Note from the Planning Committee

Thank you so much for participating in this CME Activity! Please ensure that your presentation meets the following requirements:

- Includes a disclosure for every presenter
- Is free from commercial bias (uses generic rather than trade names, no logos, balanced discussion of therapeutic options)
- Uses language that is inclusive of all members of the health care team and is non-stigmatizing (eg, “provider” or “clinician” instead of “physician” and “patient” instead of “addict”)
- Uses 20 point font or higher for all content (except for references)

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Compassionate Care: The Scientific and Clinical Rationale for Methadone Split Dosing

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4/1/2022

#ASAMAnnual2022

Disclosure Information (Required)

Compassionate Care:
The Scientific and Clinical Rationale for Methadone Split Dosing during Pregnancy

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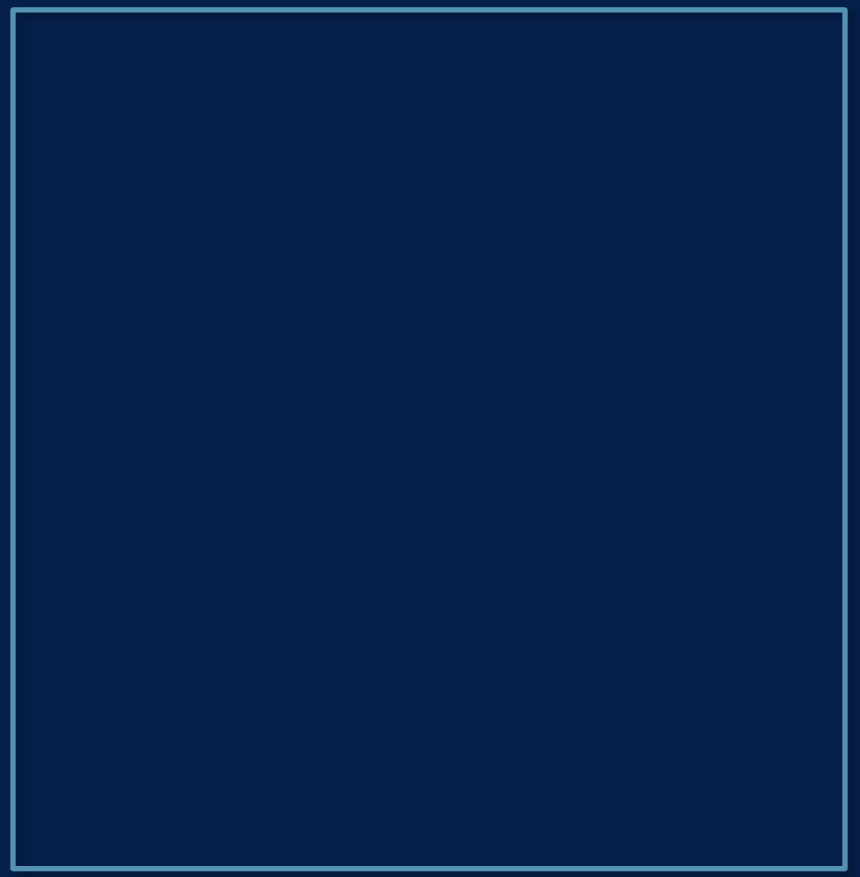
- NO DISCLOSURES



Learning Objectives

- Describe Methadone and rationale behind split dosing
- Describe split dose benefits for fetus, birthing parent and provider
- Describe Washington state pilot to standardize Methadone split dosing

"Whenever you face a tough question in biology just say enzymes. It is the correct answer to most questions in biology."

- Quote by Feng Zhang, CRISPER researcher, from his high school AP biology teacher
- From The Codebreaker, by Walter Isaacson on Jennifer Doudna and Emmanuelle Charpentier, Nobel laureates in Chemistry 2020 for developing a CRISPR gene editing tool

Pregnancy Questions

- **Why is dosing methadone in pregnancy more complicated and demanding than 'routine' methadone patients?**

ANS: enzymes

Why is divided dosing of methadone necessary for maternal/fetal stability?

ANS: enzymes

- **Why is the postpartum period especially important for monitoring serum methadone levels?**

ANS: enzymes

Pregnancy:
A Predictable Metabolic Gene Inducer

- Increases of progesterone during the luteal phase of the menstrual cycle induce transcription of the 2D6 enzyme. So, if conception occurs, the metabolic system is primed to accelerate metabolism. As pregnancy hormones increase, so does metabolism.

- The system is designed to protect the fetus from toxins. What we are dealing with, in trying to use medications in pregnancy, is an evolutionary system designed to frustrate us.

- We have to adapt. So how do we give medications in pregnancy to have them both safe and effective.

Problems Achieving Optimal Methadone Dosing

- Genetic variability of methadone metabolism is a clinical challenge at the extremes of the metabolic spectrum: ultra-rapid and ultra slow. Most non-pregnant patients (maybe only 70%) do well with once daily dosing based on just clinical assessment because they have a ½ life of about 24 hrs.

- However, ½ lives between 6 and 50 hours have been reported. When dosing is pharmacokinetically blind (the doctor doesn't know an individual's metabolism) some patients will be underdosed, reducing efficacy, and some will be overdosed, increasing risks.

- Optimizing MAT requires individualized science-based dosing, not regulation-based dosing.

- Assessing metabolic genes is not clinically useful. But, with therapeutic drug monitoring we can measure the net metabolic effect of all the genes involved.

https://pixabay.com/photos/baby-belly-body-child-expectant-18937/

Why Split Dose Methadone in Pregnancy Matters

- A pregnant patient has unique pharmacokinetics
  - Increased:
    - metabolism (maternal and placental, and fetal)
    - renal clearance of methadone
    - P-glycoprotein (multidrug resistance protein)
  - Altered pharmacokinetics decrease methadone concentration in serum and at the mu receptor

Federal Regulations Prevent Optimal Care of Pregnant Patients

Regulations presume a 24 hr ½ life, which is not the case during pregnancy. It's not true for perhaps 8% of non-pregnant. 6-12 hour is the norm for most pregnant patients. This translates into 3-4 x day dosing although all start twice daily.

Regulations restrict the dosing flexibility required to manage methadone under conditions of increasing clearance. Programs say they can't accept a transfer from hospital on divided doses or they can't divide doses more than BID which is not true. Use of multiple bottles is OK and 10mg tablets may also be fine

Regulations presume no one is to be trusted. "Compliance typically drops sharply with twice-daily dosing, diversion worsens, and costs increase" (Adinoff, Am J Psychiatry). There is an excellent rebuttal to this speculation

Reimagining patient-centered care in opioid treatment programs: Lessons from the Bronx during COVID-19.

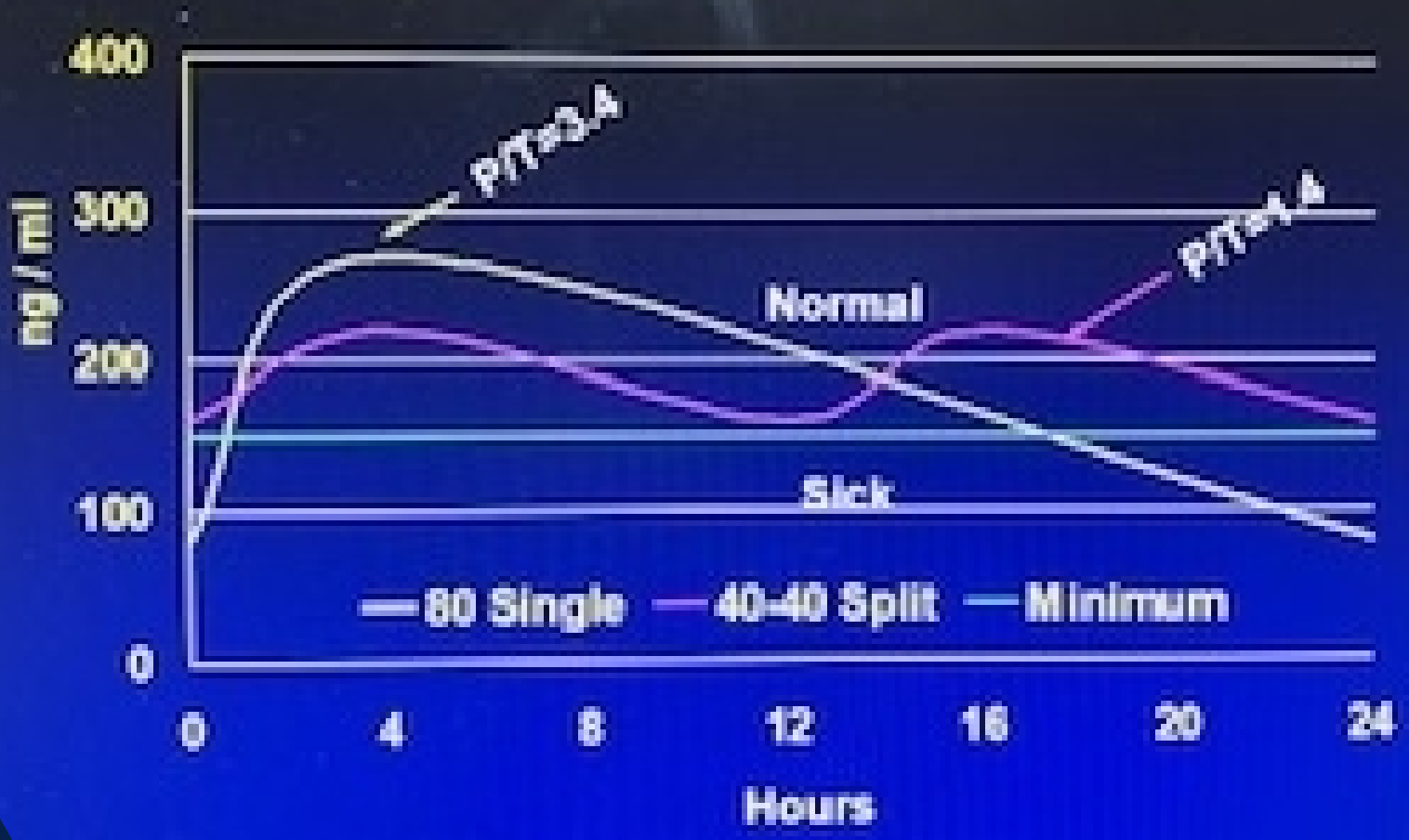
- Shift the focus away from rigid clinical guidelines and regulations; concentrate instead on patient-centered measures—engagement in care, and patient goals
- In deciding how to distribute take-home doses of MOUD, rely less on toxicology testing and more on patient-centered measures

https://pixabay.com/photos/mother-baby-parent-parenthood-951190/

Torres-Lockhart et al. Reimagining patient-centered care in opioid treatment programs: Lessons from the Bronx during COVID-19. *J Subst Abuse Treat*. 2021(Mar);122:108219. doi:10.1016/j.jsat.2020.108219

Pregnancy Case Study @ 6 mo.

"I wake up sick & my baby moves a lot!"



Split Dosing in Pregnancy: Maternal Benefits and Risks

Benefits

- **Safety**
  - Prevents over-sedation
  - Prevents potential QT prolongation
- **Efficacy**
  - Avoids insufficient trough levels = prevents withdrawal
- **Engagement**
  - Patient involvement in effective dosing = facilitates trust
- **Trauma-responsive**
  - A take-home dose reduces nighttime withdrawal fear

Risks

- **Diversion**
  - Someone could take the dose from her
- **Less Structure**
  - Taking the take home dose early might reduce stability

Therapeutic Drug Monitoring: Three Methadone Serum Laboratory Tests

Trough serum levels have established therapeutic ranges (V. Dole:150-600ng, other studies show 400ng for best efficacy). They reassure the mother (and the doctor) about fetal exposure. Methadone dose is not an accurate proxy for fetal exposure. Only the serum level measures fetal exposure.

Peak/trough ratio (PTR): Peak is 3-4 hrs after the AM dose and trough is just before the next AM dose. A ratio of serum methadone at peak divided by methadone at the trough of 2 or greater means ultra-rapid metabolism, e.g. 800ng peak/400ng trough =2. The drop of 400ng is too much to assure stability of mu receptor occupancy. A drop from 800 to 200 (PTR = 4) would cause major withdrawal.

Methadone/metabolite serum ratio (MMR) . The ratio of parent drug to its metabolite is a tool of pharmacogenetic research on genes coding for P450 enzymes that metabolize most medicines. That research has categorized drug metabolism as: Ultra rapid (URM), Extensive, normal (EM), Intermediate (IM), and Ultra slow (USM). All P450 substrate medications have a spectrum of metabolism because people have different metabolic genetics

What is the Methadone/Metabolite Ratio (MMR?)

- **A numeric ratio measuring the speed of conversion of methadone to its inactive metabolite EDDP. The average MMR range of randomly selected patients on methadone is roughly 10-13.**

- **The MMR measures a metabolic phenotype: the net effect of an individual's genes coding for the CYP 450 enzymes which metabolize methadone (e.g. 2B6, 3A4, 2D6, 2C9, 2C19, 1A2) expressed at the time of the test.**

- **The MMR is stable from day to day, but can change over days and weeks depending on induction or inhibition of genes by environmental factors, especially pregnancy and co-medications.**

The Use of the Methadone/Metabolite Ratio (MMR) to Identify an Individual Metabolic Phenotype and Assess Risks of Poor Response and Adverse Effects: Towards Scientific Methadone Dosing

McCarthy JJ, Graas J, Leamon MH, Ward C,
Vasti EJ, Fassbender C.

- San Diego Reference Lab, Dr. Joe Graas
- 1700 patient PTRs, i.e. 3400 paired peak/trough serum levels for methadone and EDDP
- The samples were ordered by physicians across the country, most likely suspecting rapid metabolism, but there was no patient information on any samples, i.e. dose or dose regimen
- The MMR stratified by established pharmacogenetic metabolic categories had distribution of:
  - ultra-rapid (URM, range <5) — percent URM of 3400 samples = 8.5%
  - extensive (EM normal, range 5-11) — percent EM = 65.5%
  - intermediate (IM, range 12-15) — percent IM =19%
  - ultra-slow (USM, range >15) — percent USM =7%

Changes in the MMR during Pregnancy and Post-partum

- **Average serum MMR in two studies of <u>non-pregnant</u> methadone maintenance patients is roughly 11-13**
- **First trimester mean 7.2**
- **Second trimester 5.9**
- **Third trimester 5.1**
- **Postpartum 7.2**

Split Dosing in Pregnancy: Fetal Benefits and Risks

Benefits

- Normalizes fetal movement
- Normalizes cardiac rhythm

Risks

- No risks to the fetus of divided doses, per se.
- If the mother's take home dose was taken from her, the fetus could experience some withdrawal

vectors/scales-balance-symbol-justice-36417/ Jansson LM, Dipietro JA J Matern Fe

Split Dosing in Pregnancy: Medical Provider Benefits and Risks

Benefits

- Increased **safety** of medication use
- Increased **efficacy** of medication use
- Better effective patient-provider **working relationship**
- Increased **patient cooperation** and feedback to improve stabilization
- Evidence for **improved urine sample compliance**
- **Reduced cocaine use**

Risks

- **Responsibility for providing take home doses** to patients new to treatment
- **Opposition** from internal organizational risk management
- **Increased time** spent with the patient which may not result in increased billing
- **Possible diversion** of take-home doses

DePetrillo P, Rice J. Int J Addict. 1995;30: 207–217.

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Rigid Regulations

Regulations presume a 24 hr ½ life, which is not the case during pregnancy

Regulations restrict the dosing flexibility required to manage methadone under conditions of increasing clearance

Changing Regulations that Harm Pregnant Patients (JAM 2020)

- Single dose methadone causes fetal physiologic abnormalities and maternal oversedation and withdrawal
- Regulations that impose barriers to appropriate, science-based dosing cause maternal and fetal harm
- There needs to be a pregnancy exception to Federal regulations that makes physician determination of dose and dose regimen the default, allowing for split dosing of all pregnant and post-partum women without regard for time in treatment or urine drug screens

Washington Pilot:
Standardize split dose for birthing and postpartum people

Regulations to embrace patient's Voice and choice; to offer split Methadone dose to every patient

Regulations to encourage the split dosing flexibility to manage methadone stability under conditions of increasing clearance

Final Takeaways/Summary

- Provider education and state rules facilitate safe care and evidence-based medication regimens
- Pregnant people deserve compassionate care that responds to changing pharmacokinetic needs
- Methadone split dose facilitates healthy outcomes for birthing people and newborns

https://pixabay.com/photos/mother-son-family-mom-baby-love-5469312/

References (Required)