Slaying the fentanyl dragon

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META:PHI
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PARTNERS IN HEALTH INTEGRATION

Recent experience with fentanyl users…

- I don’t cover the WCH RAAM clinic very often so have little experience with initiating OAT in fentanyl users
- A few weeks ago I saw two fentanyl users who were just started on methadone and SROM
- Methadone dose was 60 mg and SROM dose was 200 mg
- Both reported that methadone/SROM gave them no relief at all of withdrawal symptoms
- The man ‘nodded off’ during the visit, even though he had not yet taken methadone/SROM – had just taken fentanyl
- This was profoundly counter to my experience prescribing methadone to hundreds of patients over thirty-five years

Another experience (1)

- Fentanyl user contacted our service on the weekend – missed his appointment with his provider and needed a methadone script
- Just started methadone with a community provider but was often missing doses
- I suggested methadone + SROM and the following week he approached his provider about this who refused - “That’s not our practice”

Another experience (2)

- He switched to our service
- At the beginning I gave him a couple of carries per week because he was very far from his pharmacy
- He has done very well with methadone 120 mg + SROM 1000 mg

What does the literature say?

Rate of treatment drop out high, and climbing (Krebs 2021)

- Study of OAT discontinuations in BC (37,207 opioid users between 2012-2018)
- Monthly discontinuation rate 21.2% for bup/nal and 10.0% for methadone
- Overall monthly rate increased from 10.6% in 2012 to 14.9% in 2018

Risk of OAT drop out is greatest in first few weeks of treatment (Sadek 2022)

- Analysis of 1867 patients started on OAT in Nova Scotia
- 23% dropped out within first two weeks of treatment – no difference between methadone or buprenorphine/naloxone

Methadone has higher retention than bup/nal (Sadek NS; Gomes ON)

Opioid agonist	Median days to drop out	Hazards ratio drop out
Methadone	101 (NS), 265 (ON)	1 (NS, ON)
Bup/nal	58 (NS), 104 (ON)	1.61 (NS), 1.43 (ON)

OAT is highly protective against overdose (Gomes 2022)

	Overdose rate per 100 patient years (< 30 days of treatment)	Overdose rate/100 years (> 30 days of treatment)
Methadone	9.1	3.6
Bup/nal	4.9	1.9

OAT is highly protective against overdose

	Overdose rate after discontinuation (< 30 d after OAT start) (per 100 patient years)	Overdose rate after discontinuation (> 30 d after OAT start) (per 100 patient years)
Methadone	23.4	13.1
Bup/nal	20.3	18.9

Take-home doses improve treatment retention and reduce overdose death

- “Among individuals receiving daily dispensed methadone (n = 5852), initiation of take-home doses was significantly associated with lower risks of opioid overdose (6.9% vs 9.5%/person-year; weighted hazard ratio [HR], 0.73 [95% CI, 0.56-0.96]), treatment discontinuation (51.0% vs 63.6%/person-year; weighted HR, 0.80 [95% CI, 0.72-0.90]), and treatment interruption (19.0% vs 23.9%/person-year; weighted HR, 0.80 [95% CI, 0.67-0.95]) compared with no change in take-home doses.”

- Gomes T et al, Association Between Increased Dispensing of Opioid Agonist Therapy Take-Home Doses and Opioid Overdose and Treatment Interruption and Discontinuation. JAMA. 2022 Mar 1;327(9):846-855. doi: 10.1001/jama.2022.1271.

Conclusions and thoughts: Methadone

- First question is, why are drop out rates so high, especially in first 2-3 weeks?
- Based on my experience:
  - Fentanyl users experience minimal relief from methadone doses < 60-70 mg. So why should they go to the pharmacy every day when they can get immediate relief of withdrawal/cravings with fentanyl
- The standard methadone titration protocols may be too slow to keep fentanyl users engaged in treatment:
- Methadone 30 mg + 10-15 mg q 3-5 days,

Methadone (2)

- The gradual rate was designed to prevent toxicity from bioaccumulation, due to methadone's long half life
- But someone who feels nothing from 60 mg is not going to overdose if you increase the dose to 75 mg on day 2 rather than day 3
- Risk of drop out and subsequent overdose vastly exceeds the risk of methadone toxicity
- Accelerated protocol should be considered e.g. methadone 40 mg start, increase by 15 mg q 2 days
- Note: There are no guidelines or studies to support this more aggressive protocol

Methadone: Missed doses

- Current protocol: Reduce dose to 30 mg if five or more days missed
- There is no evidence to my knowledge to support this in fentanyl users – we just don't know
- This leads to a vicious cycle: Restart at 30 mg – patient doesn't bother to go to pharmacy every day because they get no relief from 30 mg – impossible to titrate to an effective dose
- ? Maybe reduce dose by 20 mg and increase again by 10 mg/day with frequent assessments
- This is "tolerance testing"

Buprenorphine

- Buprenorphine/naloxone has consistently been shown to have lower retention rates than methadone
- Should probably remain first line for prescription opioid users given safety profile
- But fentanyl users should probably be started on bup/nal and quickly switched to depot buprenorphine
- Depot bup has markedly higher and more constant serum level than bup/nal
- Higher serum levels have been shown in preclinical studies to offer greater protection against fentanyl induced respiratory depression

Buprenorphine (2)

- The combination of macrodosing bup/nal with early induction onto depot bup (within one day) appears to be safe and effective
- Louisa Marion-Bellemare, Julia Samson, Anita Srivastava and I are doing an observational cohort study on patients in Timmins General Hospital who were macrodosed in the ED, and induced onto depot bup within 1-2 days
- Preliminary results: No safety concerns; fentanyl users who are on depot bup had markedly reduced pre-post overdose rates
- Note: Treatment retention for depot bup has not been directly compared to bup/nal or to methadone

SROM as monotherapy

- RCTs used starting doses of up to 200 mg
- This is equivalent to about 25 mg methadone
- Since SROM bioaccumulation is not an issue, higher starting doses eg 4-500 mg might be considered for fentanyl users
- Note: No published evidence to support this

SROM combined with methadone

- SROM reaches a peak level around 10 hours post dose, just as methadone is wearing off
- Ontario OAT clinicians using this combination have reported good results – safe, effective
- But no published studies yet

Take-home doses

- Ontario study suggests that giving carries early in treatment may be warranted if it helps retain the patient in treatment
- Most patients on OAT intensely dislike daily observed dosing
- This may be a factor in treatment drop out especially if initial doses of methadone have minimal effect

What should we do?

- These recommendations are supported by little or no evidence
- They are contrary to current and past guidelines:
  - CPSO methadone guidelines
  - CRISM and other guideline groups
  - Established protocols in their own clinics
- The old guidelines were developed before the fentanyl era, for prescription users and heroin users
- They placed far greater emphasis on preventing methadone toxicity and diversion than on treatment drop out

What to do (2)

- We have to take steps to retain patients in treatment, despite the lack of evidence:
  - Dose more aggressively
  - Be more flexible with carries
- Risks and benefits of aggressive vs traditional dosing:
- Traditional dosing: Risks of treatment drop out and subsequent overdose death are very high
- Accelerated dosing: Risks of OAT toxicity are minimal

What to do (3)

- META:PHI is preparing a survey of OAT prescribers on their experiences with SROM and methadone + SROM
- The survey will ask about dosing protocols and the clinical outcomes they've observed
- In addition, clinicians need to write up case reports and case series
- And share their experiences through conferences, the META:PHI listserv and other venues

Thank you!

References

- Krebs E, Homayra F, Min JE, MacDonald S et al. Characterizing opioid agonist treatment discontinuation trends in British Columbia, Canada, 2012-2018. Drug Alcohol Depend. 2021; 225; 108799.
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- Gomes T et al, Duration of use and outcomes among people with opioid use disorder initiating methadone and buprenorphine in Ontario: a population-based propensity-score matched cohort study. Addiction 2022; Vol. 117 Issue 7 Pages 1972-1981