National Opioid Treatment Guideline

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Disclosure

No connection to pharmaceutical companies

Not Paid for this presentation

I was external reviewer for the BC Opioid Treatment Guideline and current reviewer for the National Guidelines

All information today is referenced to the BC guidelines and their references which as the template for the National Treatment Guidelines

Overview

- Introduction and defining problem
- Opioid Treatment Guidelines
- Withdrawal Management
- Opioid Agonist Therapy
- SROM (slow release oral morphine)
- Psychosocial and Residential Treatment
- Harm Reduction
- Stepped, Integrated care and Tapering
- Summary of Recommendations

Alberta Health

Opioids and Substances of Misuse

Alberta Interim Q1 Report 2017

Analytics and Performance Reporting Branch

April 7, 2017

Alberta Government

Apparent drug overdose deaths related to fentanyl[1]

- Updated data shows that in 2016, **349** individuals died from an apparent drug overdose death related to fentanyl.
- In the first six weeks of 2017, **51** individuals died from an apparent drug overdose death related to fentanyl. That compares to **28** who died in the same period in 2016.
- There continues to be a high number of apparent drug overdose deaths related to fentanyl in Alberta.

Figure 1: Number of individuals who died from an apparent drug overdose related to fentanyl[1] in Alberta, by week for the period of October 1, 2016 to February 11, 2017

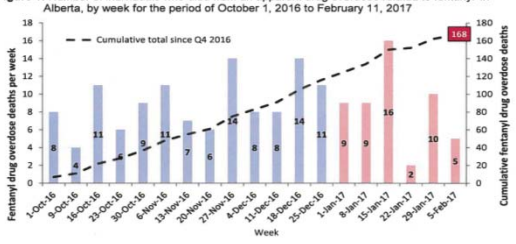


Table 1: Number and rate of fentanyl[1] related drug overdose deaths per 100,000 population.

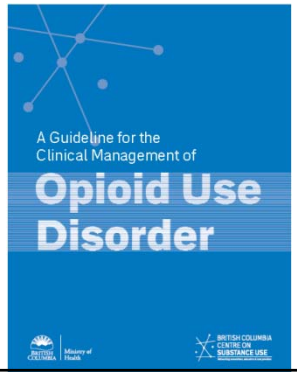
	2014		2015		2016		2017 YTD	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate
South	11	3.7	17	5.6	16	5.3	<5	1.3
Calgary	30	1.9	82	5.2	152	9.4	25	1.5
Central	13	2.8	34	7.1	37	7.7	<5	0.4
Edmonton	35	2.7	72	5.4	112	8.3	12	0.9
North	28	5.8	52	10.6	30	6.1	8	1.6
Unknown	0	--	0	--	2	--	0	--
Alberta	**117**	**2.9**	**257**	**6.1**	**349***	**8.2**	**51***	**1.2**

*Carfentanil was involved in 30 deaths in 2016, and 15 deaths in 2017, YTD.

YTD = January 1, 2017 to February 11, 2017

[1] fentanyl, norfentanyl, acetylfentanyl, 3-methylfentanyl, carfentanil, butyrylfentanyl

Clinical Management of Opioid Use Disorder



Evidence Selection and Review

- 180 references
- structured review of the literature
  - meta-analyses of randomized clinical trials
  - individual clinical trials,
  - observational reports
  - expert opinion
- Grading of Recommendations Assessment, Development and Evaluation (GRADE)
  - quality of evidence (study design, risk-benefit ratios, potential biases, scope and consistency of results)
    - Rated low, moderate or high
  - Strength of Recommendation
    - Rated weak or strong
- Committee recommendation, Internal and External Review of experts and stakeholders

Introduction and background

- Opioid Use Disorder ~ 2% prevalence in US
- Recent increase in OD and deaths
- Increasing potency of street opioids
  - Fentanyl and carfentanyl
- Public health concern
- Treatment for OUD remains inadequate
- No consistent approach
  - Withdrawal management only
  - Abstinence programs (outpatient and inpatient)
  - Methadone maintenance vs buprenorphine/naloxone
  - Naltrexone

Withdrawal management

Withdrawal management alone is not an effective treatment for opioid use disorder regardless of method used.

- Traditional rapid inpatient withdrawal (<7days) for other substances to reduce withdrawal complications like alcohol withdrawal seizures and DTs does not apply to opioids
- Rates of dropout and relapse to opioid use are high
- Loss of tolerance and relapse to current high potency opioids (fentanyl and its derivatives) results in increased overdose risk and deaths
- HIV and hepatitis C transmission, are higher for individuals who have recently completed withdrawal management compared to individuals who receive no treatment
- Treatment OAT recommended as first line

WITHDRAWAL MANAGEMENT

- Opioid withdrawal management should be a bridge to treatment,
  - access to long-term opioid agonist treatment (preferred)
  - intensive outpatient treatment or residential treatment with OAT
  - Intensive outpatient or residential treatment without OAT should be started immediately
- Patients who request withdrawal management alone
  - Should be provided with clear, concise information about the known risks to personal and public safety,
  - Engaged in supportive, constructive discussion about safer treatment options
  - Provided with harm reduction supplies and information
  - consider initiating buprenorphine/naloxone treatment to address withdrawal symptoms
  - And then slowly tapering under outpatient supervision.
  - Individuals who are unsuccessful with this approach may be offered agonist therapy again
  - For individuals resistant or inappropriate for OAT, long term outpatient slow tapering is less disruptive

PSYCHOSOCIAL TREATMENT INTERVENTIONS PROVIDED WITH OPIOID WITHDRAWAL MANAGEMENT

- Psychosocial treatment interventions may be beneficial adjuncts
- Insufficient evidence to favor any specific psychosocial treatment modality
- Currently limited evidence due to small study sample sizes and varying assessment and outcome measurements
- If withdrawal management alone is pursued, psychosocial treatment interventions likely do not protect against the elevated risk of HIV infection or fatal overdose

Opioid agonist treatments

- opioid agonist treatments are superior to withdrawal management alone
  - retention in treatment,
  - sustained abstinence from opioid use
  - reduced risk of morbidity and mortality
- choice of agonist treatment (methadone vs Buprenorphine/naloxone) depends on
  - comorbidities (liver disease, prolonged QTc interval)
  - drug–drug interactions,
  - treatment preference, and
  - Previous response
  - prescriber experience and appropriate authorization

Opioid agonist treatments should

- Incorporate provider-led counselling
- long-term substance use monitoring
  - regular assessment,
  - follow-up
  - urine drug tests
- comprehensive preventive and primary care
- Harm reduction strategies
- psychosocial treatment interventions
- psychosocial supports
- specialist care as required

Methadone

- Methadone more effective than non-pharmacological outpatient treatment
  - Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009(3):CD002209
  - higher doses (60–120 mg) more effective than lower doses
  - treatment retention
  - reducing heroin
  - higher methadone doses (> 75 mg/day) can be protective against overdose
  - reduce injection risk behaviors, hepatitis C and HIV
  - increased adherence to antiretroviral therapy

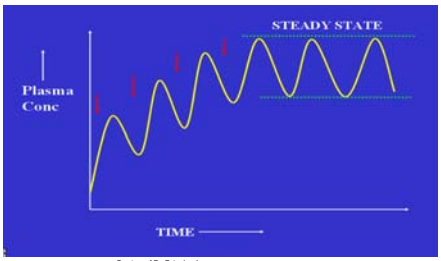
Methadone concerns

- Unique pharmacological properties
  - narrow therapeutic index, long elimination half-life
  - interactions with alcohol and other drugs
  - increase risk of toxicity and adverse events
- Methadone related emergency room visits occur 6 and 23 x higher than other prescription opioids
- In US methadone identified > 1/3 of prescription-opioid-related overdose deaths
- BC methadone identified in ~ 25% of prescription-opioid-related deaths
- Overall increase risk of overdose during initiation and stabilization
- Strict provincial standards and guidelines and requirement of daily dosing

Methadone Pharmacokinetics

- High oral bioavailability
- Tissue binding once absorbed
- Peak plasma 2 - 4 hours, oral administration
- ½ life of 24 - 36 hours

Methadone Steady State



Courtesy of Dr. Peter Lawlor

Buprenorphine

- Synthetic opioid for the treatment of opioid addiction
- France (1996), USA (2002), Canada (2010)
- Partial opioid agonist with a high affinity and slow dissociation for mu receptor
  - Ceiling effect – greater safety (low risk of respiratory depression)
  - Precipitated withdrawal because of high affinity for receptor
- Degree of physical dependence and withdrawal syndrome less severe.
- Less abuse potential but possible.
- Easier to switch from buprenorphine/naloxone to methadone,

20

Buprenorphine

- Available as sublingual tablets – combo with naloxone (Suboxone) There is low oral bioavailability
  - Sublingual buprenorphine has adequate bioavailability
  - Addition of naloxone decreases abuse potential for tablets (decreased iv use)
  - Sublingually
    - Buprenorphine will be well absorbed
    - Naloxone absorption will be minimal
  - Intravenously
    - Naloxone is 100% bioavailable
    - Precipitated withdrawal occurs in opioid-maintained patients

21

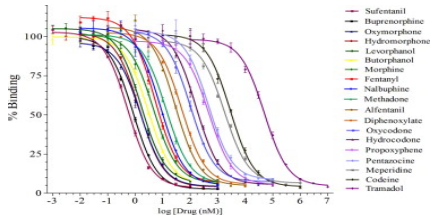


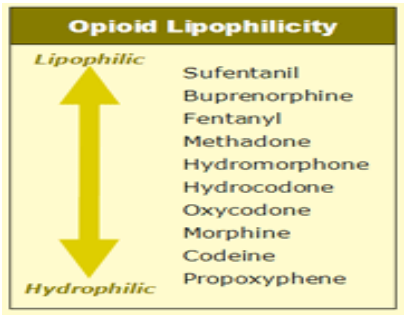
Fig. 3. Competitive binding data for opioid drugs. Symbols represent mean ± SE of three wells. Solid line is the nonlinear fit of the binding data.

Donna A. Volpe, Grainne A. McMahon Tobin, R. Daniel Mellon, Aspandiar G. Katki, Robert J. Parker, Thomas Colatsky, Timothy J. Kropp, S. Leigh Verbois

Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs ★

Regulatory Toxicology and Pharmacology, Volume 59, Issue 3, 2011, 385–390

http://dx.doi.org/10.1016/j.yrtph.2010.12.007



Buprenorphine effectiveness

Retention in Treatment

- Doses greater than 2 mg/day > placebo
- Compared to methadone,
  - Low doses (≤ 6 mg/day) < low doses of methadone (≤ 40 mg/day)
  - Medium doses (7–16 mg/day) and = medium doses methadone (40–85 mg/day)
  - High doses (≥ 16 mg/day) = high doses methadone (≥ 85 mg/day).

Reducing illicit opioid use

- Buprenorphine (>16 mg) = methadone
- Recent meta-analysis comparing buprenorphine and methadone for prescription opioid dependence reached similar conclusions

Older trials had not shown this due to low buprenorphine doses and slow induction rates. Newer studies show sublingual buprenorphine achieves equivalent outcomes to methadone when a sufficient dose, appropriate induction rate and flexible dosing are used

Buprenorphine safety

- Buprenorphine preferable in terms of reduced overdose potential.
  - UK study over 6 years 19 million prescription
    - buprenorphine was 6X safer than methadone for overdose risk

      Marteau D, McDonald R, Patel K. The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. BMJ Open. 2015;5(5):e007629
  - Methadone has a 4X higher risk of fatal overdose
    - 71. Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. Drug Alcohol Depend. 2009;104(1–2):73–77.
    - 72. Luty J, O'Gara C, Sessay M. Is methadone too dangerous for opiate addiction? BMJ. 2005;331(7529):1352–1353.
- Buprenorphine has a lower potential for respiratory depression
  - Standard doses are well below the threshold lethal dose for opioid-naïve adults
  - compared to standard methadone doses, which often exceed the threshold lethal dose.
- methadone has higher potential for adverse drug–drug interactions with many common medications (e.g., antibiotics, antidepressants, antiretroviral) and increased risk of cardiac arrhythmias as a result of QT prolongation

Buprenorphine disadvantages

- May not be appropriate for all patients
  - Intolerable symptoms during the partial opioid withdrawal that is required for initiation
  - Risk of precipitated withdrawal
  - Inpatient detoxification and treatment facility for more intensive monitoring, support and symptom management for patients with challenging inductions
- Potentially higher risk of drop-out
- Doses may be suboptimal for individuals with high opioid tolerance
- At high doses, may block the analgesic effect of concurrent opioid medications for pain

SLOW-RELEASE ORAL MORPHINE

- Since November 2014, slow-release oral morphine **(24-hour formulation, brand name Kadian®)** has been approved by Health Canada's Non-Insured Health Benefits (NIHB) Program for the treatment of opioid use disorder
  - Health Canada and Express Scripts Canada. NIHB Newsletter (Fall 2014): 1-4. Non-Insured Health Benefits (NIHB) Program. Released Fall 2014. Available at: http:// health.chiefs-of-ontario.org/sites/default/files/files/ Health Canada NIHB Pharmacy Newsletter Fall 2014.pdf. Accessed 13 Jan 2015
- Cochrane review three randomized trials
  - no difference in treatment retention to other OAT
  - higher incidence of adverse events compared to methadone
  - low number of studies included in the review limited conclusions
- Collectively less evidence regarding slow-release oral morphine in comparison to other opioid agonist therapies
- important to note that only the once-daily, 24-hour formulation of slow-release oral morphine has been studied for the treatment of opioid use disorder
- Other formulations of oral morphine have not been empirically studied and are not recommended for treatment of opioid use disorder

SLOW-RELEASE ORAL MORPHINE

- Providers should have Section 56 exemption from the *Controlled Drugs and Substances Act* to prescribe methadone
- Specialist consultation should be sought
- Practitioner who lacks experience prescribing slow-release oral morphine must consult a specialist
- Strict policies to prevent misuse, diversion and to ensure patient safety are required
- Regular scheduled and random urine drug testing required with GCMS/LCMS
- Daily witness dosing required and take home not recommended

Psychosocial Treatment Interventions and Supports

- Clinicians should provide medical management, general support and unstructured counselling
- Clinicians should be familiar with the principles of trauma-informed practice
- Consider undertaking cultural safety training for Indigenous clients
- Attention to assessing, treating and monitoring emotional and mental health is an essential component of care
  - high prevalence of concurrent medical and mental health diagnoses in substance use disorders
  - Evidence that inclusion of psychosocial treatment interventions can improve outcomes for individuals with concurrent and other mental health disorders
  - There are limited number of controlled studies of psychosocial treatment interventions for substance use disorders

Psychosocial Treatment Interventions and Supports

- The addition of psychosocial supports
  - helpful in supporting overall recovery in terms of improving individuals' psychosocial circumstances and survival needs.
- Although no systematic reviews have examined the impact of providing supports for various social needs (e.g., housing support, vocational and skills training, social supports, financial assistance),
  - previous studies have demonstrated housing and other survival needs may have a significant impact on opioid agonist treatment outcomes.
  - Benefit for opioid use disorder care being offered in interdisciplinary care teams that are equipped to address above needs.
  - Where patients have struggled to engage in care, intensive case management, peer navigation and outreach may also be effective at improving retention in addictions treatment.

Harm reduction strategies

- Harm reduction refers to policies, programs and practices
  - reduce the adverse health, social and economic consequences of licit and illicit substance use
    - needle/syringe distribution programs,
    - overdose prevention with take-home naloxone
    - supervised injection or consumption services
- No evidence that participation in any of the above services leads to increased opioid use or initiation of injection use
- Substantial evidence that harm reduction services
  - decreases in substance-related harms and risky behaviors, HIV and hepatitis C infection, and overdose deaths
- Harm reduction services is not treatment and can promote entry into addiction treatment which should be concurrently offered and encouraged

Residential Treatment

- No systematic reviews or meta-analyses on residential treatment programs for opioid use disorder and no large clinical trials comparing to other interventions
- Overall lack of evidence does not mean residential treatment is ineffective, but under-studied
- Observational cohort studies in the UK have found that relapse is relatively common following discharged from residential treatment for opioid use disorder
  - Smyth *et al.* (2010) reported after six-week residential treatment program in Ireland
    - 80% relapse within one month
    - 59% relapsed within one week
  - National Treatment Outcome Research Study (NTORS)
    - 57% heroin use within 30 days
    - 31% relapsing to regular heroin use at 1-year follow-up
  - NTORS at 4–5 years follow-up,
    - injecting rates dropped from 61% at intake to 29%
    - abstinence increased from 23.2% to 48.6%
    - improvements in safer injection practices, psychological and physical health, and reductions in criminal behavior

Residential treatment US data

- varied results
- One randomized trial in treatment outcomes for residential treatment
  - < 7 weeks no difference compared to no treatment
  - > 7 weeks, improved outcomes
    - increased likelihood of employment or enrolment in school,
    - decreased likelihood of criminal conviction or incarceration, and
    - decreased likelihood of heroin use
- An additional study found 4 week residential treatment decreased maladaptive cognitive and behavioral patterns that may contribute to ongoing substance use problems in adults with opioid use disorder
- Another randomized clinical trial found that a combination of community reinforcement and family training was associated with improved retention in treatment and reductions in opioid and other drug use
- providers should be aware of risks associated with loss of tolerance for patients who attend residential treatment programs when not using opioid agonist therapy (risk is 2 x)

naltrexone

- Naltrexone is an opioid receptor antagonist
- May increase the risk of overdose for patients who stop taking the medication and relapse to opioid use,
  - non-randomized study of naltrexone-associated mortality rates in Australia 3 to 7 X higher than methadone-related mortality rates
- Oral naltrexone (currently the only formulation available in Canada), have limited benefits over placebo
  - 2011 meta-analysis found no statistically significant differences in retention or abstinence rates for oral naltrexone compared to placebo or no treatment
  - Across studies, treatment retention rates were low with oral naltrexone treatment
- However, there are some circumstances where oral naltrexone may be an appropriate option
  - individuals who wish to avoid OAT who are highly motivated to stay abstinent, including individuals in safety sensitive positions that prohibit opioid agonist treatment
- Several randomized controlled trials have found that injectable naltrexone is superior to placebo in terms of improved retention in treatment, increased abstinence rates and decreased opioid cravings

Combination approaches and movement between approaches

- residential treatment facilities and opioid agonist treatment programs have often operated independently
- excluding participants on stable opioid agonist treatment from residential treatment create barriers
- Best approach is the integration of both strategies particularly for polysubstance users

STEPPED CARE STRATEGY

(comparing initiation on buprenorphine/naloxone and escalation to methadone if necessary) vs standard methadone treatment

- relatively superior safety profile of buprenorphine/naloxone (in the absence of concurrent alcohol or benzodiazepine use)
- ease of transitioning from buprenorphine/naloxone to methadone
- Improved cost of buprenorphine due to reduced need for daily dosing
- Result
  - stepped care approach was equally efficacious compared to optimally delivered methadone treatment
  - Conclusion that due to safety profile of buprenorphine that it be used as first-line treatment for opioid use disorder

TAPERING

- limited evidence to guide strategies for transitioning off agonist therapies
- majority of tapers from methadone treatment appear to be unsuccessful (approximately 87%)
- increased odds of success when doses are reduced gradually with longer periods
- Voluntary taper as shared decision more successful than forced tapering
- Large gap in evidence in this area and relies heavily in practitioner and patient relationship and evaluation of bio-psycho-social-spiritual stability
  - Go slow and continually monitor

Summary and recommendations

1. Withdrawal management alone (detoxification without immediate transition to long-term addiction treatment) is not recommended
2. Initiate OAT with buprenorphine/naloxone whenever feasible
3. Initiate OAT with methadone when treatment with buprenorphine/naloxone is not preferable
4. If withdrawal management is pursued, for most patients, this can be provided more safely in an outpatient rather than inpatient setting. During withdrawal management, patients should be immediately transitioned to long-term addiction treatment to assist in preventing relapse and associated harms
5. For individuals responding poorly to buprenorphine/naloxone, consider transition to methadone
6. For individuals responding poorly to methadone, or with successful and sustained response to methadone desiring treatment simplification, consider transition to buprenorphine/naloxone
7. For individuals with a successful and sustained response to OAT taper, consider slow taper (e.g., 12 months)

Summary of Recommendations

8. Psychosocial treatment interventions and supports should be routinely offered in conjunction with pharmacological treatment
9. For patients wishing to avoid long-term OAT, provide supervised slow (> 1 month) rather than rapid (< 1 week) inpatient opioid agonist taper
   - During withdrawal management, patients should be transitioned to long-term addiction treatment to prevent relapse and associated harms
   - Oral naltrexone can also be considered as an adjunct upon cessation of opioid use
10. For patients who have been unsuccessful with first- and second-line treatment options, opioid agonist treatment with slow-release oral morphine (prescribed as once-daily witnessed doses) can be considered
11. Harm reduction
    - Information and referral to take-home naloxone programs and other harm reduction services should be routinely offered as part of standard care for opioid use disorder

Thank You