Buprenorphine Macro-Induction Cases in a Virtual Setting

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ASAM Annual Conference April 5, 2024

Disclosure Information

No speakers have any conflicts or disclosures

April 5, 2024, 1500-1615PM

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- No disclosures

Overview

- Review information surrounding the opioid crisis in Canada
- Discuss buprenorphine, pharmacology, and the theories of micro-induction
- Introduce macro-dosing of buprenorphine and the published cases in relation to macro-dosing
- Review of Alberta's treatments
- Review the Virtual Opioid Dependency Program (VODP) teams and the macro-dosing cases within those teams with discussion surrounding straightforward and complex cases
- Question period

The Opioid Crisis in Canada

- Public Health Agency of Canada
  - There were, on average, 22 deaths per day from January to June 2023[1]
  - This is 5% higher when compared to 2022[1]
  - 84% of these overdoses involved fentanyl; fentanyl overdoses have increased drastically from 2016 by 47%[1]
  - A large proportion of the overdoses were polysubstance related, and the number of co-occurring substances with fentanyl has increased drastically from 2012 to 2022[2]

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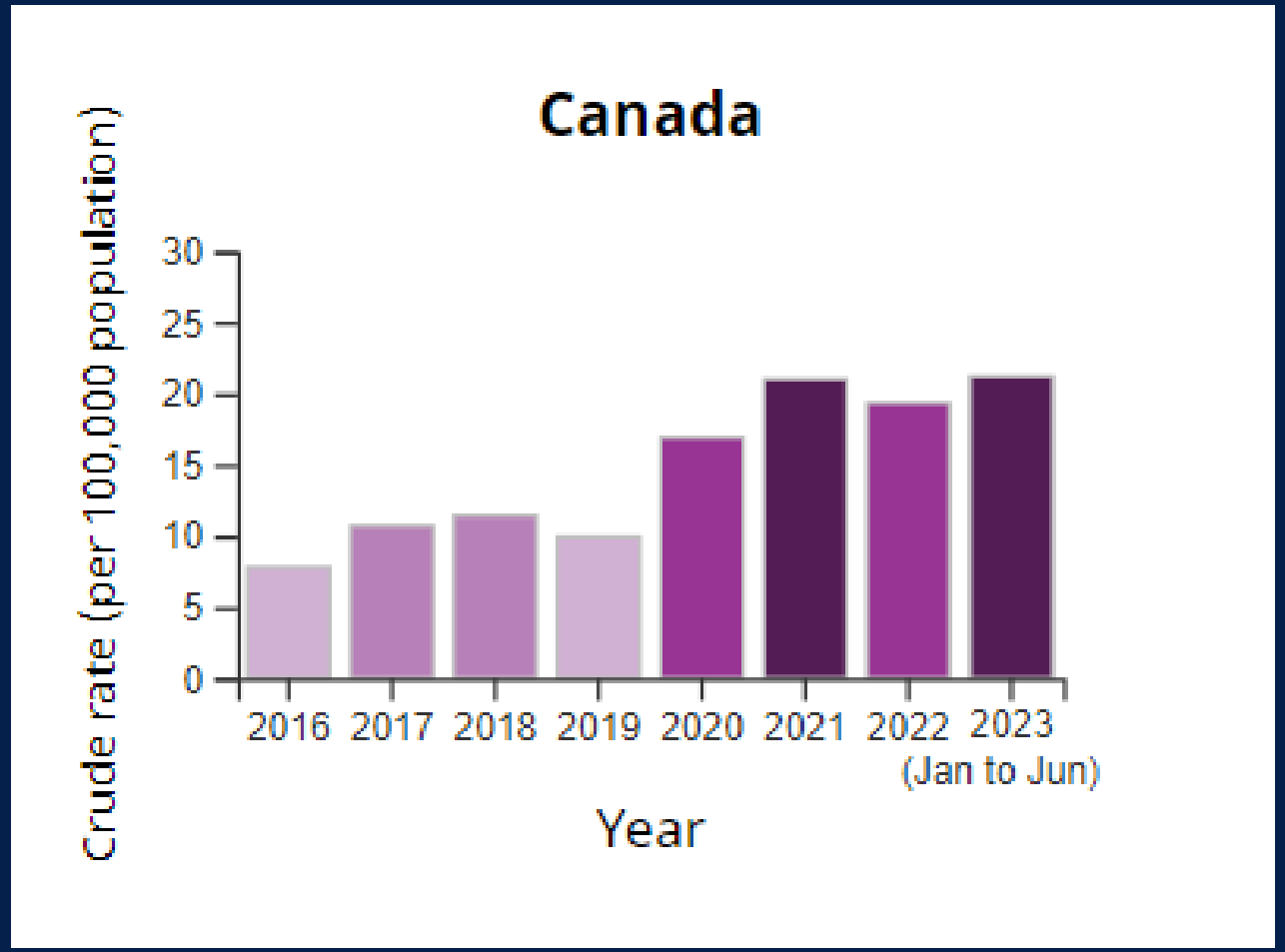
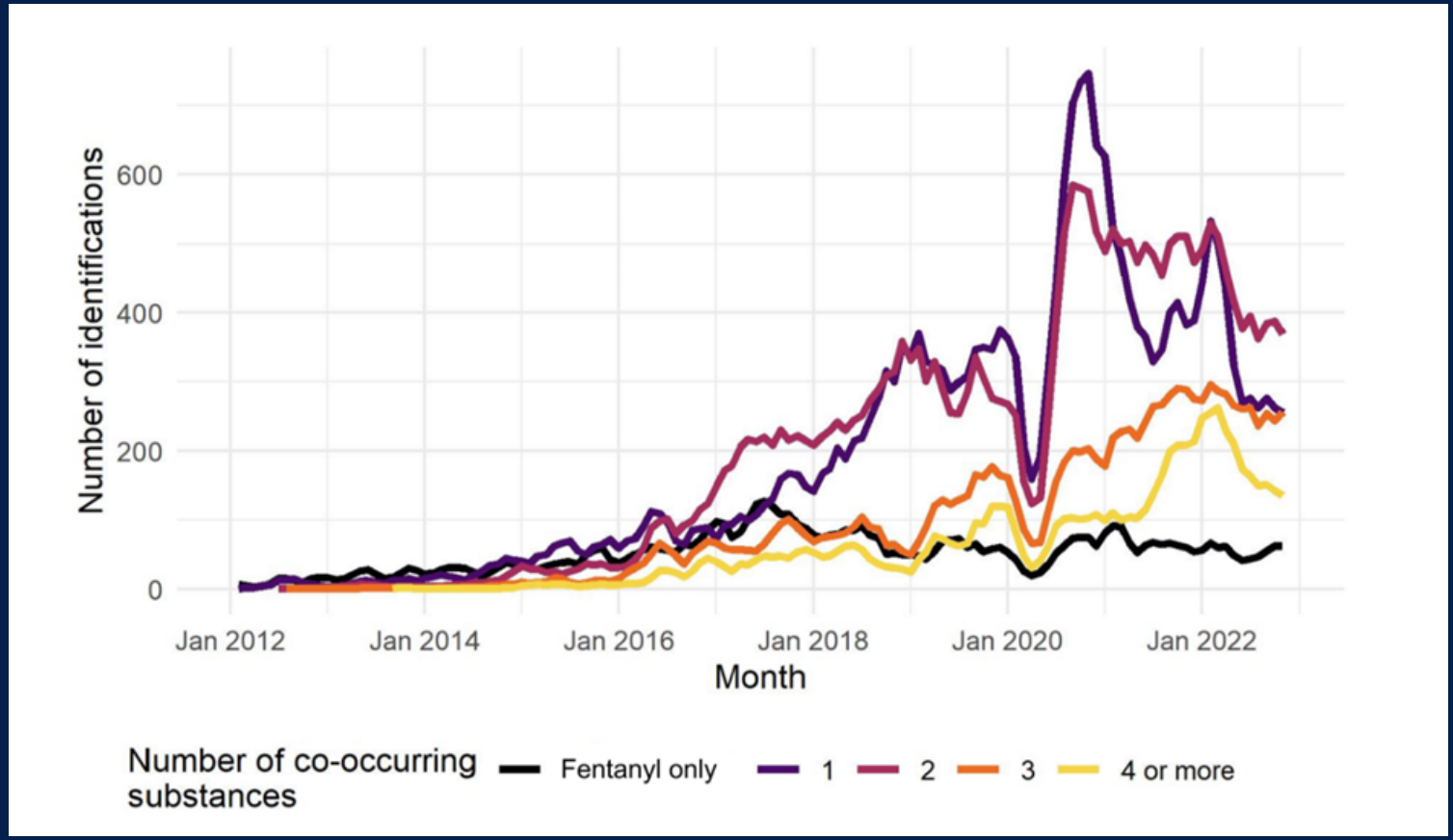
Overdose Fatalities in Canada



Case Study: Narcan Failure

- Patient 1 is a 45-year-old female who has been brought to the ER by EMS. The patient is nonresponsive, and a quick assessment of her vitals reveals a RR of 3 and an O2 Sat of 87%
- The patient has a history of using 1 gram of fentanyl via IVDU, and her friends report she last used “about an hour ago.” Her friends reported that when she wasn’t responding, they gave her 2 doses of Narcan, but nothing worked. EMS also reports they gave an additional dose of Narcan with limited effect.
- Why is Narcan not working to reverse this patient’s somnolence?

Polysubstance Use



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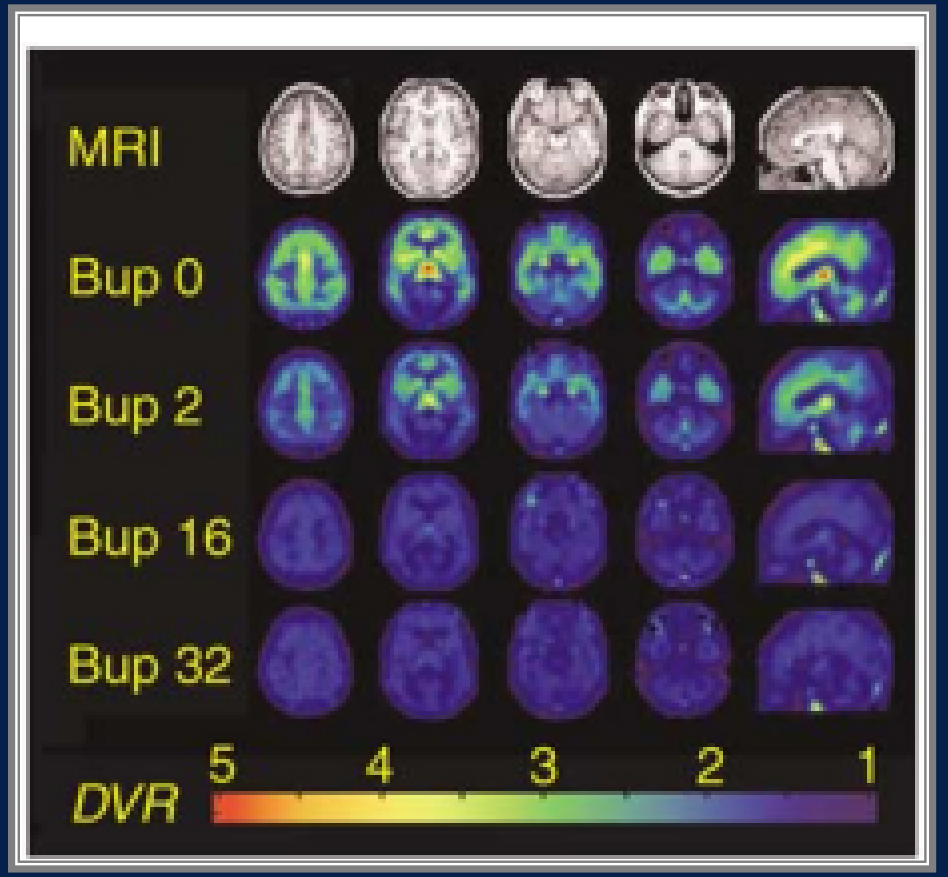
Buprenorphine

- Partial opioid agonist developed in 1966
- FDA approved in 2002 for the treatment of opioid use disorder, often combined with naloxone to discourage misuse
- Studies shown that it does not provide similar stimulation effects as full opioid agonists even at higher doses
- Shown to have an intensely high affinity for mu opioid receptors with a slow dissociation from the same (also shown to have antagonistic effects at delta and kappa binding sites)

Benefits of Buprenorphine

- Blocking of the opioid receptors allows for a protective barrier due to its high affinity; buprenorphine is more likely to be in a bound state to the opioid receptor
- Well documented reduction in overall mortality
- History of being utilized as a source of pain relief with potential significant benefits
- More manageable side effect profile

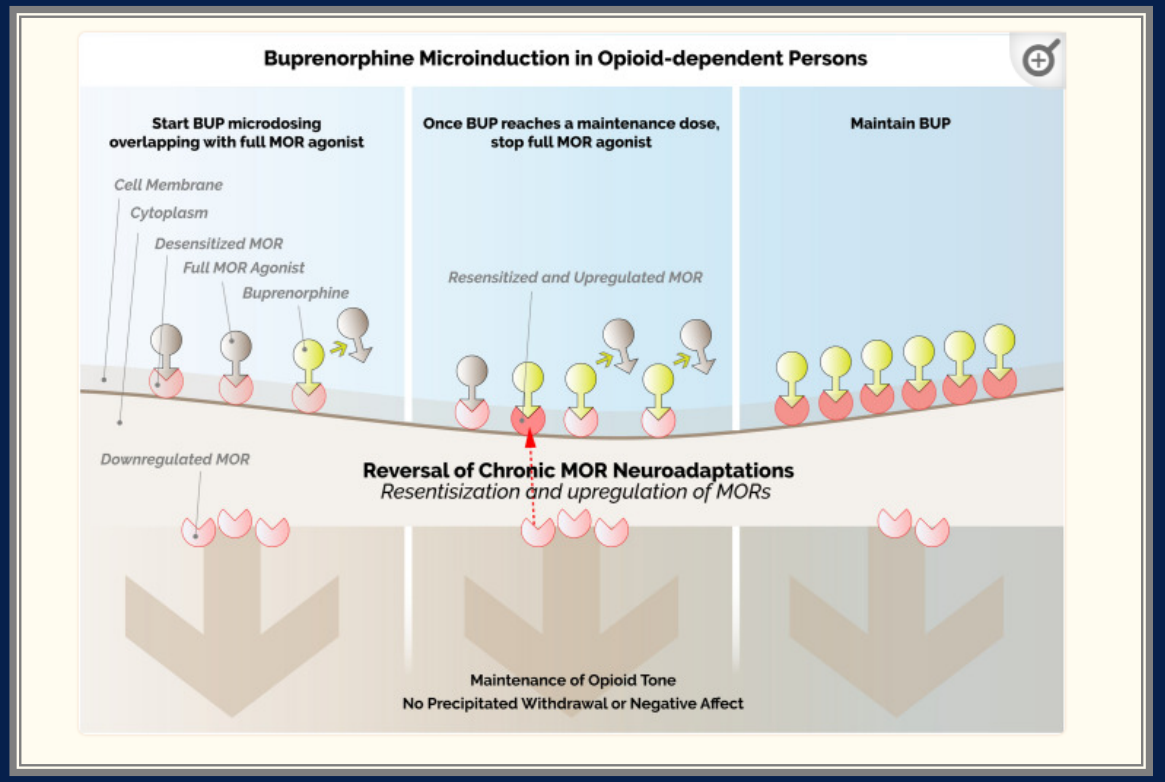


The Complication of Precipitation

- Due to buprenorphine's high affinity for the opioid receptor, there is, theoretically a drastic decrease in opioid agonist effect
- This leads to the so-called precipitated withdrawal
  - 'The worst withdrawal I've ever had in my life'
  - 'I thought I was going to die'
- Patients can be fearful to reinitiate

Micro-dosing/Low-dose Inductions

- Slow increase of buprenorphine dose in the presence of ongoing or recently discontinued full opioid agonist use
- Initiated to avoid precipitated withdrawal



Differing Micro-dosing Strategies

Table 3. Protocol Use in Patient 2

Protocol day	Buprenorphine total daily dose, mg	Methadone total daily dose, mg	Maximum pain score, 0–10
0	0	100	7
1	1.0	100	8
2	1.5	100	6
3	3	100	8
4	6	100	7
5	8	100	8
6	8	100	8
7	12	100	6
8	16	0	6
9	16	0	8
10	20	0	8
11	24	0	6

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Day	Buprenorphine/naloxone Dose	Other Opioids
1	0.5mg/0.125mg twice daily	Continue use
2	0.5mg/0.125mg three times daily	Continue use
3	1mg/0.25mg twice daily	Continue use
4	2mg/0.5mg twice daily	Continue use
5	2mg/0.5mg three times daily	Continue use
6	4mg/1mg three times daily	Continue use
7	12mg/3mg once daily	Stop use

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fraserhealth

Take Home Suboxone (buprenorphine-naloxone)

Before you start, make sure you are very dope-sick (bad withdrawal)

Do you have at least 4 of these signs? ...or score yourself using the scale on Page 2

- Joint and bone aches
- Bad chills or sweating
- Restless, can't sit still
- Twitching, tremors or shaking
- Big (enlarged) pupils
- Goosebumps
- Heavy yawning
- Runny nose, tears in eyes
- Feel sick, throwing up, or diarrhea

How long has it been?

It should be at least... **24 hours** since you used heroin / fentanyl / oxycodone
48 hours since you used long-acting morphine (Kadian)
If you take methadone, talk to your Opioid Agonist Treatment (OAT) Clinic

Wait as long as you can! Start it too early and you might feel very, very sick

Once you are very dope-sick (in bad withdrawal)

How to take Suboxone:
- Put the tablet under your tongue
- **Do not** swallow it – it won't work
- **Do not** take with alcohol or sleeping pills (sedatives)
- **Do not** take when sleepy

How soon it will work:
- Must melt under your tongue to work
- Takes up to 10 minutes to dissolve
- Takes 20 to 45 minutes to work

**Always keep Suboxone away from children

Day 1			Day 2 and Day 3
Step 1	**Step 2**	**Step 3**	
Place 1 tablet (2 mg*) under your tongue Wait 1 hour	Place 1 tablet (2 mg*) under your tongue Wait 1 hour	Still feel sick? Take 1 tablet every hour **Stop** when: You feel better **or** You have taken all 6 tablets (12 mg*)	Place all the tablets needed for Day 1 under your tongue at one time Can take up to 6 tablets each day Go to an OAT Clinic for more Suboxone (see Page 2)

Step 1 + Step 2 + Step 3 = no more than 6 tablets or 12 mg

If you feel a lot worse at any time, **stop** taking Suboxone - Return to the Emergency Department

*Dose based on mg of buprenorphine (each Suboxone tablet contains 2 mg of buprenorphine and 0.5 mg of naloxone)

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11, 23-26

Case Study: Too Much Time

- Patient 2 is a 22-year-old male who presents to your clinic wanting an initiation on methadone replacement therapy
- He reports a history of using “a ball” (3.5g) of fentanyl every other day, mixed with methamphetamines “sometimes.”
- Buprenorphine treatment is discussed; however, he reports, “I’ve been started on it lots of times. I always just end up not finishing.”
- Why could there be concerns with buprenorphine retention with similar patients?

Micro-dosing concerns

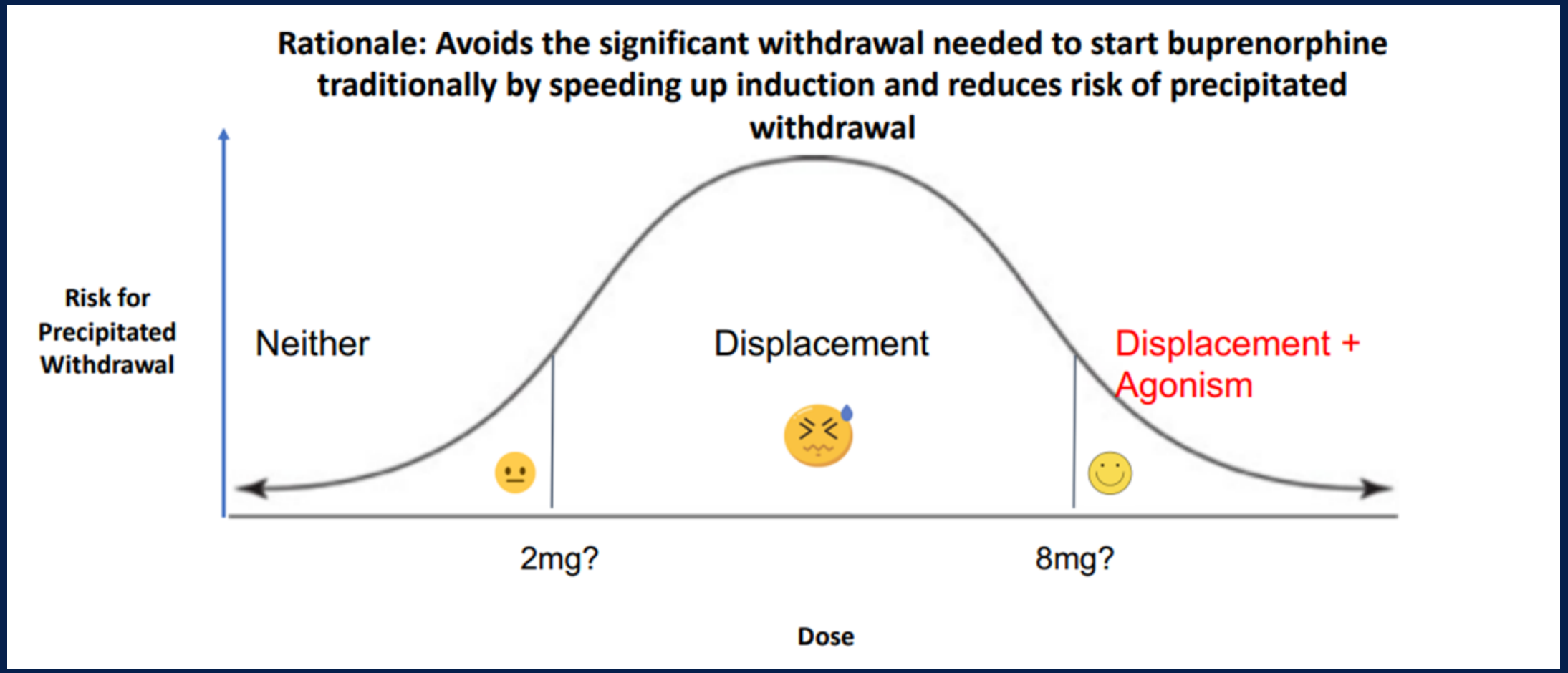
Variability in practice/timing can be a barrier to patients continuing treatment

- Centers conducting micro-dosing initiations
  - Starting low, increasing slowly
  - Sometimes reaching 12mg over a 7–10-day period
  - Concerns that slow incremental increases has led to poor retention in treatment

Case Study: Low Dose Precipitation

- Patient 3 is a 36-year-old female who contacts your clinic wanting an initiation on methadone replacement therapy
- She reports a history of using 1 gram of fentanyl and ½ to 1 gram of methamphetamines daily. She admits to intermittent IVDU.
- She states that she last used 18 hours ago and that she is “in horrible withdrawal.”
- You discuss buprenorphine as an alternative treatment option; however, she adamantly refuses, “I tried that whole take 1 pill every hour, and I got sick after taking 2 of them. I’m never going back on that!!”
- What could have occurred to cause this patient’s precipitation?

Precipitated withdrawal is more likely to occur at lower doses of buprenorphine



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Case study: Initiation, No Relief

- Patient 4 is a 47-year-old male with a 15-year polysubstance use history, he currently reports use of 1-2 grams of fentanyl daily mixed with 1 gram of methamphetamines. He also states he will drink 26 oz of vodka on the weekends.
- As you review his medical record, you note multiple initiations onto methadone in the last 5 years, ranging from 30-60mg before the patient discontinues presenting for his medication.
- You discuss buprenorphine as an option for this patient, his response “I tried that stuff before. I took 4 of the little pills on the first day and I was still dope sick. It didn’t work for me.”
- Reviewing his chart, you do confirm that 3 years ago he did have a single day prescription for buprenorphine SL tablets 2mg/hour up to 12mg.
- Why would the patient not respond well to the medication?

Illicit Opioids

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Introduction to Macro-dosing

Theoretical Benefits of Macro-Dosing

- Rapid increase of medication leads to a rapid opioid overdose suppression
- Theorized to increase retention
- Higher doses of buprenorphine theoretically leads to a decreased risk of precipitated withdrawal
- Due to a more rapid transition from displacement to displacement + agonism, patients should be able to be initiated onto buprenorphine with a lower abstinence period

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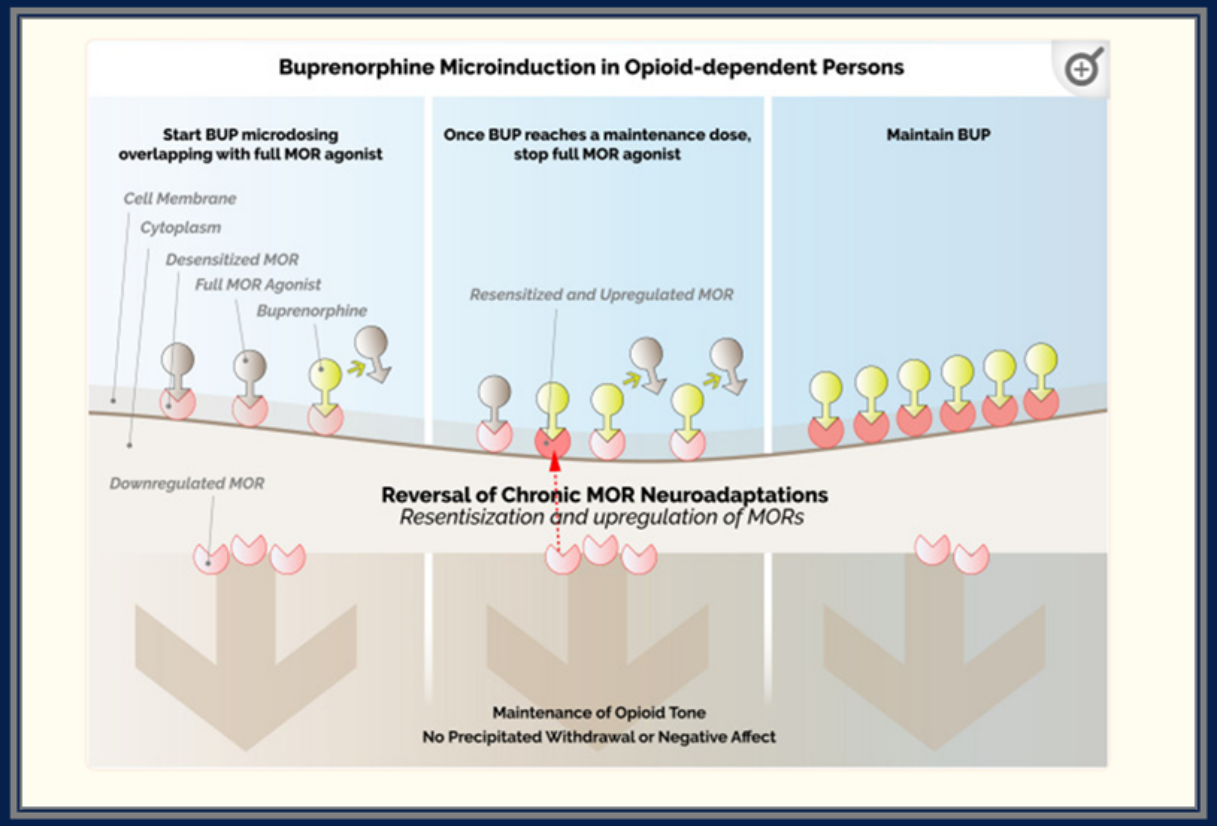
Why Would Macro-Dosing Work?



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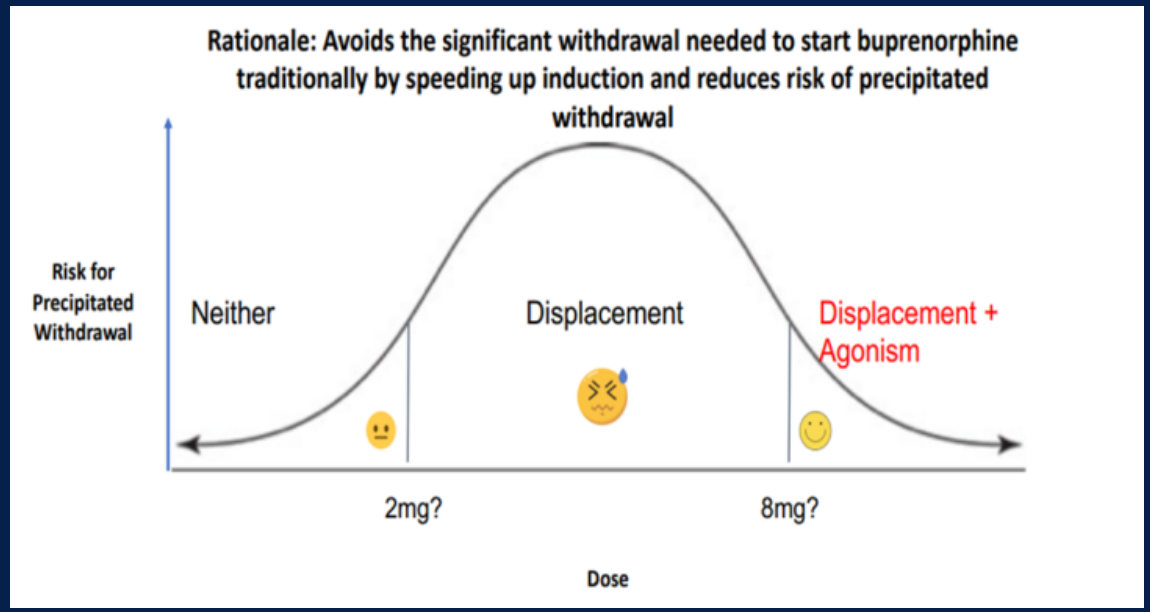

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Small Clinical Trials

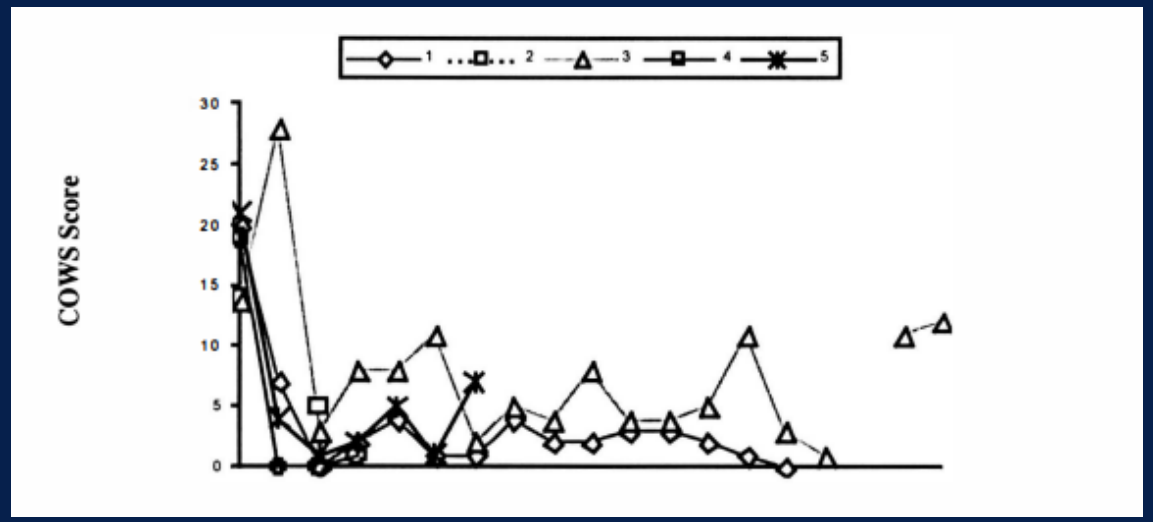
Heroin detoxification with a single high dose of buprenorphine

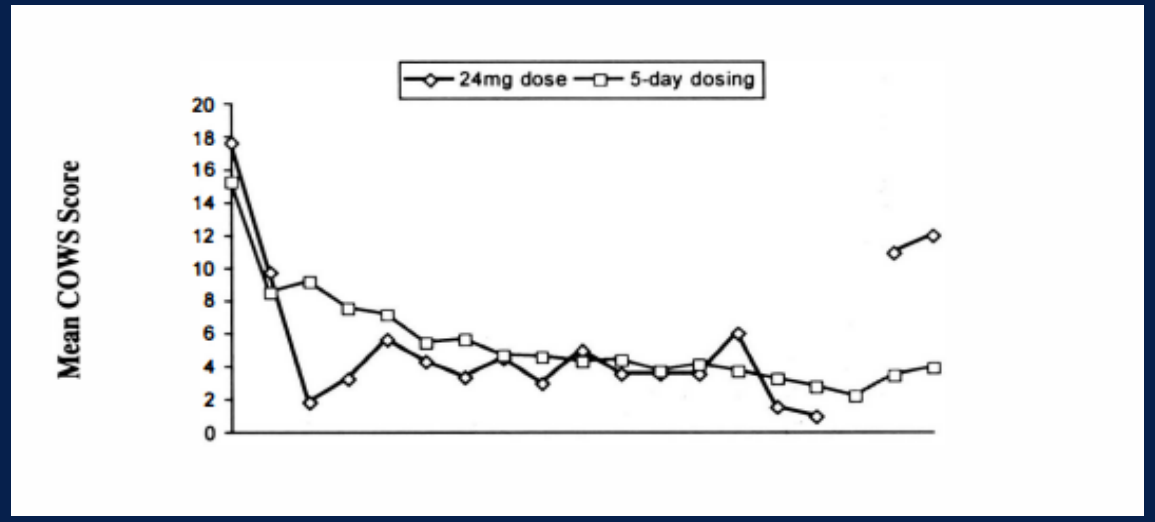
Ilan Kutz [1], Victor Reznik

Rapid heroin detoxification using a single high dose of buprenorphine

I Kutz [1], V Reznik

COWS Reduction





Better Retention?

Effects of a high-dose fast tapering buprenorphine detoxification program on symptom relief and treatment retention

Tom Palmstierna [1]

The ED

Managing Opioid Withdrawal in the Emergency Department With Buprenorphine

Andrew A Herring [1], Jeanmarie Perrone [2], Lewis S Nelson [3]

High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder

Andrew A Herring [1 2], Aidan A Vosooghi [1 3], Joshua Luftig [1], Erik S Anderson [1 2], Xiwen Zhao [4], James Dziura [4 5], Kathryn F Hawk [5], Ryan P McCormack [6], Andrew Saxon [7], Gail D'Onofrio [5 8]

The Alberta Model: Recovery Oriented Care

The Alberta Model:
A Recovery Oriented System of Care

Rx Coverage	Recovery Communities	Indigenous Partnerships
NORS/DORS	Overdose Prevention	ODPs & Other

The Virtual Opioid Dependency Program (VODP)

- Founded in 2017 in response to the opioid crisis
- Completely virtual
- Hours are 0800 to 2000, 7 days a week, patients can receive help anywhere in the province of Alberta

Some VODP Statistics

2017/2018

- 201 unique clients
- Median wait time of 6 days
- 40 home communities served

2022/2023

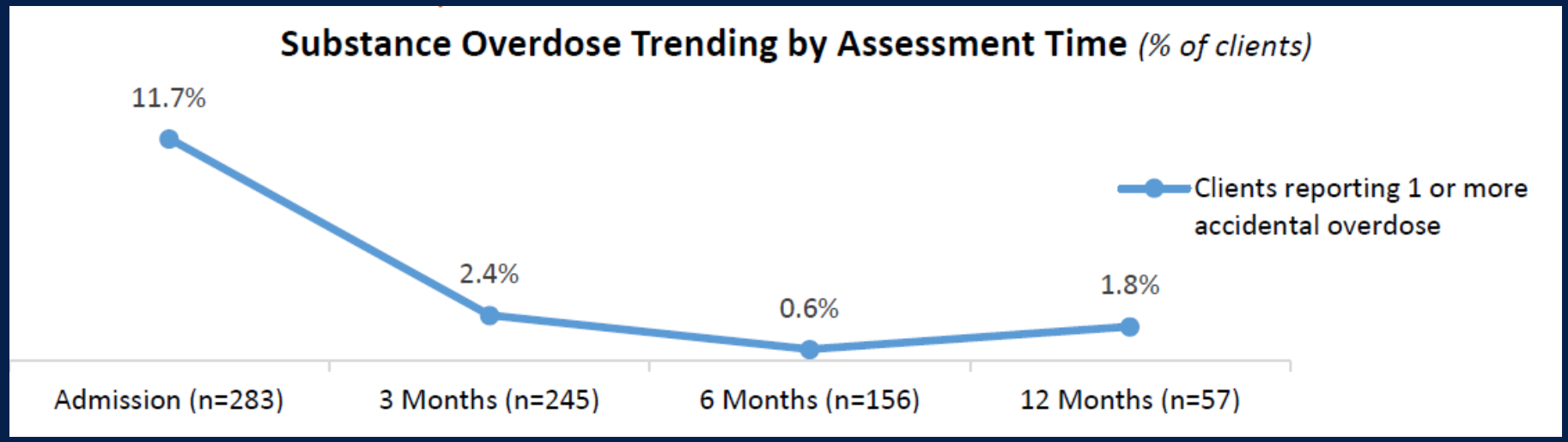
- Over 7000 unique clients served in multiple differing settings (community, detox/rehab sites, overdose prevention locations, Police holding cells)
- Median wait time is 0.0 days
- 369 home communities served

VODP Patients

VODP Referrals by Referral Source *(for the last two fiscal years)*

	2021/2022		2022/2023	
Referral Source	**# of Clients**	**Percent (%)**	**# of Clients**	**Percent (%)**
Self	*3573*	*72.8%*	*4673*	*59.4%*
Corrections	474	9.7%	1307	16.6%
Police Services/RCMP	281	5.7%	1316	16.7%
Detox	165	3.4%	130	1.7%
Community Physician/Psychiatrist	137	2.8%	150	1.9%
ER	127	2.6%	70	0.9%
Children's Services/PcHAD	N/A	N/A	6	0.1%
Inpatient Referral	58	1.2%	27	0.3%
Other Opioid Dependency Program	34	0.7%	27	0.3%
Community Hospital/Clinic	20	0.4%	15	0.2%
Community AMH Services	17	0.3%	6	0.1%
Other	13	0.3%	131	1.7%
Nurse/Nurse Practitioner/Paramedic	8	0.2%	14	0.2%
TOTAL	**4907**	**100%**	**7872**	**100%**

Impact of VODP Services



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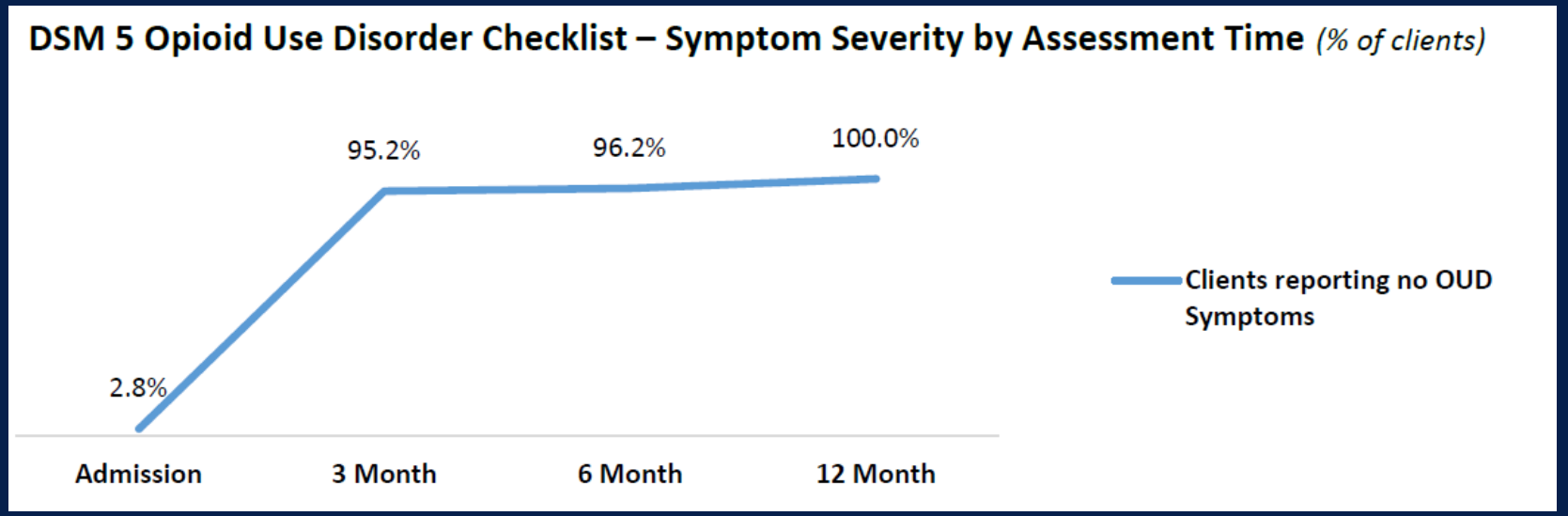


VODP Same Day Start Team (SDS)

- Team was started in 2019
- Patients can be given VODP emergency line via pharmacists, General Practitioners, Emergency Physicians, or Local Community Sources
- Patients can connect with VODP from their own communities to be assessed for MOUD
- Patients can be given life saving MOUD within an hour of their assessment, which can occur over a phone
- Service runs 0800-2000, 365 days/year
- The SDS team handled 4,727 cases in 2022/2023

The SDS Process

Patient contacts VODP and is put through to the SDS team

A pre-history is obtained by a case manager to determine patient's opioid and substance use severity, as well as risk acuity

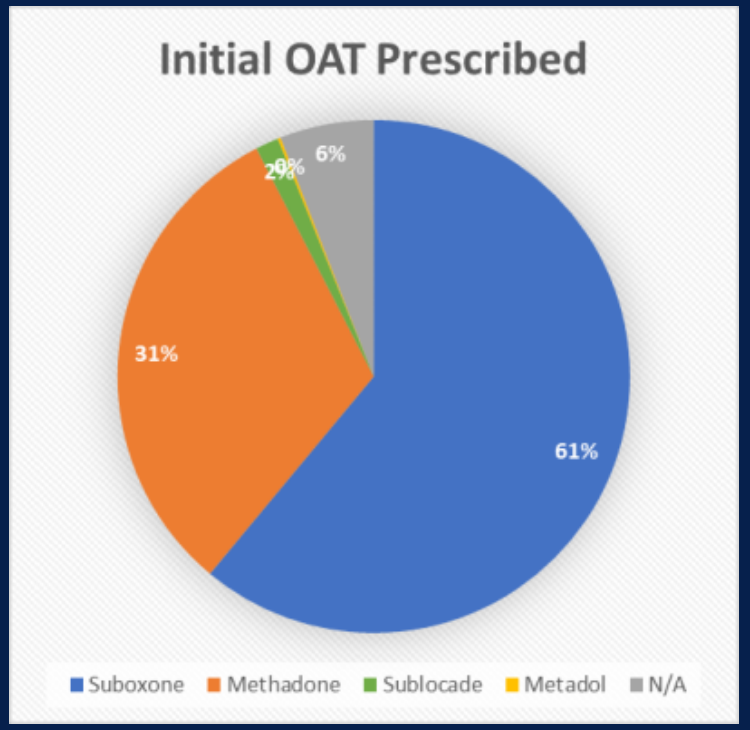
The case manager contacts the on-call physician to report on the patient

The physician contacts the patient directly, and a treatment discussion/decision is agreed upon

An Rx is sent to pharmacy within an hour

SDS Data

- Data assessed from November 6, 2022, to March 6, 2023
- A total of 1096 cases were recorded
- 71% of these cases were using fentanyl and/or carfentanyl
- Use ranged from 0.1 grams to 7 grams daily
- A few cases were using both fentanyl and/or other forms of opioids (dilaudid oxycocets, percocets, etc.)



SDS Data Cont'd

- 569 cases were offered macro-doses
  - 60% were recommended to dose up to 32mg
  - 27% were recommended to dose up to 24mg
  - 13% were recommended to dose up to 16mg
- 31% of these patients either did not initiate their treatment, or we were not able to confirm if they picked up their initial prescription

SDS Data Cont'd

- 339 initiated buprenorphine treatment
  - 75% cases successfully initiated via macro-dose to their recommended initiation dose
    - ***We had 1 case of precipitated withdrawal***
  - 25% of the patients did not initiate to the recommended dose
    - 60% of those patients still required a higher dose the following day

Case Study: An SDS

- Patient 5 is a 28-year-old male who calls in to your clinic seeking MOUD.
- He reports a history of using ½ gram to 2 grams of fentanyl daily. He has had 4 overdoses in the last 2 years. He states he last used 36 hours ago, and he is feeling “super sick.”
- Would you micro-dose this patient? Would you macro-dose this patient? What dose would get to on the first day?

Case Study: Complications

- Patient 6 is a 33-year-old female who calls in wanting to be initiated on medication. She reports that she has been using “a ball” (3.5 grams) of fentanyl per day, with some methamphetamine use via smoking. She denies any other substance use. She states that she last used 4 hours ago, and “not really in withdrawal yet.”
- During your review of her electronic medical record, you discover that she has been admitted in the past for a withdrawal seizure.
- Would you still initiate this patient in community? Would you still macro-dose this patient? Would you provide the patient with other medications?

Low Barrier Urgency Access Team (LBUA)

- Team that was developed to provide MOUD to patients who have significant barriers to stability:

Transience and/or difficulties with regular contact	Patients who are unhoused and unsheltered	Patients who are under Police Detention (cells starts)	Patients contacting from Overdose Prevention Sites

LBUA Macro-doses

- Cells Starts
  - 1594 referrals in the fiscal year of 2022/2023, with 1228 prescriptions sent
  - Reviewed data from 2 of our centers (Edmonton and Calgary) from October 1, 2023, to Feb 15, 2024
    - 148 cases were reviewed via random sample
    - 117 Macro-doses were offered
    - ***0 reported cases of precipitated withdrawal***
  - 40% of the sample of patients who were released from Edmonton Police Services contacted the VODP for ongoing care after their release

Benefits of VODP for Cell Starts

- Individuals in Police custody no longer suffer in state of withdrawal, they reach a state of comfort
- Police and staff no longer address the side effects of sustained withdrawal and can focus on other pertinent job tasks
- Cell inmates receive the same benefits of those in Police custody; no withdrawal or agitation
- Cell staff receive the same benefits of Police; no longer addressing withdrawal or agitation
- Creates a safer environment for all parties involved

Case Study: Rapid Cells Start

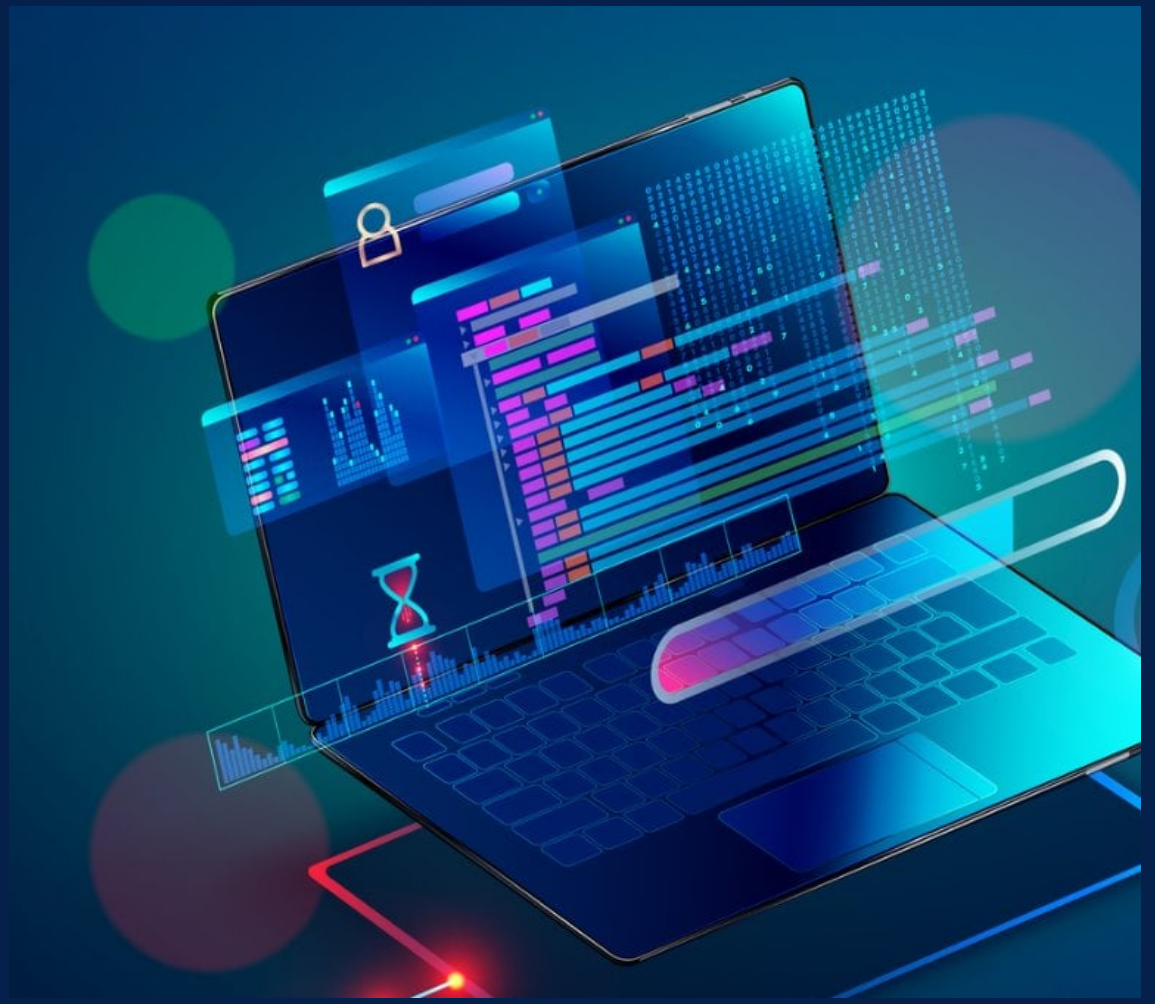
- Patient 7 is a 22-year-old female who is calling from holding cells and is asking to be restarted on her MOUD.
- She reports a history of ½ gram of fentanyl daily, drinking a 26 oz of vodka on the weekends, and using benzodiazepines “when I can get my hands on ‘em’.” She reports using 11 hours ago and feels in significant withdrawal. She also admits to a history of 10 accidental overdoses and “5 or 6” intentional overdoses.
- Reviewing her medical record, you find that she was prescribed methadone from an external provider, and that she last dosed 10 days ago.
- Would you macro-dose this patient on buprenorphine?

Case Study: Somnolent

- Patient 8 is a 42-year-old male who is currently in Police holding cells and has called for an initiation onto MOUD.
- He reports that he's been using 2 points to 2 grams of "down" daily and states that he last used "I dunno, last night."
- As you begin to ask the patient further history questions, he continues to muffle his words, sometimes needing several prompts before he'll answer a question. He states "I'm just really tired, I haven't slept in, like, 3 days."
- Would you feel safe initiating macro-dosing with this patient?

Edmonton Remand Centre (ERC)

- Largest correctional facility in Canada (can house 2000 inmates)
- Inmates arriving on MOUD were continued on treatment
- Inmates arriving in withdrawal could request access to MOUD but wait times could be months before assessment
- VODP collaborated with Alberta Health Services Corrections services
- Asynchronous telehealth is now utilized to reduce wait times for MOUD assessment to <1 day of arrival



ERC Macro-doses

- Random sample of ERC starts from March to December 2023:
  - Total of 317 consultations
  - 62% were given macro-inductions
  - 29% were deemed as non-starters
  - 8% were continued on previous medications
    - 11 cases were Methadone
    - 1 case was Slow-release oral morphine
    - 7 cases were Long-acting injectable buprenorphine
  - ***0 precipitated withdrawal cases***

Case Study: Rapid ERC

- Patient 9 is a 39-year-old male who was incarcerated today and is requesting to be started on buprenorphine tablets. He reports a history of using 0.3 grams of fentanyl daily intravenously.
- He states that he last used 2 days ago. He reports that he did contact VODP while in holding cells, and he was able to get a dose of medication.
- A review of his medical record reveals that he has been admitted 3 times in the last 2 years for suspected opioid overdose. He has also had previous UTT's positive for fentanyl, norfentanil, and norcarfentanil
- Would this patient require initiation onto MOUD?

Case Study: Is that Opioid Use Disorder?

- Patient 10 is a 25-year-old male who is being consulted for opioid use disorder. He has recently been incarcerated 10 days ago.
- He reports a history of using ½ gram of fentanyl daily via IVDU. He also reports a history of using illicit benzodiazepines and cocaine. Finally, he reports that he drinks a 26 oz of whiskey daily.
- He states that he last used 12 days ago, and he is in an 8/10 withdrawal state.
- You review his medical record, and find several urine toxicology's positive for methamphetamines, as well as admissions for "query alcohol use" and "acute psychosis." No documentation nor lab work suggests a history of opioid use.
- Would you start this patient on MOUD?

Case Study: ED Consultation

- You receive a call from an Emergency Department physician in regard to a 29-year-old female who presented in acute opioid withdrawal. The physician informs you that the patient was recently on Methadone, and that she last dosed 30mg 3 days ago. She also reports that the patient's COWS is at 13. The physician tells you that she (the physician) does not have her certification to prescribe methadone and is uncertain how to proceed.
- Reviewing the patients medical record, you do note that the patient was dispensed 30mg of methadone 3 days previously, and that she had dosed 40mg 2 days before then.
- Would you advise buprenorphine?

Case Study: Precipitation

- A nurse practitioner contacts the emergency line very distressed. She reports that a 45-year-old male patient was reinitiating buprenorphine at detox, and after dosing to 6mg he has begun to vomit, sweat, and is noticeably agitated. The patient's COWS is currently at 21.
- You quickly review the patient's medical record and note that this patient was on buprenorphine tablets, total dose of 24mg for 5 months while incarcerated.
- Would you advise the NP to macro-dose the patient?

Case Study: That's Too Much

- Patient 13 is a 68-year-old woman who has admitted to you that she has been using illicit opioids; specifically, she has been "sucking on my husbands used fentanyl patches" without his knowledge. She is embarrassed and is hoping to get started on treatment.
- You initiate this patient onto a standardized treatment approach; giving her 2mg of buprenorphine hourly, up to a max dose of 16mg on day 1.
- She calls back the next day to report; "I took the first 3 pills, and honestly, I felt like I was stoned, almost like I drank too much alcohol or something."
- What happen to this patient to have her respond in this manner?

VODP Successes

Continued expansion of services since 2017

Recruiting and retaining the top physician specialist in addiction medicine

Until 2021, we exclusively micro-dosed patients onto buprenorphine

From 2021 onwards, we began macro-dosing patients; from this change in practice, we witnessed:

- Significantly reduced rates of precipitated withdrawal
- Increased uptake of buprenorphine initiations
- Improve treatment response
- Faster patient stabilization in their recovery

Final Takeaways

- The Opioid Crisis is affecting both the USA and Canada
- Buprenorphine is a well studied and life-saving medication
- Micro-dosing has been utilized to avoid precipitated withdrawal and sedation
- Due to elevated tolerance levels, patients may be considered for a higher initiating dose of buprenorphine than previous guidelines suggest

Final Takeaways (Cont'd)

- Macro-dosing has many theoretical benefits when compared to micro-dosing, however there are limited cases currently published
- The VODP has conducted large volumes of macro-dosing initiations within multiple differing environments with ***limited precipitated withdrawal cases***
- There is some evidence supporting increased retention with macro-dosing buprenorphine in a virtual setting, further analyses of VODP data is underway

Contributors and Thanks

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Questions

References

1. Government of Canada. (2023, December). *Opioid- and Stimulant-related Harms in Canada*. Health-Infobase.canada.ca. https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/
2. Canada, H. (2023, March 15). *The evolution of Fentanyl in Canada over the past 11 years*. Www.canada.ca. https://www.canada.ca/en/health-canada/services/publications/healthy-living/evolution-fentanyl-canada-11-years.html
3. *Nitazenes (CCENDU Drug Alert) | Canadian Centre on Substance Use and Addiction*. (n.d.). Www.ccsa.ca. Retrieved February 22, 2024, from https://www.ccsa.ca/nitazenes-ccendu-drug-alert
4. Ellis, C. R., Kruhlak, N. L., Kim, M. T., Hawkins, E. G., & Stavitskaya, L. (2018). Predicting opioid receptor binding affinity of pharmacologically unclassified designer substances using molecular docking. *PLOS ONE*, *13*(5), e0197734. https://doi.org/10.1371/journal.pone.0197734
5. *Xylazine Increasingly Found in Canada's Illegal Drug Supply*. (n.d.). Medscape. https://www.medscape.com/viewarticle/animal-tranquilizer-xylazine-increasingly-found-canadas-2024a10002vp?form=fpf
6. Davis, M. P., Pasternak, G., & Behm, B. (2018). Treating Chronic Pain: An Overview of Clinical Studies Centered on the Buprenorphine Option. *Drugs*, *78*(12), 1211–1228. https://doi.org/10.1007/s40265-018-0953-z
7. Sansone, R. A., & Sansone, L. A. (2015). Buprenorphine Treatment for Narcotic Addiction: Not Without Risks. *Innovations in Clinical Neuroscience*, *12*(3-4), 32–36. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4420168/
8. Miller, S. C., Fiellin, D. A., Rosenthal, R. N., Saitz, R., & American Society Of Addiction Medicine. (2019). *The ASAM principles of addiction medicine*. Wolters Kluwer.
9. Zuurmond, W. W., Meert, T. F., & Noorduin, H. (2002). Partial versus full agonists for opioid-mediated analgesia--focus on fentanyl and buprenorphine. *Acta Anaesthesiologica Belgica*, *53*(3), 193–201. https://pubmed.ncbi.nlm.nih.gov/12461829/#:~:text=However%2C%20there%20are%20significant%20differences
10. Heidbreder, C., Fudala, P. J., & Greenwald, M. K. (2023). History of the discovery, development, and FDA-approval of buprenorphine medications for the treatment of opioid use disorder. *Drug and Alcohol Dependence Reports*, *6*, 100133. https://doi.org/10.1016/j.dadr.2023.100133

References Con't

11. De Aquino, J. P., Parida, S., & Sofuoglu, M. (2021). The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clinical Drug Investigation*, *41*(5), 425–436. https://doi.org/10.1007/s40261-021-01032-7
12. Volpe, D. A., Tobin, G. A. M., Mellon, R. D., Katki, A. G., Parker, R. J., Colatsky, T., Kropp, T. J., & Verbois, S. L. (2011). Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. *Regulatory Toxicology and Pharmacology*, *59*(3), 385–390. https://doi.org/10.1016/j.yrtph.2010.12.007
13. Walsh, S. (2003). The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. *Drug and Alcohol Dependence*, *70*(2), S13–S27. https://doi.org/10.1016/s0376-8716(03)00056-5
14. Moss, L. M., Algera, M. H., Dobbins, R., Gray, F., Strafford, S., Heath, A., van Velzen, M., Heuberger, J. A. A. C., Niesters, M., Olofsen, E., Laffont, C. M., Dahan, A., & Groeneveld, G. J. (2022). Effect of sustained high buprenorphine plasma concentrations on fentanyl-induced respiratory depression: A placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients. *PLOS ONE*, *17*(1), e0256752. https://doi.org/10.1371/journal.pone.0256752
15. Bai, S. A., Xiang, Q., & Finn, A. (2016). Evaluation of the Pharmacokinetics of Single- and Multiple-dose Buprenorphine Buccal Film in Healthy Volunteers. *Clinical Therapeutics*, *38*(2), 358–369. https://doi.org/10.1016/j.clinthera.2015.12.016
16. Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., Ferri, M., & Pastor-Barriuso, R. (2017). Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*, *357*, j1550. https://doi.org/10.1136/bmj.j1550
17. Ray, L. A., Meredith, L. R., Kiluk, B. D., Walthers, J., Carroll, K. M., & Magill, M. (2020). Combined Pharmacotherapy and Cognitive Behavioral Therapy for Adults With Alcohol or Substance Use Disorders. *JAMA Network Open*, *3*(6), e208279. https://doi.org/10.1001/jamanetworkopen.2020.8279
18. Santo, T., Clark, B., Hickman, M., Grebely, J., Campbell, G., Sordo, L., Chen, A., Tran, L. T., Bharat, C., Padmanathan, P., Cousins, G., Dupouy, J., Kelty, E., Muga, R., Nosyk, B., Min, J., Pavarin, R., Farrell, M., & Degenhardt, L. (2021). Association of Opioid Agonist Treatment with All-Cause Mortality and Specific Causes of Death among People with Opioid Dependence. *JAMA Psychiatry*, *78*(9). https://doi.org/10.1001/jamapsychiatry.2021.0976
19. Raffa, R. B., Haidery, M., Huang, H.-M. ., Kalladeen, K., Lockstein, D. E., Ono, H., Shope, M. J., Sowunmi, O. A., Tran, J. K., & Pergolizzi, J. V. (2014). The clinical analgesic efficacy of buprenorphine. *Journal of Clinical Pharmacy and Therapeutics*, *39*(6), 577–583. https://doi.org/10.1111/jcpt.12196
20. Clark, N. C., Lintzeris, N., & Muhleisen, P. J. (2002). Severe opiate withdrawal in a heroin user precipitated by a massive buprenorphine dose. *The Medical Journal of Australia*, *176*(4), 166–167. https://pubmed.ncbi.nlm.nih.gov/11913917/

References Con't

21. Greenwald, M. K., Johanson, C.-E., Moody, D. E., Woods, J. H., Kilbourn, M. R., Koeppe, R. A., Schuster, C. R., & Zubieta, J.-K. (2003). Effects of Buprenorphine Maintenance Dose on μ-Opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-Dependent Volunteers. *Neuropsychopharmacology*, *28*(11), 2000–2009. https://doi.org/10.1038/sj.npp.1300251
22. Greenwald, M. K., Herring, A. A., Perrone, J., Nelson, L. S., & Azar, P. (2022). A Neuropharmacological Model to Explain Buprenorphine Induction Challenges. *Annals of Emergency Medicine*. https://doi.org/10.1016/j.annemergmed.2022.05.032
23. *Opioid Use Disorder*. (n.d.). https://www.bccsu.ca/wp-content/uploads/2022/02/Opioid-Use-Disorder-Practice-Update-February-2022.pdf
24. Casadonte, P., & Srivastava, A. (n.d.). *PCSS Guidance Topic: Buprenorphine Induction*. https://pcssnow.org/wp-content/uploads/2021/12/PCSS-GuidanceBuprenorphineInduction.Casadonte.pd
25. Randhawa, P. A., Brar, R., & Nolan, S. (2020). Buprenorphine–naloxone "microdosing": an alternative induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market. *Canadian Medical Association Journal*, *192*(3), E73–E73. https://doi.org/10.1503/cmaj.74018
26. *Take Home Suboxone (buprenorphine-naloxone)*. (n.d.). Retrieved February 22, 2024, from https://patienteduc.fraserhealth.ca/file/substance-use-take-home-suboxone-buprenorphine-na-420867.pdf
27. Herring, A. A., Schultz, C. W., Yang, E., & Greenwald, M. K. (2019). Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. *The American Journal of Emergency Medicine*, *37*(12), 2259–2262. https://doi.org/10.1016/j.ajem.2019.05.053
28. Huhn, A. S., Hobelmann, J. G., Oyler, G. A., & Strain, E. C. (2020). Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug and Alcohol Dependence*, *214*, 108147. https://doi.org/10.1016/j.drugalcdep.2020.108147
29. Kahan, M., Marion-Bellemare, L., Samson, J., & Srivastava, A. (2023). "Macrodosing" Sublingual Buprenorphine and Extended-release Buprenorphine in a Hospital Setting: 2 Case Reports. *Journal of Addiction Medicine*, *Publish Ahead of Print*. https://doi.org/10.1097/adm.0000000000001148
30. Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews*, *2*. https://doi.org/10.1002/14651858.cd002207.pub4

References Con't

31. Hser, Y.-I., Saxon, A. J., Huang, D., Hasson, A., Thomas, C., Hillhouse, M., Jacobs, P., Teruya, C., McLaughlin, P., Wiest, K., Cohen, A., & Ling, W. (2013). Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction*, *109*(1), 79–87. https://doi.org/10.1111/add.12333
32. Whelan, P. J., & Remski, K. (2012). Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. *Journal of Neurosciences in Rural Practice*, *3*(1), 45. https://doi.org/10.4103/0976-3147.91934
33. Herring, A. A., Perrone, J., & Nelson, L. S. (2019). Managing Opioid Withdrawal in the Emergency Department With Buprenorphine. *Annals of Emergency Medicine*, *73*(5), 481–487. https://doi.org/10.1016/j.annemergmed.2018.11.032
34. Chen, C., & Friday, B. (2021). *Alternative Buprenorphine Induction Strategies*. https://sites.rutgers.edu/mat-coe/wp-content/uploads/sites/473/2021/06/06.04-ECHO_FINAL-1.pdf
35. *"Gray Death" drug mixture reaches Indiana, puts first responders at risk*. (n.d.). Https://Www.wave3.com. https://www.wave3.com/2020/02/04/gray-death-drug-mixture-reaches-indiana-puts-first-responders-risk/
36. *Opioid Addiction a Guideline for the Clinical Management of*. (2015). https://www.bccsu.ca/wp-content/uploads/2016/10/opioid-addiction-guideline.pdf
37. Bisaga, A. (2019). What should clinicians do as fentanyl replaces heroin? *Addiction*. https://doi.org/10.1111/add.14522
38. *Buprenorphine for the Treatment of Opioid Dependence.pdf*. (n.d.). OCPInfo.com. Retrieved February 22, 2024, from https://www.ocpinfo.com/document/buprenorphine-for-the-treatment-of-opioid-dependence-pdf/
39. *Homepage*. (n.d.). META:PHI. Retrieved February 22, 2024, from https://www.metaphi.ca/
40. *CA Bridge*. (n.d.). Public Health Institute. Retrieved February 22, 2024, from https://www.phi.org/our-work/programs/california-bridge/

References Con't

41. Ang-Lee, K., Oreskovich, M. R., Saxon, A. J., Jaffe, C. A., Meredith, C., Mei Ling Ellis, Malte, C. A., & Knox, P. (2006). Single Dose of 24 Milligrams of Buprenorphine for Heroin Detoxification: An Open-label Study of Five Inpatients. *Journal of Psychoactive Drugs*, *38*(4), 505–512. https://doi.org/10.1080/02791072.2006.10400589
42. (2023). Bridgetotreatment.org. https://bridgetotreatment.org/resource/buprenorphine-bup-hospital-quick-start/
43. Kutz, I., & Reznik, V. (2001). Rapid Heroin Detoxification Using a Single High Dose of Buprenorphine. *Journal of Psychoactive Drugs*, *33*(2), 191–193. https://doi.org/10.1080/02791072.2001.10400484
44. Kutz, I., & Reznik, V. (2002). Heroin detoxification with a single high dose of buprenorphine. *The Israel Journal of Psychiatry and Related Sciences*, *39*(2), 113–119. https://pubmed.ncbi.nlm.nih.gov/12227226/
45. Palmstierna, T. (2004). Effects of a high-dose fast tapering buprenorphine detoxification program on symptom relief and treatment retention. *Journal of Psychoactive Drugs*, *36*(2), 273–277. https://doi.org/10.1080/02791072.2004.10399738
46. Wikipedia Contributors. (2019, December 19). *Provinces and territories of Canada*. Wikipedia; Wikimedia Foundation. https://en.wikipedia.org/wiki/Provinces_and_territories_of_Canada
47. Canada, H. (2021, July 22). *Safer supply: Prescribed medications as a safer alternative to toxic illegal drugs*. Www.canada.ca. https://www.canada.ca/en/health-canada/services/opioids/responding-canada-opioid-crisis/safer-supply.html
48. Gunn, C. (n.d.). *Alberta investing additional $60 million in addiction and mental health supports*. Lethbridge News Now. Retrieved February 22, 2024, from https://lethbridgenewsnow.com/2022/03/15/alberta-investing-additional-60-million-in-addiction-and-mental-health-supports/
49. *Opioid Agonist Therapy Gap Coverage Program | Alberta.ca*. (2024, January 17). Www.alberta.ca. https://www.alberta.ca/opioid-agonist-therapy-gap-coverage-program#:~:text=health%20benefits%20coverage.-
50. *Toward an Alberta model of wellness Recommendations from the Alberta Mental Health and Addictions Advisory Council A FRAMEWORK FOR TRANSFORMATIVE CHANGE*. (n.d.). https://open.alberta.ca/dataset/bf379eb9-bd13-42b3-ac5c-2220e9e72a97/resource/7a0338fb-ab4c-4681-beea-27fdcb20d56e/download/health-toward-an-alberta-model-of-wellness-2022.pdf

References Con't

51. *Alberta to invest $275M in addictions and mental health; advocates want outcomes data for recovery model*. (2023, February 21). Edmonton. https://edmonton.ctvnews.ca/record-breaking-addictions-and-mental-funding-to-come-but-advocates-ask-for-data-showing-recovery-model-is-working-1.6283264
52. *"This is the answer that we have": As opioid EMS calls spike, Smith touts "Alberta model" as solution*. (n.d.). Ground News. Retrieved February 22, 2024, from https://ground.news/article/this-is-the-answer-that-we-have-as-opioid-ems-calls-spike-smith-touts-alberta-model-as-solution
53. *About*. (n.d.). NATIONAL OVERDOSE RESPONSE SERVICE (NORS). https://www.nors.ca/about
54. *Opioid response – Options for care | Alberta.ca*. (n.d.). Www.alberta.ca. https://www.alberta.ca/opioid-response-options-for-care
55. Zobell, J. & Day, N. (2024). Virtual Access to Opioid Agonist Treatment in Corrections/Law Enforcement. Presented at the Custody and Caring Conference, Saskatchewan. February 21, 2024.
56. Virtual Opioid Dependency Program. (2023). Annual Utilization & Clinical Outcomes Report (2022/2023 Fiscal Year). Alberta Health Services.
57. Russell C, Nafeh F, Pang M, MacDonald SF, Derkzen D, Rehm J, et al. Opioid agonist treatment (OAT) experiences and release plans among federally incarcerated individuals with opioid use disorder (OUD) in Ontario, Canada: a mixed-methods study. BMC Public Health. 2022 Mar 4;22(1).
58. *Why every student should study computer science (opinion) | Inside Higher Ed*. (n.d.). Www.insidehighered.com. https://www.insidehighered.com/views/2019/10/28/why-every-student-should-study-computer-science-opinion