Improving Outcomes and Mortality from Fentanyl – MOUD split dose, Toxicology, Breastfeeding: Physiologic Changes & Methadone Considerations

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- No conflicts of interest to disclose

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- ML served as a research consultant receiving consultant fees from Berkshire Biomedical, Braeburn Pharmacueticals, and Journey Colab in the past 24 months.

Learning Objectives

- Describe pregnancy-related changes that affect methadone pharmacokinetics and OUD treatment
- Describe alternative methadone dosing strategies and their benefits and unknowns during pregnancy
- Describe experiences of people who took methadone during pregnancy

Physiologic changes in pregnancy

- Increased cardiac output
- Increased circulating blood volume
- Increased body fat and decreased protein levels
- Increased liver and renal blood flow
- Increased renal clearance
- Increased activity of many liver enzymes including CYP3A4 that metabolize bup and methadone (& UGT enzymes that conjugate bup and norbuprenorphine)
- These changes contribute to lower circulating concentrations of medication such that there may be a need for higher doses and/or split doses of methadone and buprenorphine during pregnancy

For review see: McCarthy JJ et al. 2021

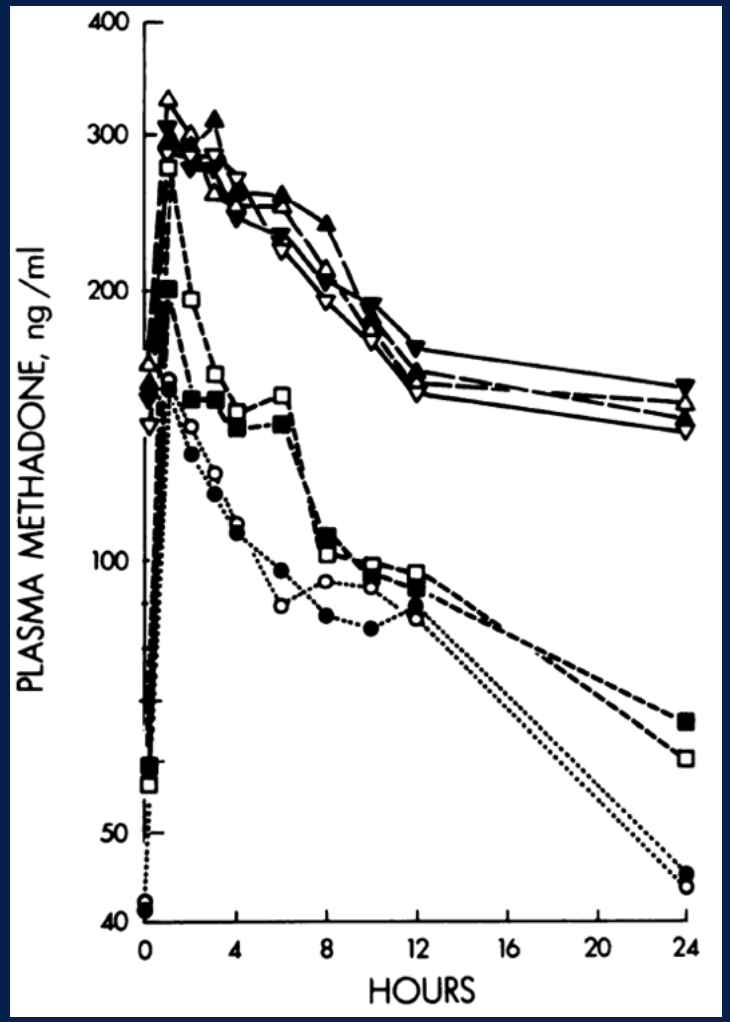
Changes with methadone

- Increases in estrogens and progesterone induce genes that code for enzymes that metabolize methadone to its inactive metabolite, EDDP, starting within first trimester and accelerating in later trimesters
- Methadone half-life speeds up by more than 2x
- Methadone doses will need to increase and ideally split into multiple daily doses
- Multiple daily dosing helps fetus to avoid high peak and low trough methadone concentrations that occur with once daily dosing and can results in fetal hypo- and hyper-activity, respectively
- Split doses helps mom and fetus avoid experiencing opioid withdrawal – a significant physiologic and psychologic stressor

For review see: McCarthy JJ et al. 2023

Serum Methadone During/Post Pregnancy

- Maintained on ~stable doses of methadone
- Starting & ending serum methadone levels lower during pregnancy
- Significantly higher 3-9 weeks after delivery



Pond et al., 1985

Split Dosing Less Disruptive of Fetal Measures

Table III. Fetal neurobehavioural measure by time and methadone dosing condition ($n = 40$).

	Single dose		Split dose		Time:trough to peak	Dose:split vs. single	Time × dose
	Trough mean (SD)	Peak mean (SD)	Trough mean (SD)	Peak mean (SD)	*F*	*F*	*F*
Heart rate (bpm)*	138.26 (8.56)	130.39 (8.75)	139.50 (9.98)	133.39 (1.29)	63.11***	6.60*	1.15
Heart rate variability[a]	5.93 (1.51)	4.11 (1.51)	6.27 (2.14)	4.58 (1.29)	61.60***	11.16**	0.22
Accelerations[b]	3.60 (3.24)	1.10 (1.88)	4.08 (4.09)	1.28 (1.82)	36.22***	2.08	0.18
Motor activity[b]	5.74 (2.12)	4.62 (1.41)	6.07 (2.38)	5.64 (2.21)	3.56	8.21**	0.83
FM-FHR coupling[c]	0.23 (0.09)	0.13 (0.09)	0.22 (0.09)	0.17 (0.10)	23.55***	1.95	7.73**

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Jansson et al., 2009

Reduced Severity of NOWS?

- N=62, all receiving 3-4 doses of methadone per day in equal doses
- Average daily methadone 152mg (20-415mg)
- Mean EGA 38.2w, Mean birthweight 2903g, 13% LBW, 18% premature
- 18 neonates (29%) required pharmacotherapy for NOWS
- Treated LOS 23.8d, Untreated LOS 9.8d

Mccarthy et al., 2015

Many Unanswered Questions

- Recent systematic review identified only 8 studies examining split-dosing of methadone in pregnancy
- No comparisons of any outcomes to single-dosed methadone
- No evaluations of concentrations in breastmilk, considerations postpartum, how to divide the dose (evenly or unevenly)
- Still – there is enough potential benefit to recommend considering split-dosing methadone

Khan et al., in preparation

Variability in Use of Split-Dosing

- OTPs vary in use of split dosing
- Physician/NP/PA knowledge
- Program concerns about diversion, risk
- Regulations limit unsupervised dosing, and varied interpretations

SAMHSA
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May 3, 2022

Dear State Opioid Treatment Authorities,

Dividing the dose of methadone or buprenorphine in two daily doses (also known as "split dosing") taken 10-12 hours apart, rather than a single daily dose, can help manage the impact of metabolic changes on serum levels, particularly for women in the third trimester of pregnancy.

The take-home flexibilities statement issued in March 2020 indicated: *The state may request a blanket exception for all stable patients in an OTP to receive 28 days of take-home medication and they may request up to 14 days of take-home medication for those patients who are less stable but who the OTP believes can safely handle this level of take-home medication.* Based on this guidance, a take-home exception is not automatically required to initiate or continue split dosing regimens. If exceptions are needed, they can be processed via the OTP Extranet at https://otp-extranet.samhsa.gov .

Included in Final 42CFR8 Rule

(3) *Special services for pregnant patients.* OTPs must maintain current policies and procedures that reflect the special needs and priority for treatment admission of patients with OUD who are pregnant. Pregnancy should be confirmed. Evidence-based treatment protocols for the pregnant patient, such as split dosing regimens, may be instituted after assessment by an OTP practitioner and documentation that confirms the clinical appropriateness of such an evidence-based treatment protocol. Prenatal care and other sex-

42 CFR Part 8, Effective April 2, 2024

What Are Patient's Experiences?

- N=59 people who took methadone during pregnancy
- 4 (7%) received a split dose in pregnancy
- 66% said medical staff talked to them about methadone and pregnancy interact
- 12% said nobody talked to them about it
- 44% knew a pregnant person metabolizes methadone more quickly
- 52% thought taking higher doses would address this

Hand et al., in preparation

What Do Patients Think?

- 73% thought split doses were a right vs. a privilege
- 73% thought split dosing should be based on medical need vs. treatment compliance
- 63% thought take-home doses not a diversion risk
- 27% thought they'd be a target for violence or theft
- 78% said they were confident asking to be evaluated for a split dose

Hand et al., in preparation

Final Takeaways

- Pregnancy induces changes in methadone and buprenorphine pharmacokinetics that necessitate increased and split doses.
- Split-dosing methadone is less disruptive to fetal neurobehavior and may confer maternal-neonatal outcome benefits, many unanswered questions
- Regulations much more forgiving, but a gap in knowledge and comfort exists to allow split-dosing
- Patients want it, and view treatment that meets their physiology as a right.

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