Initiation and Rapid Titration of Methadone and Slow-Release Oral Morphine (SROM) in an Acute Care, Inpatient Setting: A Case Series

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Case Report

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Abstract

Background: Methadone titration in an outpatient setting typically involves initiation with subtherapeutic doses with slow titration to mitigate the risks of respiratory depression and overdose. In pregnancy, subtherapeutic doses of methadone and slow titrations are associated with poorer outcomes in terms of retreatment retention and ongoing illicit opioid use. We aim to describe rapid titration of OAT in an inpatient setting for pregnant injection opioid users with high opioid tolerance secondary to a fentanyl-based illicit drug supply. *Methods*: Retrospective case series of patients admitted to a tertiary center with a primary indication of opiate withdrawal and treatment for severe opioid use disorder in pregnancy. *Results*: Twelve women received rapid methadone titrations with or without slow-release oral morphine for opioid use disorder during a total of fifteen hospital admissions. All women included in the study were active fentanyl users (12/12). Methadone dosing was increased rapidly with no adverse events with a median dose at day 7 of 65mg (IQR 60-70mg) and median discharge dose of 85mg (IQR 70-92.5mg). Slow-release oral morphine was used in half of the titration admissions (8/15) with a median dose of 340mg (IQR 187.5-425mg) at discharge. The median length of admission was 12 days (IQR 9.5-15). *Conclusions*: A rapid titration of methadone was completed in an inpatient setting with or without slow-release oral morphine, without adverse events showing feasibility of this protocol for a pregnant population in an inpatient setting. Patients achieved therapeutic doses of methadone (and/or SROM) faster than outpatient counterparts with no adverse events.

Background

The opioid crisis continues to be a significant public health concern globally with significant and increasing mortality risks(1–3). This has increased with the prevalence of fentanyl as the opiate used by those with opiate use disorder(4). Opioid agonist treatment (OAT) has been shown to be safe and effective treatment for opiate use disorder, significantly reducing the mortality risk associated with illicit opiate use(5, 6). The risk associated with titration of a full opiate agonist such as methadone in the first 30 days of titration has been the basis for titration protocols in many guidelines. However, much of the risk associated with early methadone titration is based on titration prior to the high prevalence of fentanyl(7–9).

An emerging second line OAT in patients involves treatment with slow-release oral morphine (SROM). SROM is an effective substitute for methadone or buprenorphine for those who fail first line treatment with methadone and / or buprenorphine or for those with dose limiting issues including QT prolongation(10). Observed doses of once daily SROM provide effective management of opiate withdrawal and manage opiate cravings(11). Emerging evidence for the use of slow-release morphine as an adjunct to typical forms of OAT is growing(11, 12).

Retention in treatment to an opiate agonist therapy reduce in mortality for those with opiate use disorder(13). Treatment satisfaction, and higher methadone doses have played a role in predicting treatment retention for patients stabilizing on methadone maintenance treatment (14). Given the higher potency of fentanyl to heroin, novel methods of initiation of methadone should be considered. Single case reports have shown safety of rapidly titrating methadone in an inpatient setting(15–18).

Pregnancy presents a unique circumstance where the titration of OAT and management of opiate withdrawal is considered a primary indication for hospital admission due to risk to the pregnancy and fetus(19, 20). In pregnancy, subtherapeutic doses of methadone and slow titrations are associated with poorer outcomes in terms of retreatment retention and ongoing illicit opioid use(21, 22). We aim to describe rapid titration of OAT in an inpatient setting for pregnant injection opioid users with high opioid tolerance secondary to a fentanyl-based illicit drug supply. This study aims to describe the safety and feasibility of rapid OAT induction within this population.

Methods

This case series aims to describe patients who had rapid methadone titration with and without the addition of slow-release oral morphine (SROM) titration in an inpatient setting where the primary indication for admission was rapid titration in the context of pregnancy. All Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)(23) reporting guidelines for cohort studies were incorporated into reporting of this case series. Ethics approval was granted by the St. Michael's Hospital Research Ethics Board (REB #20–093).

Setting

St. Michael's Hospital is a large, tertiary care institution located in some of Toronto's lowest income postal codes. There are high rates of patients with serious mental health, addictions, and homelessness in this geographic area. The consultation, inpatient perinatal addictions team can admit pregnant patients for stabilization of OUD with OAT at any gestation on the antepartum unit at the hospital. The patients are followed by addiction medicine as well as a primary care obstetrics team with expertise in substance use in pregnancy.

Inclusion Criteria

Inclusion criteria consisted of adult patients (> 18 years of age) with opiate use disorder admitted to hospital during their peripartum period for opiate withdrawal and titration of opiate agonist therapy (OAT). Cases were included if there was an admission to the antenatal unit for the purpose of initiating opioid agonist treatment as a new start or to restart opioid agonist treatment (after missed dosing necessitating a new start of OAT). Treatment refers specifically to methadone with or without the addition of sustained release oral morphine (SROM) or immediate release (IR) morphine. Admissions between January 1, 2016 and August 1st, 2020 were included in the study.

Exclusion Criteria

Predetermined exclusion criteria were admission for less than or equal to 3 days, which would not permit significant titration or monitoring. Notably, two cases were excluded, in order to avoid duplication, as they have been reported and published separately. Admissions for buprenorphine titration or rotation were also excluded.

Data Collection and Statistical Analysis

Demographic and clinical variables were obtained from the electronic and paper medical records from St. Michael's Hospital. Cases were still included if demographic or clinical variables were missing; however, all cases had complete medication administration records (MAR). Data collected included age at admission, gestational age at admission, sexually transmitted infections, bloodborne viral infections (HIV status and hepatitis C [HCV] status). Details regarding injection drug use were self-reported (substance, amount, and route) and compared to urine drug screen (UDS) results when available.

The MAR was used to determine the total daily dose of opioid agonist therapy (methadone and/or SROM) in addition to the total daily dose of opioids (including both scheduled and as needed (PRN) medications). Opioid agonist therapy is reported as the total daily dose but was administered with split dosing in some cases. Where available, the dose of OAT at the time of presentation to labor and delivery was recorded as an indicator of retention in treatment between titration and delivery (if admitted on a similar dose of OAT) or not retained in treatment (not currently receiving OAT at the time of admission for labor). A morphine equivalent of 8:1 methadone to morphine, as has previously been published and utilized in other methadone studies, was used for calculation purposes(24).

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as median with interquartile range (IQR) as the data are not normally distributed and from a small sample. Descriptive statistics

were performed using Excel 2019.

Protocol

The rapid methadone titration protocol was based on the inpatient methadone titration guidelines from the University of California San Francisco. The majority of patients were started on methadone 30 mg and titrated by 10 mg daily to a maximum of 70 mg at which time this dose was held for three days to reach steady state. After that time patients were offered a maximum of a 15 mg increase and held at this dose for a minimum of 5 days before another methadone dose was undertaken. When SROM was added an initial dose of 100 mg was added approximately 8 hours after methadone to avoid the peak effect of methadone. Given the high tolerance of our patient population, and to avoid withdrawal which may lead to obstetrical complications, standing doses of immediate release (IR) morphine 30–50 mg every two hours were provided with equivalent as needed doses available for pain, withdrawal, or cravings. Approximately every two days, 50% of the total morphine IR was converted to SROM and the standing dose of morphine was reduced until the patient was only on SROM (Fig. 1).

Results

Twenty-four admissions for opiate withdrawal were identified. Four patients had two titration admissions within the same pregnancy (one titration was excluded as the length of stay in hospital was 3 days). An additional admission was excluded as consultation was for continuation of methadone during antenatal hospitalization, and no titration in hospital was required. Other excluded admissions were postpartum titration (n = 2) buprenorphine inductions (n = 1) or scheduled opioid rotations to buprenorphine and oral morphine (n = 2). In total, 15 titration admissions were considered in 12 patients.

The mean age at admission was 31 (+/- 5.1 years). Demographic data is summarized in Table 1. Most patients reported polysubstance use (75%, 9/12), with crack-cocaine and/or methamphetamine use reported with opioid use in all cases. The self-reported opioid use and / or urine toxicology confirmed fentanyl as the opioid of choice in all patients. All patients used fentanyl via injection. Nicotine use was also common, with 83% of women reporting cigarette smoking (10/12). There were no women who reported concurrent alcohol use.

Table 1
Demographics

	N = 12 (n, %)	Median (IQR)
Age		30.5 (27-33.75)
Single	5 (42)	
No fixed address	6 (50)	
Income	7 (58)	
Social Assistance	1 (0.83)	
Employment	4 (33)	
Unknown		
Fentanyl use	12 (100)	
Injection use	12 (100)	
Prior OAT* **	6 (50)	
*** ever previously receiving OAT		

Table 1. Demographics of patients initiated on OAT in hospital.

All patients remained in hospital for the duration of their opioid agonist titration. Half of the women were starting OAT for the first time, with 6 women reporting previously receiving OAT (50%, 6/12). The median length of stay was 12 days (IQR 9.5–15 days). The median daily dose of methadone at discharge was 85mg (IQR 70-92.5mg), equal to 680 mg morphine equivalents (MEq). SROM was used as an adjunct for 9 titrations (60%, 9/15) and the median dose of SROM at discharge was 340mg (187.5–425). For women that had combined methadone and SROM, the median combined MEq was 1020 mg. Overall, women rarely missed doses of methadone in hospital (n = 2 titrations, each with a single missed dose when the patient was not present in the room). There were no significant adverse events including no sedation, respiratory suppression, or opioid overdose.

Table 2
Opioid Agonist Treatment

	Median (IQR)	N = 15 titrations (n, %)
Methadone (mg)	30 (30-42.5)	15 (100)
Day 1	50 (42.5–60)	15 (100)
Day 4	70 (65–75)	15 (100)
Day 8	85 (70-92.5)	15 (100)
Discharge Dose		
Slow-release oral morphine (mg)	110 (105–115)	2 (12.5)
Day 1	130 (87.5–200)	8 (50)
Day 4	260 (200–300)	8 (50)
Day 8	340 (187.5–425)	8 (50)
Discharge Dose		
Hospital Adverse events		0
Planned discharges		15/15
Patients seen in follow up		9/12
Maintained OAT until delivery		5/11*(45)
**Exclusion of incarcerated individual*		

Table 2. Doses and characteristics of OAT received by women who were initiated on rapid titrations.

Post-discharge from titration, 9/12 (75%) women were followed on an outpatient setting within a week of discharge. Of the 3 who did not follow-up as an outpatient after methadone titration, one of these women was incarcerated, one had delivered during admission and did not have postpartum follow-up, the last was lost to follow-up. Of the 9 women who had ongoing follow up on an outpatient basis, none had adverse effects of their OAT including sedation, or respiratory depression post-discharge.

Discussion

We describe a group of patients, highly tolerant to opioids and actively using illicit fentanyl, who were hospitalized for rapid methadone (+/- SROM) titration. Admissions to hospital for primary OAT titration are available only to pregnant patients in our geographical area. Therefore, this is a unique population where admissions for primary OAT titration in an inpatient setting are possible. The population identified in this study had evidence of psychosocial instability: over 50% were homeless, almost half were not partnered, and over 90% were unemployed and/or on social assistance. All women were actively using fentanyl via injection. To our knowledge, this represents the first case series of patients using fentanyl in pregnancy in which OAT was rapidly titrated, complementing a recent case study showing feasibility of this method of titration(17).

There is an emerging concern that current methadone guidelines internationally are inadequate to retain patients in care and reduce their illicit substance use, especially in light of the increase in highly potent fentanyl analogues (25). It is also felt that patients who use fentanyl are even less likely to experience methadone toxicity because of a high

degree of opiate tolerance(26). Fentanyl is associated with an increase in overdose deaths, and higher doses of methadone may be more protective against overdose death(27). Furthermore, higher doses of methadone (considered to be > 80mg/day) have been associated with reduced illicit drug use in non-fentanyl using pregnant populations(28). In pregnancy, doses over 60 mg of methadone are associated with better treatment retention and reduction in illicit substance use(29), however these data are not available for primarily fentanyl-using populations. It is reasonable to assume that higher doses may be required in fentanyl-using populations. Therefore, there is an urgent need for protocols that will allow rapid titration of methadone and full-opioid agonists that will stabilize patients on methadone equivalents in the 60–80 mg range as a minimum. Our protocol demonstrates that in an inpatient-setting we are able to exceed or meet this target more rapidly than as an typical outpatient titration would allow.

Guidelines, both national and international, have similar recommendations for initial dosing of methadone for opioid use disorder. Dose initiation in the WHO guidelines is suggested to be much lower than our local guidelines, with starting doses of less than 20 mg recommended (30). Local protocols for methadone titration in Canada, suggest an outpatient starting doses of 10-30mg with subsequent dose increases up to 10mg every 3–5 days (31). Locally, the fastest titration to a dose of 80mg of methadone requires a minimum of 15 days. It is often also difficult to get patients to a therapeutic dose of methadone due to limitations in outpatient protocols including missed doses, and missed appointments for titration. As such, many patients are maintained on subtherapeutic doses below 60–100 mg, which impacts continuation of OAT (30). Previous cases reported by our group have highlighted novel approaches to OAT where methadone and SROM were rapidly titrated (15–18). These rapid initiation and titrations have been reported in a non-pregnant patient as well as in pregnancy. Like these cases, there were no documented adverse events within this cohort of rapid titrations based on review of the medical charts, including no doses withheld secondary to sedation, respiratory suppression or overdose, and no in-hospital complications. All women remained in hospital for at least 7 days.

Treatment retention is challenging with patients with severe opioid use disorder. In non-pregnant patients, younger age, specific substance used (cocaine and heroin), lower doses of methadone, criminal activity or incarceration, and negative attitudes towards methadone are associated with reduced retention(32). Overall, methadone is associated with longer treatment retention and fewer relapses when compared to nonpharmacologic therapy, especially at doses greater than 60–80 mg daily(14, 30, 33, 34). Rates of discontinuation of OAT in pregnancy are generally cited to be in the 0–33% range and are higher in the post-partum period(34). In this study, discontinuation, as measured by the number of patients initiated on OAT in hospital and presenting in labour on OAT, was high in our patient population. Further research is needed to determine whether a) patients using fentanyl have higher discontinuation rates (particularly on doses < 80mg of methadone) and b) whether patients who inject drugs may have higher discontinuation rates as well. It is possible that these two factors play into the discontinuation rates seen in this study, but also the lack of housing, minimal financial and social supports may also play into the rates of discontinuation.

This is a descriptive study which describes a small number of cases, adding to three cases previously published in pregnancy(15–17) and one case in a non-pregnant individual(18). Limitations of this study include important pharmacokinetic considerations in pregnancy, with the physiologic changes in pregnancy impacting methadone dosing(35, 36). Specifically, methadone clearance increases in the third trimester which can cause withdrawal symptoms necessitating a dose increases as the pregnancy continues(35). The generalizability is low, given the availability of on-demand beds specifically for the purpose of rapid methadone titrations are rare and highly experienced inpatient addiction medicine clinicians are not available routinely in acute care hospital. We acknowledge that the treatment in these cases was not in keeping with current guidelines locally or internationally. However, given the increasingly toxic illicit opioid supply and associated morbidity and mortality, trialing aggressive and novel treatment

approaches in a monitored, acute care setting is warranted. There is no proposed protocol of how to titrate unstable pregnant women who are actively using fentanyl effectively on opiate agonist therapy.

Conclusion

This is the first case series to describe a novel and inpatient protocol for rapid titration of methadone using SROM as an adjuvant to achieve high morphine equivalents (and therefore evidence-based therapeutic doses) to prevent withdrawal and cravings in highly tolerant, pregnant patients with severe OUD. We provide additional preliminary evidence that rapid methadone titration (+/- SROM) can be accomplished in a monitored setting without sedation, respiratory depression, or overdose. We advocate for inpatient monitoring in rapid titrations, or close outpatient follow up in line with the previous case report of rapid titration(17, 18). Further research is needed to review the safety of rapid outpatient titrations and what criteria would be needed to consider outpatient titrations.

Abbreviations

OUD: opioid use disorder

OAT: opioid agonist therapy

SROM: slow-release oral morphine

HCV: hepatitis C virus

HIV: human immunodeficiency virus

MEq: morphine equivalents

Declarations

Ethics

Ethics approval was granted by the St. Michael's Hospital Research Ethics Board (REB #20-093).

Consent for publication

Not applicable

Availability of data and materials

The dataset used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

EL, ST, MN and LR contributed to the conception and design of the work. EL, ST, LR and ES contributed to the acquisition and analysis of data. EL, ST, MN, LR and ES contributed to drafting and revision of the manuscript. All authors have read and approved the final manuscript.

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Dr. Turner was affiliated with St. Michael's Hospital and the Department of Family Medicine, University of Toronto at the time of the cases (and admissions) and is currently affiliated with the Department of Family Medicine, McMaster University.

References

1. Krausz RM, Westenberg JN, Ziafat K. The opioid overdose crisis as a global health challenge. Curr Opin Psychiatry [Internet]. 2021 Jul 1;34(4):405–12. Available from: http://dx.doi.org/10.1097/YCO.0000000000000712
2. Chaillon A, Bharat C, Stone J, Jones N, Degenhardt L, Larney S, et al. Modeling the population-level impact of opioid agonist treatment on mortality among people accessing treatment between 2001 and 2020 in New South Wales, Australia. Addiction [Internet]. 2022 May;117(5):1338–52. Available from: http://dx.doi.org/10.1111/add.15736
3. Kuo Y-F, Baillargeon J, Raji MA. Overdose deaths from nonprescribed prescription opioids, heroin, and other synthetic opioids in Medicare beneficiaries. J Subst Abuse Treat [Internet]. 2021 May;124:108282. Available from: http://dx.doi.org/10.1016/j.jsat.2021.108282
4. Merianne Rose Spencer, Margaret Warner, Brigham A Bastian. Drug Overdose Deaths Involving Fentanyl, 2011-2016. National Vital Statistics Reports [Internet]. 2019 Mar;68(3). Available from: https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_03-508.pdf
5. Pearce LA, Min JE, Piske M, Zhou H, Homayra F, Slaunwhite A, et al. Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: Population based retrospective cohort study. BMJ [Internet]. 2020;368(March):1–13. Available from: http://dx.doi.org/doi:10.1136/bmj.m772
6. Krawczyk N, Mojtabai R, Stuart EA, Fingerhood M, Agus D, Lyons BC, et al. Opioid agonist treatment and fatal overdose risk in a state-wide US population receiving opioid use disorder services. Addiction [Internet]. 2020 Sep;115(9):1683–94. Available from: http://dx.doi.org/10.1111/add.14991
7. Pilgrim JL, McDonough M, Drummer OH. A review of methadone deaths between 2001 and 2005 in Victoria, Australia. Forensic Sci Int [Internet]. 2013 Mar 10;226(1–3):216–22. Available from: http://dx.doi.org/10.1016/j.forsciint.2013.01.028
8. Buster MCA, van Brussel GHA, van den Brink W. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. Addiction [Internet]. 2002 Aug;97(8):993–1001. Available from: http://dx.doi.org/10.1046/j.1360-0443.2002.00179.x
9. Cousins G, Teljeur C, Motterlini N, McCowan C, Dimitrov BD, Fahey T. Risk of drug-related mortality during periods of transition in methadone maintenance treatment: a cohort study. J Subst Abuse Treat [Internet]. 2011 Oct;41(3):252–60. Available from: http://dx.doi.org/10.1016/j.jsat.2011.05.001
10. Hämmig R, Köhler W, Bonorden-Kleij K, Weber B, Lebentrau K, Berthel T, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. J Subst Abuse Treat [Internet]. 2014 Oct;47(4):275–81. Available from: http://dx.doi.org/10.1016/j.jsat.2014.05.012

11. Beck T, Haasen C, Verthein U, Walcher S, Schuler C, Backmund M, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. Addiction [Internet]. 2014 Apr;109(4):617–26. Available from: http://dx.doi.org/10.1111/add.12440
12. Jegu J, Gallini A, Soler P, Montastruc J-L, Lapeyre-Mestre M. Slow-release oral morphine for opioid maintenance treatment: a systematic review. Br J Clin Pharmacol [Internet]. 2011 Jun;71(6):832–43. Available from: http://dx.doi.org/10.1111/j.1365-2125.2011.03923.x
13. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ [Internet]. 2017;357(20):j1550. Available from: http://dx.doi.org/10.1136/bmj.j1550
14. Villafranca SW, McKellar JD, Trafton JA, Humphreys K. Predictors of retention in methadone programs: a signal detection analysis. Drug Alcohol Depend [Internet]. 2006 Jul 27;83(3):218–24. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2005.11.020
15. Turner SD, Lurie E, Nader M. Rapid Methadone and Concurrent Slow-Release Oral Morphine Titration in a Pregnant Fentanyl User. Canadian Journal of Addiction [Internet]. 2021 Mar [cited 2022 Apr 18];12(1):29. Available from: https://journals.lww.com/cja/Abstract/2021/03000/Rapid_Methadone_and_Concurrent_Slow_Release_Oral.7.aspx
16. Griffiths S, Campbell DM, Caudarella A, Guimond T, Lamba W, Lurie E, et al. Use of Injectable Opioid Agonist Therapy in a In-Patient Setting for a Pregnant Patient With Opioid Use Disorder: A Case Report. J Addict Med [Internet]. 2020 Nov 23; Available from: http://dx.doi.org/10.1097/ADM.0000000000000776
17. Ickowicz S, McLean M. Case report: rapid inpatient methadone titration during pregnancy. J Subst Use [Internet]. 2021 Jul 15;1–4. Available from: https://doi.org/10.1080/14659891.2021.1953167
18. Hemmons P, Bach P, Colizza K, Nolan S. Initiation and Rapid Titration of Methadone in an Acute Care Setting for the Treatment of Opioid Use Disorder: A Case Report. J Addict Med [Internet]. 2019;13(5):408–11. Available from: http://dx.doi.org/10.1097/ADM.0000000000000507
19. Minozzi S, Amato L, Jahanfar S, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev [Internet]. 2020 Nov 9;11:CD006318. Available from: http://dx.doi.org/10.1002/14651858.CD006318.pub4
20. Wang MJ, Kuper SG, Sims B, Paddock CS, Dantzler J, Muir S, et al. Opioid Detoxification in Pregnancy: Systematic Review and Meta-Analysis of Perinatal Outcomes. Am J Perinatol [Internet]. 2019;36(6):581–7. Available from: http://dx.doi.org/10.1055/s-0038-1670680
21. Minozzi S, Amato L, Vecchi S, Davoli M. Maintenance agonist treatments for opiate dependent pregnant women. Cochrane Database Syst Rev [Internet]. 2008;(2). Available from: http://dx.doi.org/10.1002/14651858.CD006318.pub2
22. Burns L, Conroy E, Mattick RP. Infant mortality among women on a methadone program during pregnancy. Drug Alcohol Rev [Internet]. 2010;29(5):551–6. Available from: http://dx.doi.org/10.1111/j.1465-3362.2010.00176.x
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Int J Surg [Internet]. 2014;12(12):1495–9. Available from: http://dx.doi.org/10.1016/j.ijsu.2014.07.013
24. Eder H, Jagsch R, Kraigher D, Primorac A, Ebner N, Fischer G. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. Addiction [Internet]. 2005 Aug;100(8):1101–9. Available from: http://dx.doi.org/10.1111/j.1360-0443.2005.001128.x
25. Stone AC, Carroll JJ, Rich JD, Green TC. Methadone maintenance treatment among patients exposed to illicit fentanyl in Rhode Island: Safety, dose, retention, and relapse at 6 months. Drug Alcohol Depend [Internet]. 2018 Nov 1;192:94–7. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2018.07.019

26. Collett BJ. Opioid tolerance: the clinical perspective. Br J Anaesth [Internet]. 1998 Jul;81(1):58–68. Available from: http://dx.doi.org/10.1093/bja/81.1.58
27. Crabtree A, Lostchuck E, Chong M, Shapiro A, Slaunwhite A. Toxicology and prescribed medication histories among people experiencing fatal illicit drug overdose in British Columbia, Canada. CMAJ [Internet]. 2020 Aug 24 [cited 2020 Oct 29];192(34):E967–72. Available from: https://www.cmaj.ca/content/192/34/E967
28. McCarthy JJ, Leamon MH, Parr MS, Anania B. High-dose methadone maintenance in pregnancy: Maternal and neonatal outcomes. Am J Obstet Gynecol [Internet]. 2005;193(3):606–10. Available from: http://dx.doi.org/10.1016/j.ajog.2005.03.072
29. Wilder CM, Hosta D, Winhusen T. Association of methadone dose with substance use and treatment retention in pregnant and postpartum women with opioid use disorder. J Subst Abuse Treat [Internet]. 2017 Sep;80:33–6. Available from: http://dx.doi.org/10.1016/j.jsat.2017.06.005
30. World Health Organization. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. 2009. 110 p.
31. Centre for Addiction and Mental Health. Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder [Internet]. 2021. Available from: https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf
32. O'Connor AM, Cousins G, Durand L, Barry J, Boland F. Retention of patients in opioid substitution treatment: A systematic review. PLoS One [Internet]. 2020 May 14;15(5):e0232086. Available from: http://dx.doi.org/10.1371/journal.pone.0232086
33. Jones HE, Finnegan LP, Kaltenbach K. Methadone and buprenorphine for the management of opioid dependence in pregnancy. Drugs [Internet]. 2012;72(6):747–57. Available from: http://dx.doi.org/10.2165/11632820-000000000-00000
34. Wilder C, Lewis D, Winhusen T. Medication assisted treatment discontinuation in pregnant and postpartum women with opioid use disorder. Drug Alcohol Depend [Internet]. 2015 Apr 1;149:225–31. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2015.02.012
35. Shiu JR, Ensom MHH. Dosing and monitoring of methadone in pregnancy: Literature review. Can J Hosp Pharm [Internet]. 2012;65(5):380–6. Available from: http://dx.doi.org/10.4212/cjhp.v65i5.1176
36. Wolff K, Boys A, Rostami-Hodjegan A, Hay A, Raistrick D. Changes to methadone clearance during pregnancy. Eur J Clin Pharmacol [Internet]. 2005;61(10):763–8. Available from: http://dx.doi.org/10.1007/s00228-005-0035-5

Figures

		DAY 1	Day 2	Day 3	Day 4	Day 5	Day 6
Inpatient Perinatal Protocol	Methadone *	Start 40 mg	50 mg (↑10 mg)	60 mg (↑10 mg)	70 mg (↑10 mg)	70 mg	70 mg
	Morphine IR	30-50 mg PO q2h ** 30-50 mg PO q3h PRN ^ 20 mg IM PRN q15min ~	Continue Day 1	Hold standing doses Continue 30-50 mg PO q2h PRN ^ 20 mg IM PRN q15min ~	Continue Day 3	Continue Day 3	Continue Day 3
	Morphine SROM	None	Add 50% of Day 1 morphine as SROM @1600h	Continue Day 2 dose @1000h	SROM DAY 2 DOSE + ADD 50% of total morphine IR required on Day 3 @1000h	Continue Day 4 dose @1000h	SROM DAY 4 DOSE + ADD 50% of total morphine IR required on Day 5 @1000h
Outpatient Protocol[16]	Methadone	30 mg	30 mg	30 mg	45 mg	45 mg	45 mg

* Day 1 dose given on patient arrival, other days given in AM @1000h
** Standing while awake – HOLD if patient sedated or sleeping
^ PRN for mild withdrawal
~ PRN for severe withdrawal max 3 doses

Figure 1

Legend not included with this version