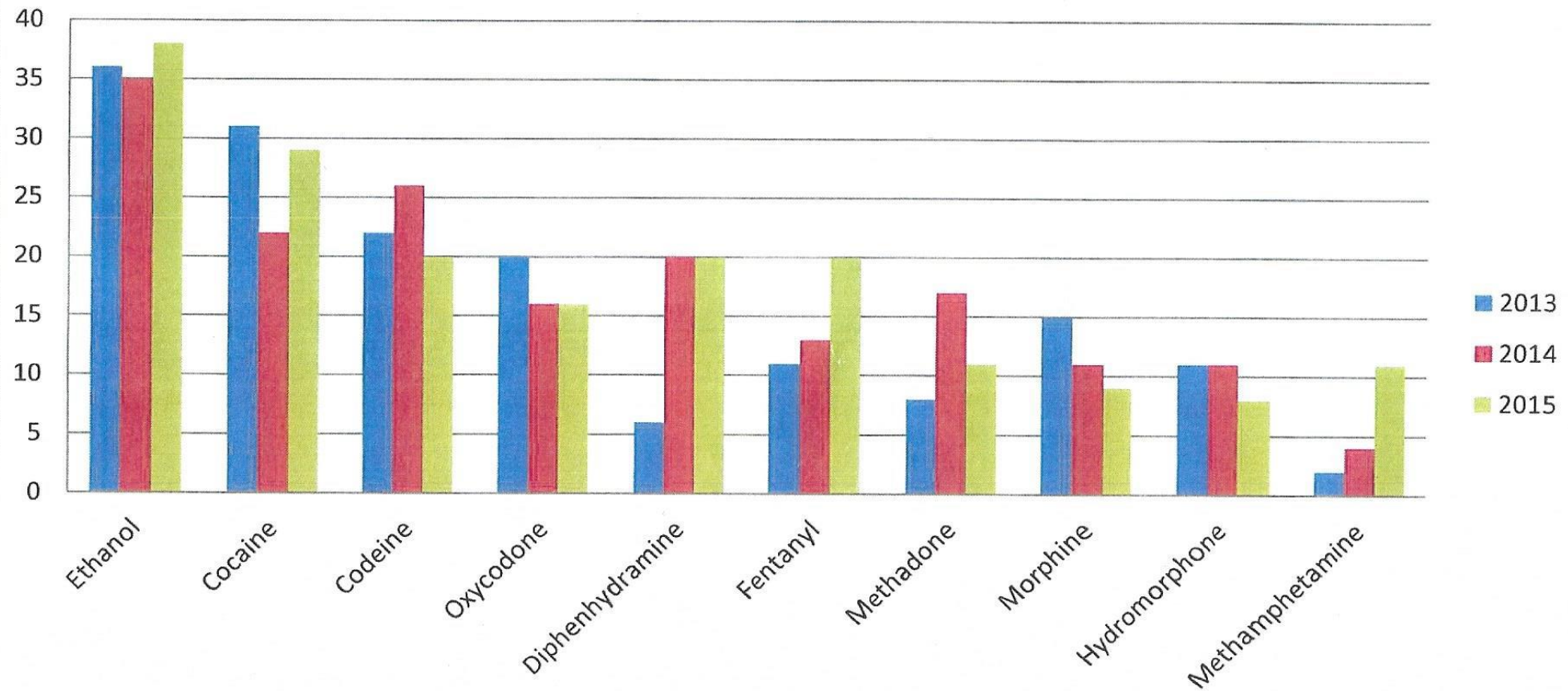
Chief Medical Examiners' Death Review

A component of the CPSM Prescribing Practices Program



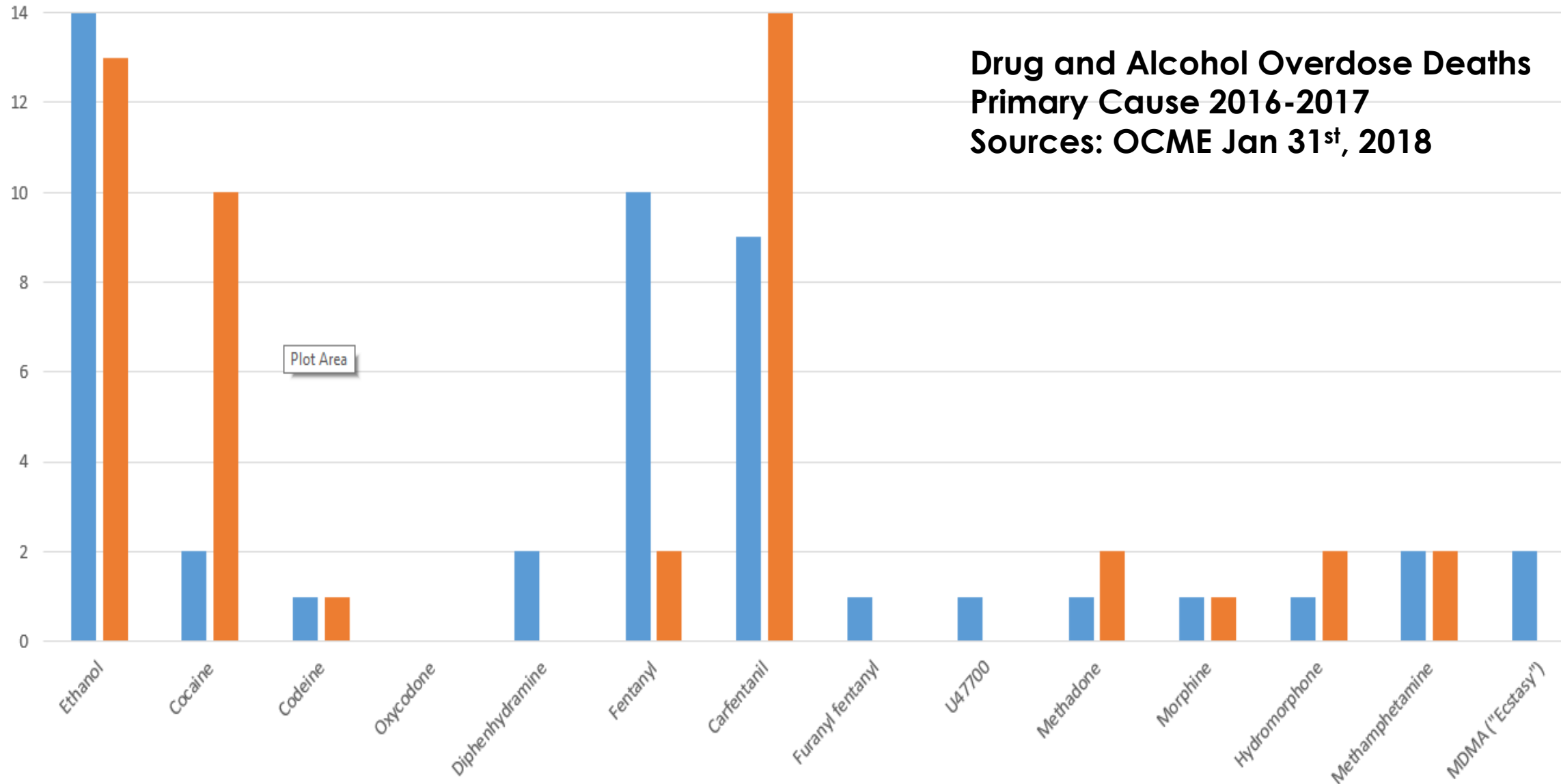
Drug and Alcohol Overdose Deaths (primary or contributing cause) 2013-2015

source: OCME Nov 3, 2016



Drug and Alcohol Overdose Deaths Primary Cause 2016-2017

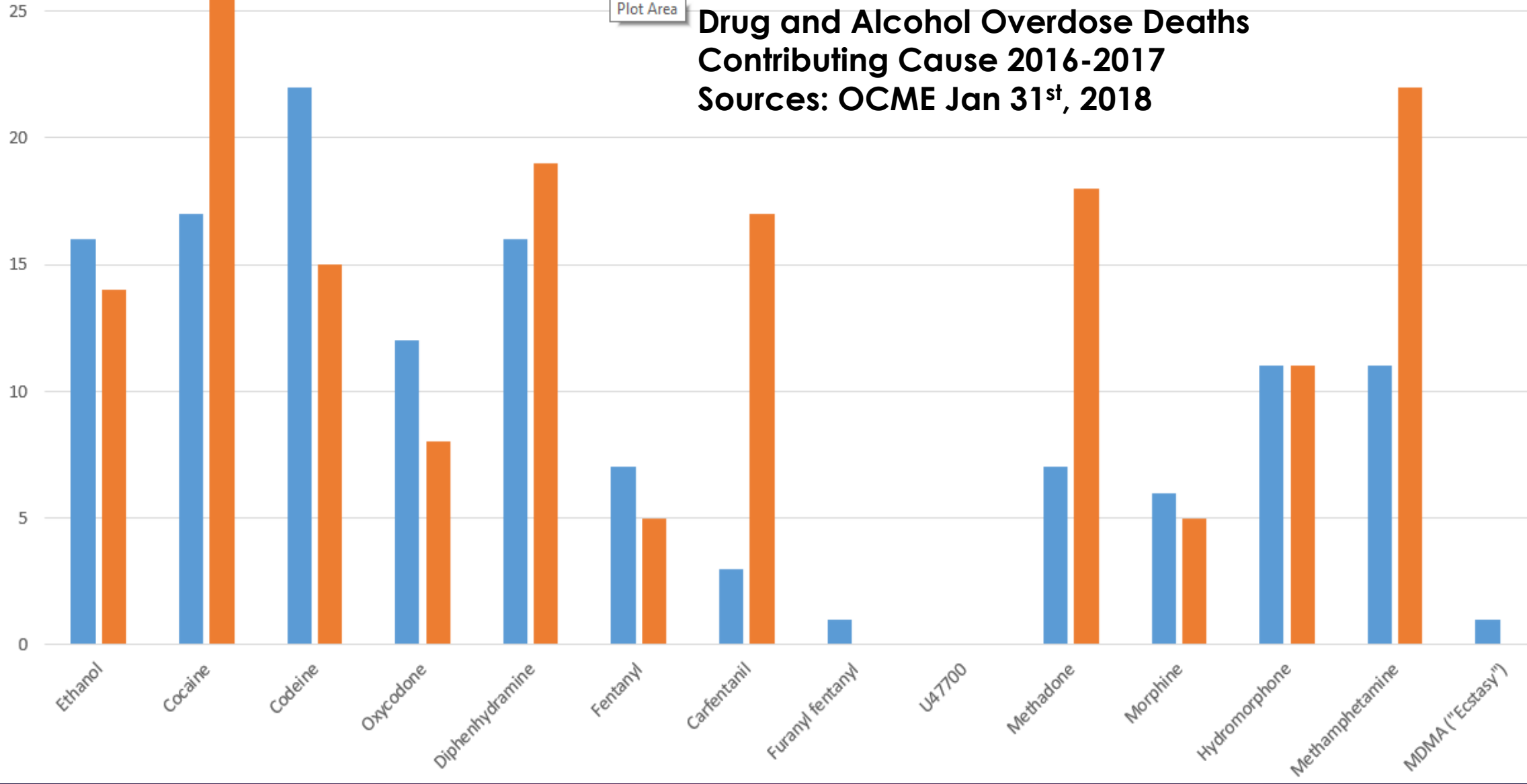
Sources: OCME Jan 31st, 2018



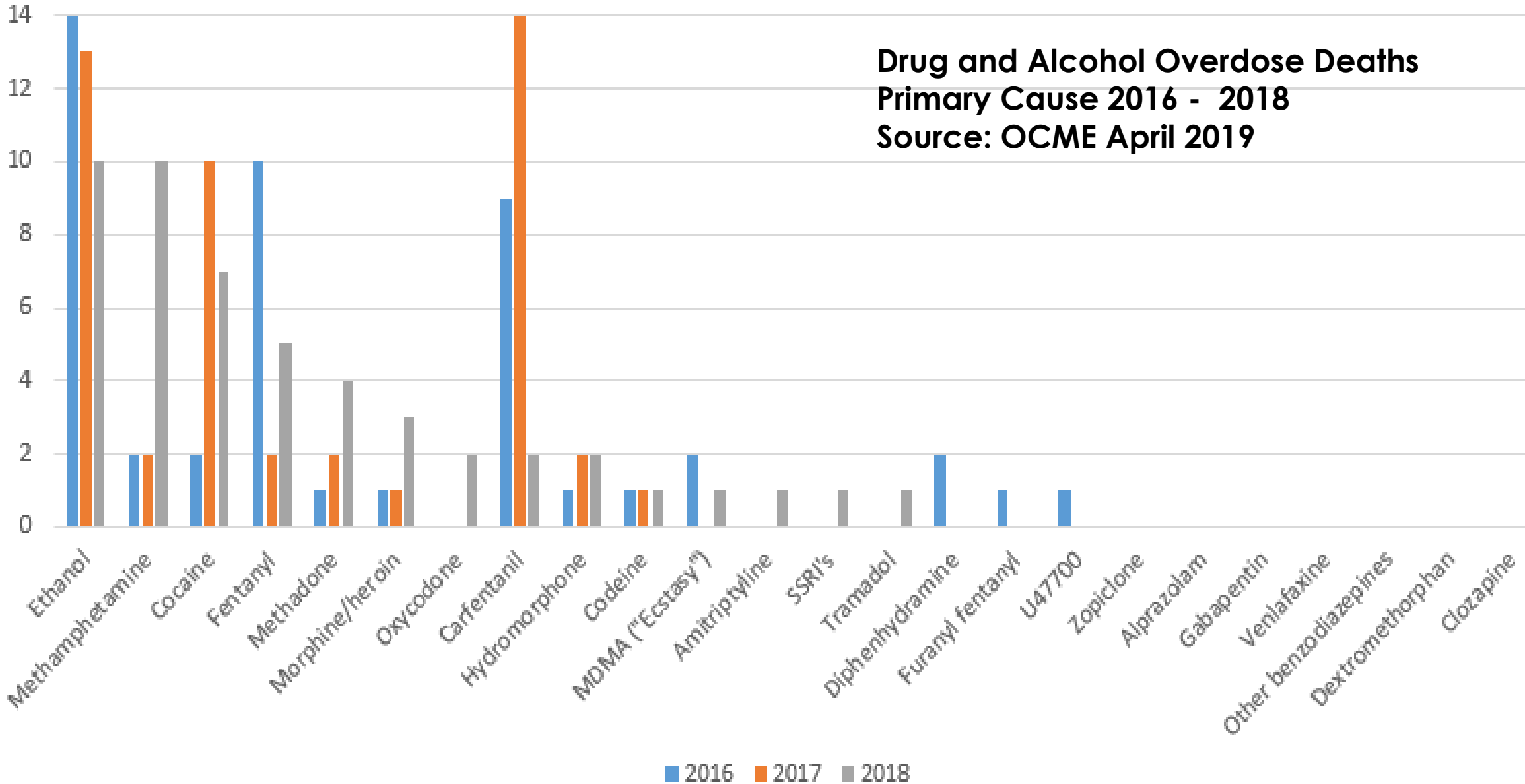
Drug and Alcohol Overdose Deaths Contributing Cause 2016-2017

Sources: OCME Jan 31st, 2018

Plot Area

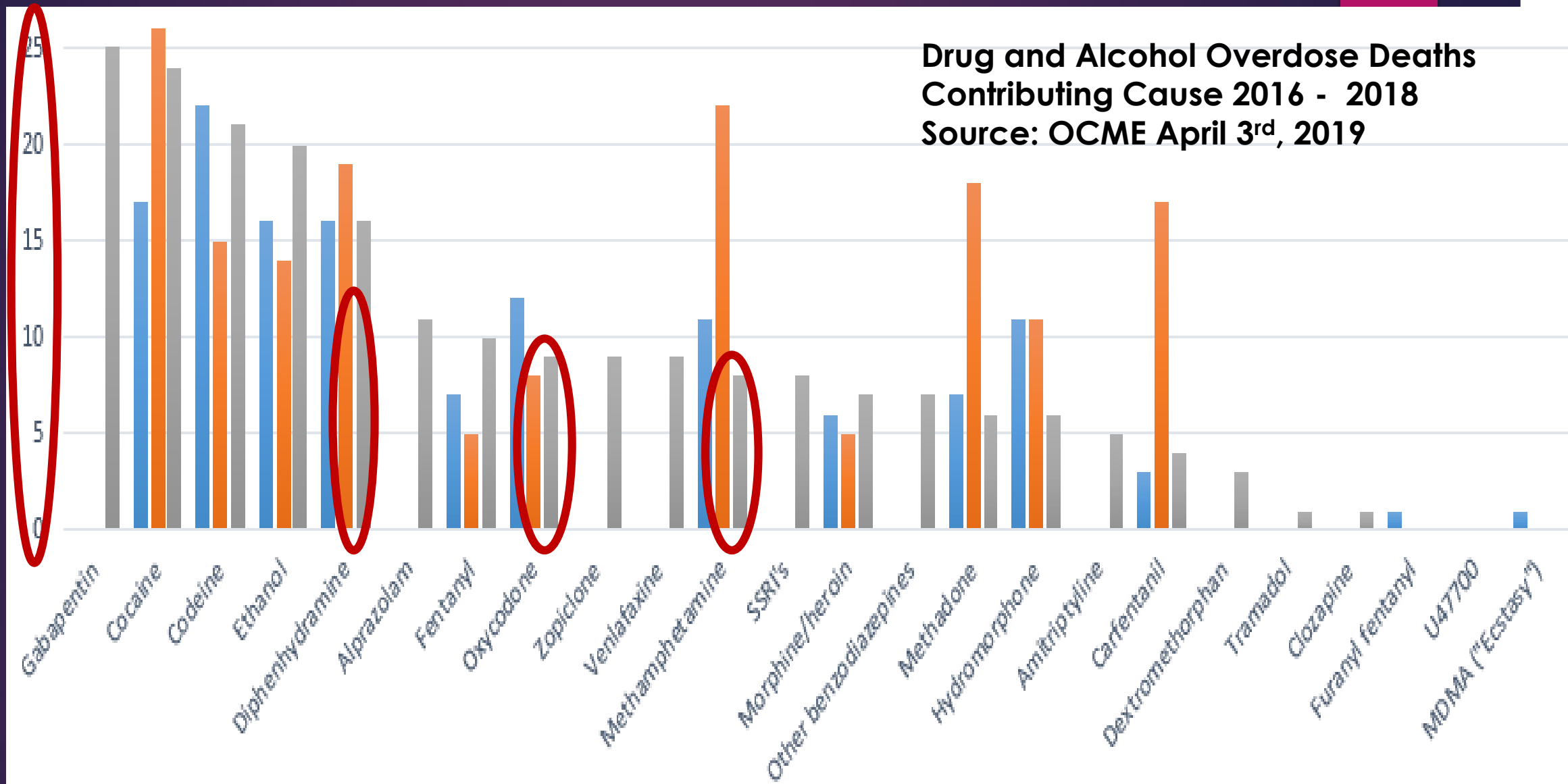


**Drug and Alcohol Overdose Deaths
Primary Cause 2016 - 2018**
Source: OCME April 2019



Drug and Alcohol Overdose Deaths Contributing Cause 2016 - 2018

Source: OCME April 3rd, 2019



Important changes in 2018

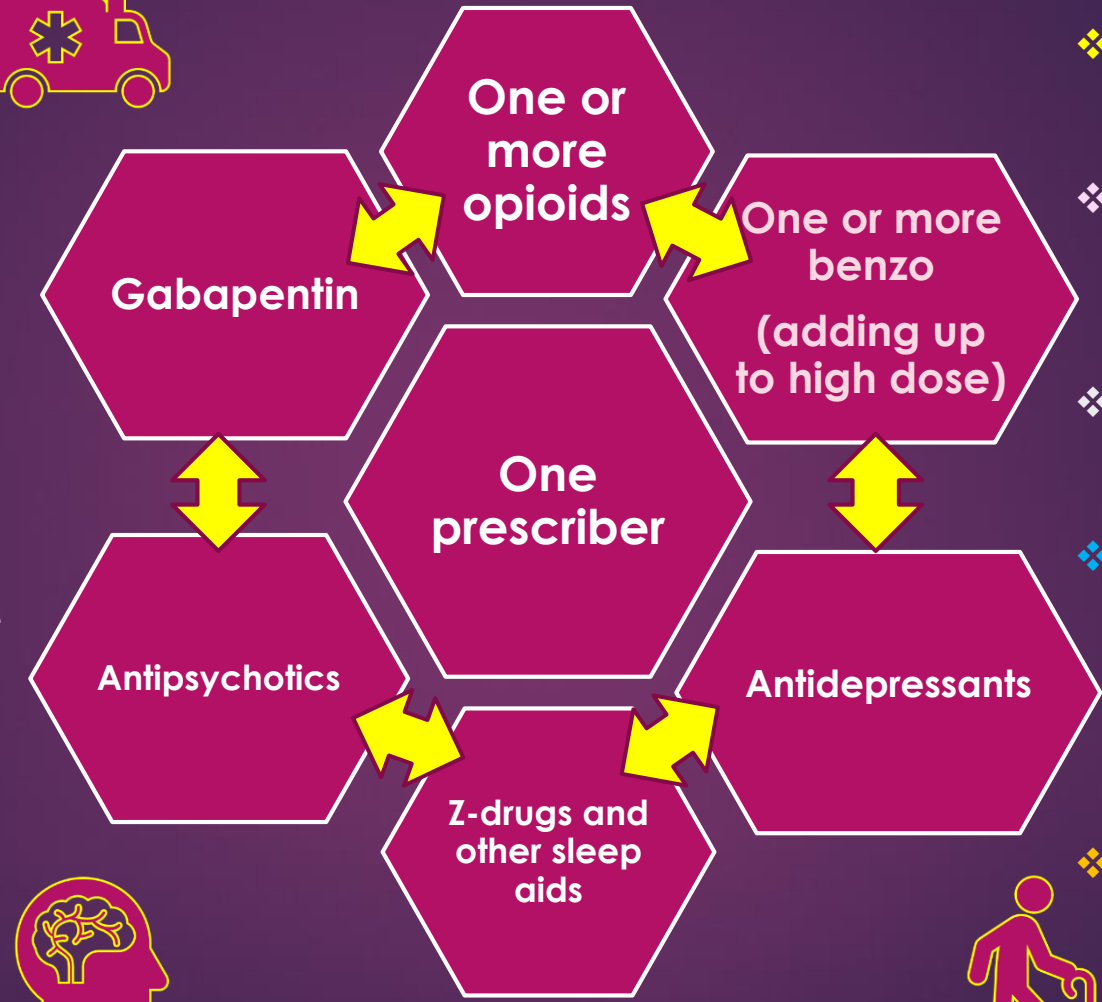
- ▶ Opioid deaths have leveled off.
- ▶ **Stimulant-related deaths are climbing rapidly. Alprazolam and gabapentin,** as well as **diphenhydramine**, have become significant drugs of abuse.
- ▶ Note that more than one drug is often involved in a given death where a drug is given as a “contributing” cause.
- ▶ 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.).

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

- ▶ You have to actively manage polypharmacy
- ▶ Set the stage at intake appointment
- ▶ Single prescriber/group of prescribers – AND one pharmacy
- ▶ 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 reduce dose if appropriate

An APPROACH to polypharmacy

- ▶ 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
- ▶ Actively collaborate with community/hospital OAT pharmacist and primary care prescriber.

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 and are worsened by long term benzodiazepine use!!!**
- ❖ **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?

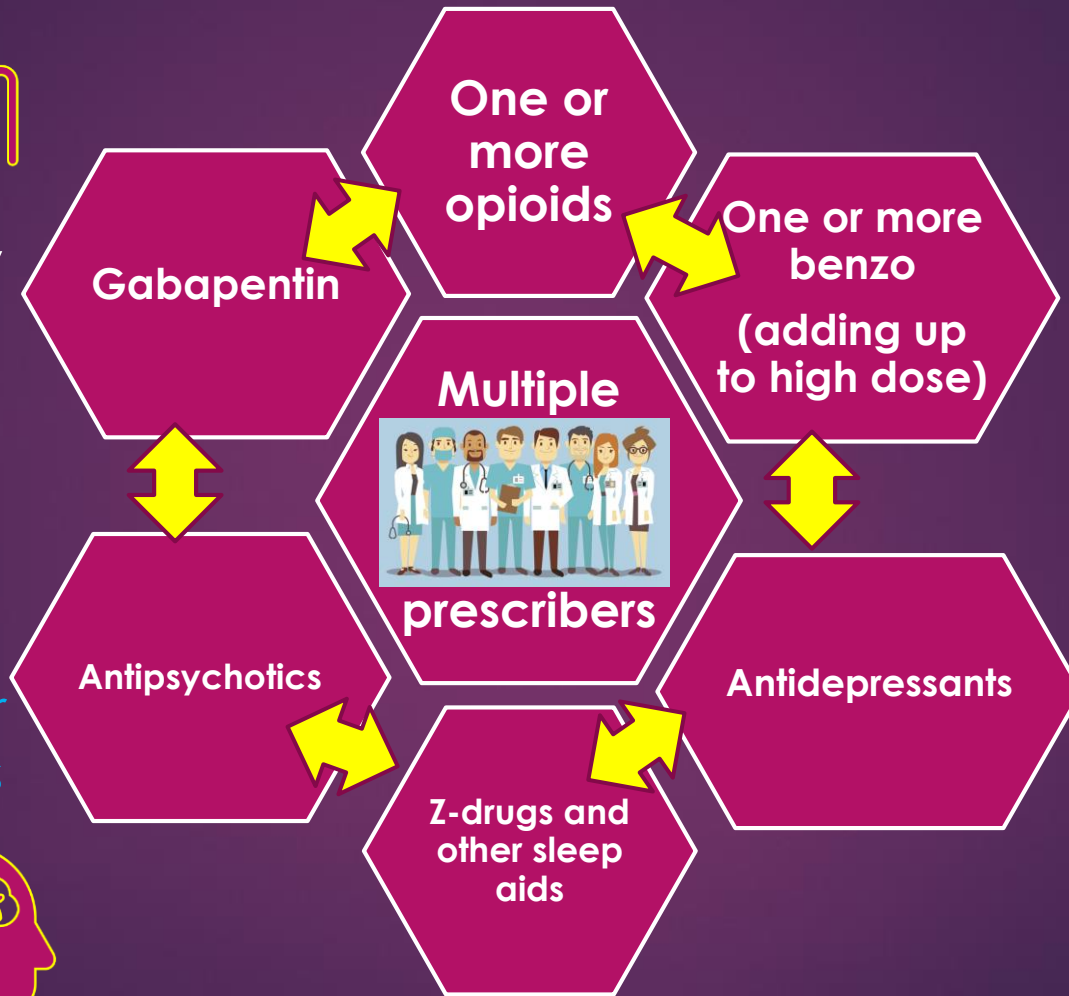
Deaths involving **multiple sedating medications** (often including an opioid and more than one benzodiazepine at a time) prescribed to the same patient by different physicians; filled at multiple different pharmacies.

❖ 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 OAT prescribers should utilize DPIN or e-Chart (ungrouped) to improve patient safety.**
- ❖ **Clear treatment agreement with OAT prescriber or group of prescribers responsible for monitored drugs prescribed concurrently with OAT.**
- ❖ **Listen to and actively collaborate with community/hospital pharmacist!**

What can we learn?

- ❖ **OTC medications used in combination 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 H₁-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.



An approach to managing OTC medication use

- Ask your patient about OTC medication use in a non-judgemental way!!
- Pay attention to collateral - “family” and pharmacists!!
- Urine drug testing (UDS) may be useful if concerning report, appearance, function or collateral information.

(Comprehensive UDS preferred)

- **Treatment intensification**; ? Residential treatment
- **Reduce carries** if concerned
- **Taper other sedating Rx meds** to offset OD risk

Key messages

- ❖ OTC medication use is common in patients on OAT and increases OD risk!!
- ❖ 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:

- ▶ The Office of the Chief Medical Examiner of Manitoba.
- ▶ 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 3rd, 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
- ▶ Barbone F, McMahon AD, et al. Association of road-traffic accidents with benzodiazepine use. Lancet. 1998;352:1331-1336.

THANK YOU

