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Pharmacologically-based Strategies for Opioid Substitution Therapy During Pregnancy

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Specific Aim 4

Specific Aim 4 compares dose reduction strategies for Suboxone or Subutex in pregnancy that are based on the pharmacodynamic and pharmacokinetic characteristics of BUP.

a) Primary Research Questions

1. Is adherence during dose reduction influenced by the magnitude or frequency of a given dose reduction?
2. Is adherence during dose reduction influenced by dosing frequency?
3. Does mu receptor sensitivity change during dose reduction?

b) Eligibility Criteria

Inclusion Criteria – must meet all of the following:

1. On a stable BID, TID or QID dosing regimen of BUP for at least 2 weeks as part of an established medication- assisted treatment (MAT) program.

2. Willingness to undergo supervised dose reduction

3. Subjects on BID, TID or QID dosing, willing to be assigned to the Magnitude, Frequency, or Dosing group, depending on their current dosing

4. Single gestation between 14-30 weeks at the initiation of dose reduction

5. On a BUP dose between 6- 24 mg daily (lower doses will not provide sufficient data points)

6. Willingness to have urine samples tested for drugs of abuse and blood samples tested for BUP+M concentrations during the Medical Supervised Withdrawal (MSW) clinic appointments

7. Willingness to attend weekly or biweekly MSW clinic appointments and to have daily contact via text messaging to complete daily logs of sleep quality, withdrawal symptoms and symptoms of craving. Subjects may consent to receiving daily text messages with a link to a REDCap where they can complete the daily questionnaires electronically. Alternatively, they may complete hard copies of the questionnaires and return them during their weekly clinic visits.

8. Willingness to attend psychosocial support meetings, as needed.

Exclusion criteria – cannot meet any of the following:

1. Current use of cocaine, heroin, benzodiazepines, barbiturates, phencyclidine (PCP), or opioids other than BUP

2. Currently taking more than two mental health medications

3. Active moderately severe depression (PHQ-9 score ≥15 or suicidal ideation)
4. Current incarceration
5. Lack of a phone or transportation to and from clinic.
6. Major fetal malformation
7. Mother with significant vaginal bleeding or serious medical or obstetrical complication that could adversely affect study
8. Planned delivery at another institution
9. HIV or AIDS
10. Diagnosis of schizoaffective disorder or psychosis

c) Pre-Study Screening

The following information will be obtained for consented patients 1-2 weeks prior to initiation of the dose reduction:

1. Demographic information: age, race, weight, height
2. Medical history: medical disorders, mental health disorders
3. Obstetrical history, including the outcome of all prior pregnancies
4. Social history: alcohol, tobacco, and illicit drug use
5. Depression Screening (Patient Health Questionnaire-2 (PHQ-2) and Patient Health Questionnaire-9 (PHQ-9), if necessary)
6. Intake questionnaire
7. Concomitant medications – Subjects who use withdrawal mitigating agents such as Benadryl or clonidine will not be excluded from the study. Research staff will track the use of all concomitant medications.
8. Project gestational age and estimated date of delivery
9. Vital signs: blood pressure, heart rate, respiratory rate
10. Maternal blood work: BUN, creatinine, albumin, total protein, ALT, AST, BUP + M concentrations, maternal DNA for drug metabolizing enzymes, and PBMC analysis (Pitt site only), (the first sample for PBMC analysis may be drawn at any time during pregnancy)
11. Urine sample will be collected and tested for the presence of drugs of abuse.
12. Obtain routine medical record release forms and review procedures for the upcoming study visit.

Notes:

- *BUN, creatinine, albumin, total protein, ALT, and AST will not be performed if results are available in the subject's medical record as part of the standard of care during this pregnancy or if testing was performed during a previous Pre-Study Screening.*

d) Study Design

The pharmacologic properties of BUP that inform this specific aim include a long half-life that suggests that any dose reduction should not occur more often than every 5 days to allow the impact of that dose change to manifest. The long half-life also suggests that a higher reduction (i.e. 2 mg) will be well tolerated as the reduction in drug exposure (i.e. the reduction in plasma concentrations over time) will be gradual over the ensuing 5 days till a new steady state is reached. The third PK and PD characteristic of BUP is that plasma concentrations are better sustained above a specified critical value with more frequent dosing.[51] Based on these pharmacologic characteristics of BUP, we will evaluate three strategies for supervised dose reduction. We will recruit 3 groups of pregnant women who are on a stable dose of BUP and are committed to supervised dose reduction. Recruitment will occur in our Pregnancy Recovery Center (PRC), from offices of other BUP writers, and from the Emergency Department (ED) at Magee. We will also enlist Dr. Craig Towers, MD at High Risk Obstetrical Consultants, in Knoxville, TN to assist in recruitment of eligible subjects at his institution for Specific Aim 4 only, pending IRB approval. Dr. Towers is an expert in dose reduction/detoxification during pregnancy and has published extensively on this topic. Dr. Towers will adhere to this multicenter protocol and Data Safety Monitoring Plan and report periodically to Dr. Caritis.

At MWH, pregnant women with an opioid use disorder generally come for initiation of methadone or BUP as part of a MAT program. They often present to the ED and are told to contact the PRC if they wish to start BUP or they are admitted if experiencing withdrawal for transition to methadone. Those who prefer to initiate treatment with Suboxone or Subutex will be targeted for recruitment. Dr. Towers is a primary provider at High Risk Obstetrical Consultants for opioid dependent women and we structured our dose reduction strategy based on his experiences.

Consenting subjects will be assessed for depression at the Pre-Study Screening. The Patient Health Questionnaire-2 (PHQ-2) will be administered as a screen for depression. If the PHQ-2 score is 3 or greater, major depressive disorder is likely and subjects will be further evaluated with the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression.

- A PHQ-9 score of ≥ 15 represents moderately severe depression. Subjects with a score of ≥ 15 at the Pre-Study Screening will be excluded from participating in the study and will be referred to a mental health provider.

Note: Question 9 on the PHQ-9 is a single screening question on suicide risk. If a subject answers yes to question 9, they are ineligible to continue with the study and will be immediately referred to a mental health provider for further assessment.

Once recruited subjects are on a stable dose of Suboxone or Subutex for 2 or more weeks, we will initiate one of three dose reduction strategies. We will compare tolerance in the same person to an alternating 1 mg vs 2 mg weekly reduction (Magnitude group, n=10). In a second group (Frequency group, n=10) we will compare tolerance in the same person to an alternating 2 mg reduction occurring weekly vs bi-weekly. All subjects in the Magnitude and Frequency groups will be on TID or QID dosing. In a third group (Dosing Group, n=10) we will compare tolerance to either the Magnitude or Frequency reduction schedule in women who are on a BID dosing regimen. The comparisons in these three groups will address those fundamental questions required for development of a rational dose reduction strategy. Each of these strategies addresses a specific question about maternal accommodation to the specified dose change. The dose reduction magnitude of 1 mg vs 2 mg and the frequency of reduction of weekly vs bi-weekly selected are based in large part on the work of Sigmon et al.[47] but larger and more frequent reductions could be considered. We chose this modest reduction strategy as we were concerned that more aggressive changes could lead to subject withdrawal and dissatisfaction. In the study of Sigmon et al.[47], only 50% of participants were opioid abstinent with the 4-week taper (i.e.1.75 mg per week). We believe a slower taper regimen could improve upon this outcome. Table 1 provides an example of the dose reduction strategy assuming, as an example, a starting dose of 16 mg daily. Subjects on TID or QID dosing will be assigned to either the Frequency or Magnitude groups based on their current dosing. Subjects on BID dosing will be assigned to the Dosing group.

- Subjects assigned to the Frequency group will have dose reductions of 2 mg on alternating intervals of 1 and 2 weeks.
- Subjects assigned to the Magnitude group will have alternating reductions of 1 then 2 mg every week.

- Subjects in the BID group will be assigned to the Dosing group. The Dosing group may follow the Magnitude (alternating 1 mg and 2 mg dose reductions weekly) or Frequency (2 mg dose reductions on alternating intervals of 1 and 2 weeks) dose reduction schedules.

In all groups, the alternating approach will continue until the subject is Suboxone or Subutex free or at the lowest dose tolerable. We appreciate that some subjects may not tolerate the recommended dose reduction especially at the lower doses. Subjects that experience withdrawal symptoms may be treated with ancillary medications such as Benadryl or clonidine. To minimize any risk of relapse, subjects who are intolerant to a given reduction will be allowed to go back to the last tolerated dose taken prior to the reduction. Visual Analog Scale (VAS) scoring will document their intolerance and this, combined with pharmacological data from the subject, will inform our development of an optimized pharmacological approach to dose reductions. After the subject has been on the higher dose for one week we will re-initiate the dose reduction strategy to which she was assigned. We will repeat this process one more time and if she remains intolerant to further dose reductions, we will not attempt further reductions but rather will maintain her on her current dose. If the subjects desires additional attempts at dose reduction, we will accommodate her request. At this time, she may elect to re-initiate the original dose reduction strategy or select an alternative reduction strategy. For all subjects, we will continue the surveillance approach we have in place throughout the pregnancy, delivery, and into the postpartum period.

In all 3 groups, daily adherence, cravings and sleep measures will be compared within and across groups. During the Pre-Study Screening, we will explain the study to the subject and ask that she completes an Intake Questionnaire to better understand any previous experiences she may have had with opioid treatment or detox programs. We will also perform urine and blood testing to assure all entry criteria are fulfilled. Once consent is obtained, we will initiate a Suboxone or Subutex dose reduction schedule similar to the one shown in Table 1. To ascertain the impact of a dose change, all subjects will complete 4 daily VAS questionnaires similar to those used by Dunn et al. [46] to assess withdrawal, cravings, sleep duration and sleep quality. The scales will range from a score of 0-10 for each question. Subjects that wish to be contacted via text will be sent a daily text with a link to the REDCap website where they can complete the VAS

questionnaire electronically throughout the dose reduction process. Subjects that are unable to receive daily text messages will be provided hard copies of the VAS questionnaire and instructed to return the completed forms to research staff at their next appointment. Clinic visits will occur weekly or biweekly at which time we will monitor plasma BUP+M, neurotransmitter and cotinine concentrations and perform a comprehensive urinary toxicology test. Additionally, at each clinic visit we will administer the Weekly Follow-up and Weekly Smoking and Alcohol Use questionnaires. We will also collect any completed VAS forms, if applicable, and perform COWS and Subjective Opioid Withdrawal Scale (SOWS) scores to assess current clinical and subjective symptoms of withdrawal and satiety. All subjects will receive psychosocial support, as needed. The timing of the subject's scheduled visits will be determined by their healthcare provider.

Since our focus is to assess whether the magnitude of the dose change, frequency of dose change and dosing frequency impact adherence during reduction, this pharmacodynamic study will be completed when the subjects are off BUP entirely or on the lowest tolerable dose. However, we will continue to see the subjects weekly or biweekly, monitor their adherence and continue to provide counseling sessions, as needed, until the 6-week postpartum visit. We will also evaluate peripheral blood mononuclear cells (PBMCs) as a surrogate marker of metabolic enzymes and transporters. The expression of drug metabolizing enzymes and transporters in the PBMCs will be correlated with the plasma concentrations of BUP and its major metabolites. Two maternal blood samples will be drawn for PBMC analysis; one during pregnancy and one in postpartum. The first sample will be drawn during the Pre-Study Screening; however, if this is not possible, it may be drawn at any time during pregnancy. The second sample will be drawn at 4-6 weeks postpartum, but as close as possible to the 6-week postpartum visit.

For subjects not enrolled in specific aim 3a or 3b, we will collect a cord blood sample at the time of delivery as well as maternal and newborn hair within 3 days of delivery, when possible. An additional cord blood sample (10 mL) will be drawn for genetic studies related to metabolizing enzymes, if the mother consents. The minimal amount of hair needed is 20 mg but we will ask for 100 mg which is still a very small amount. Hair will be removed from the mothers and baby's head (if consent is granted). Mother will decide where the hair will

be removed from her and her baby. The collection of these samples will be described in full detail during the consent process.

Note: Subjects that consent to participate in specific aims 3 (Parts 1 or 2) will already have the cord blood and hair samples collected as part of that specific aim. The collection of these biological samples only applies to those subjects not already enrolled in specific aim 3.

Table 1.

Dose Reduction Schedules if Start Dose is 16 mg Daily			
Group	**Frequency**	**Magnitude**	**Dosing**
Strategy	Reduce dose by 2 mg weekly then biweekly, repeat till dose=0 or at the lowest possible dose	Reduce dose by 1 and then 2 mg weekly, repeat above till dose=0 or at the lowest possible dose	May elect either the Frequency or Magnitude dose reduction schedule.
Dosing Frequency	**QID or TID**	**QID or TID**	**BID**
	Dose		
Week 1	16	16	Refer to the appropriate dose schedule in the Frequency or Magnitude columns
Week 2	14	15	
Week 3	14	13	
Week 4	12	12	
Week 5	10	10	
Week 6	10	9	
Week 7	8	7	
Week 8	6	6	
Week 9	6	4	
Week 10	4	3	
Week 11	2	1	
Week 12	2	0	
Week 13	0	0	

e) Statistics

The outcome(s) of interest are the pharmacodynamic endpoints that reflect the acclimatization of the mu receptors and opioid-affected brain functions. Each subject in a group will undergo alternating treatments to minimize any between subject differences that would impact the response to the decrease in dose. In this study, we will rely on scores from the self-administered VAS questionnaires. We will determine both an average and highest value for each of the VAS questionnaires weekly. The average values over the 7 days of

that given dose from the VAS questionnaires will be combined to create a single score for each week. A similar approach will be taken for the highest rather than average values. Based on the study of Dunn et al [46,47], the mean value for the withdrawal VAS questionnaire (scale 1-10) in non-pregnant subjects was 30 with a standard deviation of ~25. These values are estimates since graphs were provided but not tabular data. A difference of 25% in the VAS combined scores between any of the comparisons would seem clinically meaningful. Thus, a sample size of 10 in each group is sufficient to detect a difference in VAS scores between any of the comparison groups. The comparisons in the Frequency group will be VAS scores between the 1 vs 2 week reductions. The comparisons in the Magnitude group would be VAS scores between the 1 and 2 mg reductions. The comparison in the Dose group will be a comparison of the VAS scores during the 1 mg and 2 mg reductions. Also, VAS scores in the Dose group will be compared to the VAS scores in the Magnitude group both at the 1 and 2 mg reductions. The change in mu receptor sensitivity will be determined by comparing the BUP+M concentration each week to the subjects VAS scores on craving and withdrawal symptoms. In women who supplement their weekly BUP regimen with other opioids detected at the weekly clinic visits their VAS questionnaires on withdrawal and craving will be scored as 100. Assay Methods: BUP+M will be assayed using UPLC-MS-MS. We have developed and validated this assay and with the new TQS system the LOQ is 15 ng/ml in plasma. BUP in hair and other tissues will be measured by modification of this method and incorporating elements of methods reported in the literature [30,31,33]. Cotinine will be measured by minor modification of the published method [55].

Anticipated sum of mean VAS scores	Percent Reduction in VAS scores	Sample Size
120	0.15	25
120	0.20	15
120	0.25	10
120	0.30	7

D. Study Procedures

D.1 Screening for Eligibility

The inclusion/exclusion criteria will be reviewed with the patient's chart. Any woman who appears to be eligible will be informed about the study. If a patient appears to meet the criteria for enrollment and expresses interest in the study, she will be told about the study and asked to sign the informed consent form. She will be asked to sign a medical records

release so that the medical records may be obtained. A copy of the signed consent form will be provided to the patient.

D.1.i. Gestational Age Determination

We will use the criteria recommended by the American Congress of Obstetricians and Gynecologists (ACOG).

D.2 Informed Consent Procedures and Documentation

Written informed consent will be obtained before entry into the trial. Full disclosure of the nature and potential risks of participating in the trial will be made. Women who are not fluent in English will be enrolled by a person fluent in their language and both verbal and written informed consent obtained in that language; if such are not available, they will not be included.

D.3 Specimen Collection

Per standard research procedures for Labor and Delivery samples, Magee Womens Hospital employs staff as part of the Obstetric Specimen Procurement Unit (OSPU), which is responsible for the collection of research study samples on the Labor and Delivery unit. Labor and Delivery samples will only be collected if possible. There is a 3-day window for collection of hair samples. Maternal and infant samples will be collected as shown in Table 2.

D.4 Specimen Analysis and Collection of Negative Control Samples

Biological specimens will be collected and labeled with the study and subject number only and stored in locked freezers at MWH or the Magee Women Research Institute or in the freezers at participating institutions. Only the study research staff will have access to individually identifiable private information. Biological specimens will intermittently be sent to Dr. Venkataramanan's lab at the University of Pittsburgh for analysis. Samples sent for analysis will not contain any identifiable information.

Negative Control Samples: Biological samples from women who are not taking BUP are required as negative controls. Subjects potentially eligible as negative controls will be identified by reviewing the medical records of patients presenting for prenatal or postpartum care at private offices or the MFM offices at MWH. Patients will be approached by their care provider or a co-investigator about the study. Healthy volunteers serving as negative controls will be recruited prior to delivery or within 6 weeks after delivery. Subjects recruited as

negative controls will be asked to sign a separate consent allowing for the collection of samples.

The negative control samples will be collected during pregnancy, delivery or postpartum, as requested by Dr. Venkataramanan's lab, and according to study procedures. The biological samples may include any of the following: placenta, umbilical cord blood, umbilical cord tissue, maternal hair, infant hair, and meconium. We will enroll up to 5 women for the collection of each sample type.

D.4.i. **Eligibility Criteria**

The following criteria apply to healthy volunteers serving as negative controls:

Inclusion Criteria:

1. Age between 18 – 45 years
2. Current pregnancy or delivery within the last 6 weeks
3. Able to give informed consent and undergo study procedures

Exclusion Criteria:

1. Currently taking buprenorphine

E. Feasibility:

The sample size required in all 4 specific aims is small. Given the large opioid population in Pittsburgh (over 700 women with an opioid use disorder delivered at Magee between 2013-2015) and that number is increasing making completion of this study very feasible. Our MAT clinic sees 150 new patients annually and has received $500,000 from the state to increase its outreach efforts. I do not believe sample size will be an issue. Recruitment of subjects for specific aim 4, dose reduction may prove challenging since we have not offered this option previously at Magee; however, we performed a survey recently of potential candidates for dose reduction and detoxification and the response was very encouraging. Of 40 women asked if they would consider dose reduction or detoxification, more than 50% said they would be interested. Recruitment for specific Aim 1 may be challenging because the subject will need to be willing to allow withdrawal to occur in addition to spending time in the CRC. Time in the CRC has been an ongoing challenge to recruitment in all OPRU studies. Given that all the MAT clinic staff have been involved with our BUP research in the past and 2 BUP writers are supported by this grant, I am confident that we can recruit sufficient subjects to complete these aims.

F. Potential Problems & Alternative Strategies

For all specific aims, recruitment must be considered. Although this is unlikely to be problematic given our large population, it may be an issue. If recruitment is slower than required to achieve our goals, we will approach other research-oriented centers with a large opioid using population to assist in recruitment.

For specific aim 4, possible problems include high drug withdrawal and craving on the lowest dose reduction and a high dropout rate. The possibility that even the lowest dose reduction will lead to unacceptable rates of dropout and study withdrawal rates is not likely given the reasonable dose reduction rates reported by others with dose reductions much greater than those proposed. If this does indeed happen then we would target an even slower rate of reduction.

G. Subject Removal Criteria

For specific aim 4, if heroin, cocaine, benzodiazepines, barbiturates, phencyclidine (PCP), or opioids other than BUP are detected in the urine during the pre-study screening or at any time during the study, or if the urine drug screen results from the MAT clinic are positive at any time during her dose reduction, she will be dropped from the study and replaced. Subjects who do not return their residual drug on more than 3 occasions will be withdrawn from the study.

H. Clinical Data Management

Data from study participants will be collected on case report forms (CRFs) by research staff. These forms and all data relevant to the subjects and their babies will be kept in the subject's research folder which will be kept under lock and key in the office of the study coordinator. All data will be entered into a research database which will be on a University of Pittsburgh secured and password protected server.

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