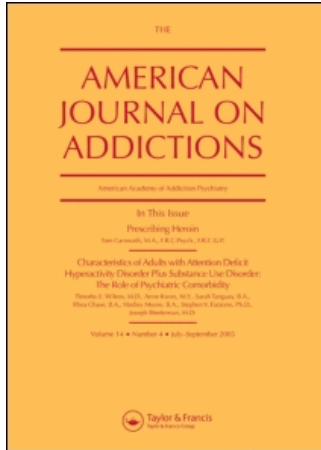


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# Transferring Methadone-Stabilized Pregnant Patients to Buprenorphine Using an Immediate Release Morphine Transition: An Open-Label Exploratory Study

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*A transition from methadone to buprenorphine without intervening withdrawal symptoms is critical for advancing the treatment of opioid-dependent patients. Four pregnant inpatients were transferred from methadone (65–85 mg) to five days of immediate release morphine (IRM) and then to buprenorphine (12–28 mg). Withdrawal scores decreased during the five days of IRM and subsequently increased over the first three days on buprenorphine. The transitional use of IRM appears safe for both mother and fetus. Withdrawal symptoms appeared during buprenorphine induction; however, these data suggest that the intensity of withdrawal symptoms may be lessened by the dose and frequency of buprenorphine administration. (Am J Addict 2006;15:61–70)*

In October 2002, buprenorphine hydrochloride was approved by the Food and Drug Administration for the treatment of opioid-dependent patients. Buprenorphine is not approved for use during pregnancy; however, it may be equally efficacious to methadone as a maintenance treatment in the mother and with a less intense neonatal abstinence syndrome (NAS) in the neonate.<sup>1</sup> Thus, it is likely that some methadone-treated women who become pregnant may transition to buprenorphine.

Transitioning from methadone to buprenorphine in non-pregnant patients is more difficult and is associated with more symptoms than the transition from heroin to buprenorphine.<sup>2</sup> The intensity of the withdrawal depends on the doses of methadone and buprenorphine and the

time interval between drug doses.<sup>3</sup> Transitioning from methadone to buprenorphine can be accomplished by reducing the dose of methadone to 30 mg while providing ancillary support to prevent relapse to illicit opioid use.<sup>4</sup> Increasing the interval between last methadone dose and initial buprenorphine dose to more than 24 hours may help avoid a buprenorphine-precipitated withdrawal.<sup>5–8</sup> Withdrawal signs may also occur if the dose of buprenorphine is insufficient to suppress withdrawal from methadone.<sup>9</sup>

The few reports of transferring pregnant women from methadone to buprenorphine indicate that it is possible to transition pregnant women in the second or third trimester from oral methadone (8 to 70 mg) to sublingual buprenorphine (up to 10 mg). The major withdrawal complaint was dysphoric mood<sup>10,11</sup>

Lowering the dose of methadone and/or increasing the time between the last dose of methadone and initial dose of buprenorphine may not be acceptable to some patients. This may be especially true where any withdrawal may make the patient vulnerable to relapse. One study in non-pregnant patients examined this issue. First, the methadone dose was decreased to 60 mg and then buprenorphine was administered by a fixed dosing schedule of 8 mg in a seven-day period. Fifteen of nineteen participants completed the transition and experienced moderate withdrawal for three days, with the most pronounced withdrawal on the first day of buprenorphine administration.<sup>12</sup>

The purpose of this open-label study was to develop a protocol transitioning methadone-stabilized pregnant women to buprenorphine. The goal was to replace methadone dependence with morphine dependence prior to buprenorphine transition. It was hypothesized that dysphoria and withdrawal discomfort would thus be minimized.

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\*Dr. Suess is now retired.

\*\*Dr. Johnson is now employed by Rickett Benckiser (the manufacturer of buprenorphine).

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## METHODS

### Design

This was an open-label exploratory study with a flexible dosing protocol. Patient responses and clinical observations determined subsequent IRM and buprenorphine dosing. Patients were first observed for two days while stabilized on methadone. Methadone was discontinued and immediate-release morphine (IRM) was administered for five days to minimize withdrawal from methadone. IRM was discontinued, and the transition to buprenorphine was then attempted over the next three days.

### Participants and Setting

Outpatients stabilized on methadone for at least four weeks were selected from the Center for Addiction and Pregnancy (CAP). CAP is a multi-disciplinary treatment program that includes both drug treatment and obstetrical care. Participants resided on the inpatient unit of the Johns Hopkins Bayview Medical Center's General Clinical Research Center (GCRC) for the entire study. During the day, participants continued their CAP therapy with instructions to return to the GCRC at assigned times. The study was approved by the Johns Hopkins Bayview Medical Center Institutional Review Board for human studies.

### Measures

#### *Subjective Opioid Withdrawal Scale (SOWS)*

The SOWS is a sixteen item opioid withdrawal symptom checklist<sup>13</sup> collected every six hours. The ordinal scale was anchored by 0 = not at all to 4 = extremely. Total scores could range from 0 to 64.

#### *Modified Himmelsbach*

This seven item scale, completed by observers, is a modification of the original Himmelsbach and does not include all of the signs of the original scale.<sup>14,15</sup> This measure was collected every six hours. The total scale scores could range from 0 to 14.

#### *Pupils*

Diameter (mm) was determined from photographs taken in constant room lighting using a Polaroid camera (Polaroid Corp. Cambridge Mass.) using a twofold magnification. Pupil diameter was collected every six hours.

#### *Fetal Assessment*

Ultrasound examinations were performed by an experienced ultrasonographer using standard techniques. Instruments were either an ATL Ultramark 9 (ATL, Bothell, Wash.), an Acuson 128 XP 10 (Acuson, Mountain View, Calif.), or a Corometrics Aloka 650 (Corometrics, Wallingford, Conn.). Fetal heart rate, Amniotic Fluid Index, and fetal movement were collected at screening, baseline while stabilized on methadone, on day 4 of IRM stabilization, and during the buprenorphine transition.

## Drugs

### *Methadone*

Methadone HCl (Methadose<sup>™</sup>) Oral Concentrate, USP 10 mg/ml (Mallinckrodt, Inc., St. Louis, Mo.) was diluted to 4 mg/ml with distilled water. Each dose (range 40–100 mg), was delivered as 40 milliliters using diluted (4:1) Concentrated Cherry Syrup (Mallinckrodt, Inc.).

### *Immediate Release Morphine (IRM)*

The total initial daily dose of oral morphine sulfate immediate release (MSIR<sup>™</sup>) (Purdue Frederick Company, Norwalk, Conn.) was to be in the range of six times the last methadone dose. In contrast to once daily methadone dosing, IRM was divided into four equal daily doses (ie, every six hours) based on duration of action. To minimize patient discomfort, a self-titration protocol was additionally instituted. At their request, patients could take 30 mg doses of IRM three hours before scheduled IRM doses. This total daily dose included both scheduled and supplemental (PRN) doses.

### *Buprenorphine*

Buprenorphine HCl (Subutex<sup>™</sup>) 2 mg tablets were delivered in various combinations to provide the range of 4–24 mg. Sublingual tablets were provided by Reckitt Benckiser Pharmaceuticals, Inc., Richmond, Va. It was initially assumed that precipitated withdrawal from the first buprenorphine dose could be minimized by dividing the total daily dose in half with the dose administrations separated by two hours, as generally recommended.<sup>2</sup>

### *Concomitant Medications*

At CAP, it is standard to give concomitant medications to ease withdrawal discomfort. The ancillary medications available included acetaminophen, antacid, prochlorperazine, dicyclomine, diphenhydramine, docusate sodium, hydroxyzine, indocin, macrodantin, metronidazole, Kaopectate, Milk of Magnesia, Maalox<sup>®</sup>, and Fleets enema<sup>®</sup>.

## RESULTS

Demographics of participants are shown in Table 1. Below are summaries of the four patients who transitioned from methadone to IRM to buprenorphine. Table 2 shows the dosing protocol used to transition participants from baseline methadone to IRM to buprenorphine. Table 3 and Table 4 shows the daily average and peak subjective and objective withdrawal assessments and the fetal assessment results, respectively, during baseline methadone, IRM, and buprenorphine induction.

**TABLE 1.** Participant characteristics

Demographics	A	B <sup>†</sup>	C <sup>‡</sup>	D
Age years	26	34	39	26
Race	Black	White	White	Black
EGA weeks	30	26	26	22
Previous pregnancies	1	3	8	4
Drug history	THC, heroin, & cocaine	heroin & cocaine	THC, heroin, & cocaine	THC, heroin, & cocaine
Mg methadone	85 mg*	65 mg*	65 mg	50 mg

\*Reported that dose too low.

<sup>†</sup>Medical history included hypothyroidism, for which she was not taking medication.

<sup>‡</sup>Depression currently treated with Prozac.

*Note:* Participants were included in the study if they were current, opioid-dependent patients stabilized in methadone for at least four weeks prior to study screening and requested a change in medication to buprenorphine: between 21–40 years of age; and between 16–30 weeks, 6/7 days of gestation. Women were excluded if they had a current alcohol abuse or dependence DSM-IV diagnosis; reported using benzodiazepines more than eight times/month and/or more than twice weekly; or if medical screening or available medical records indicated a serious concurrent medical illness making study participation unsafe. Sixteen women met initial eligibility and were asked to participate. Five refused study participation, one had child care issues precluding her from staying inpatient for the study, and two had medical and four had psychiatric issues that contraindicated study participation. Four participants provided written informed consent before participating.

Racial categories are based on those of US census.

## Case A

### *Methadone Baseline Observations*

During methadone baseline, withdrawal scores were moderate (see Table 3). She reported that the 85 mg methadone dose was too low. Fetal assessment was normal (see Table 4). Concomitant medications included diphenhydramine and acetaminophen taken daily (days 1–9).

### *Transition to IRM*

Case A was given 450 mg IRM daily (equivalent to 75 mg methadone) (see Table 2). Average and peak SOWS and Himmelsbach scores during IRM were less than methadone baseline. Pupil size may have increased slightly. Case A received one PRN 30 mg dose/day. No withdrawal was reported on days 4–6. On day 7, after her noon IRM, SOWS scores (peak of 7) but not Himmelsbach scores rose. A PRN 30 mg dose at 4 PM relieved symptoms by 6 PM. The last dose of IRM was administered at midnight. Fetal assessment was normal during IRM (see Table 4).

### *Transition to Buprenorphine*

On day 8, Case A received 4 mg sublingual dose at 10 AM. At noon Case A reported that her buprenorphine dose was too low (see Table 2). After a second 4 mg buprenorphine dose at 2 PM Case A reported feeling better. She failed to return to the GCRC from CAP group therapy but left campus, used heroin and cocaine IV, and returned at 9:45 PM. At midnight, the SOWS score and Himmelsbach scores indicated some subjective and objective withdrawal. A PRN dose of 4 mg buprenorphine was given then. On day 9, the dose of buprenorphine was “much too low,” and at noon 12 mg buprenorphine was given. At noon but, prior to dosing, there was a marked increase in SOWS scores but no change in the Himmelsbach score. At 5 PM, the SOWS

score was 0 and the Himmelsbach score was decreased. The scheduled fetal assessment indicated anhydroamniosis and fetal tachycardia, which was attributed to cocaine use. Consequently study participation was terminated, and she was returned to methadone.

### *Summary*

This case suggests that the interval of ten hours between IRM and buprenorphine may be too long and that the initial dose of buprenorphine was too low. Subsequently, the interval was changed to six hours and the target dose on day 1 was increased to 8–16 mg. In addition, the protocol was modified to allow IRM dosing during the initial buprenorphine administration to treat withdrawal, as the subject stated that her heroin use had relieved the delayed withdrawal discomfort she had experienced following her second dose of buprenorphine.

## Case B

### *Methadone Baseline Observations*

During methadone baseline, she complained of withdrawal and nervousness with mild withdrawal, as judged by the SOWS and Himmelsbach scores (see Table 3). Fetal assessments conducted on day 2 were normal (see Table 4). Concomitant medications included acetaminophen, diphenhydramine, promethazine hydrochloride, and Milk of Magnesia from days 3–9.

### *Transition to IRM*

Case B was given between 420 to 450 mg daily of IRM (equivalent to 70–75 mg methadone) (see Table 2) with little evidence of withdrawal (see Table 3). Three 30 mg IRM were given three times each on days 3–6 and twice on day 7. SOWS and Himmelsbach scores lessened over time (see Table 3). Fetal ultrasound on day 6 was normal (see Table 4).

TABLE 2. Doses and timing of medication administration

Case dosing time*	Baseline days 1-2 methadone	Day 3 IRM	Day 4 IRM	Day 5 IRM	Day 6 IRM	Day 7 IRM	Day 8 buprenorphine	Day 9 buprenorphine	Day 10 buprenorphine	Day 11 buprenorphine	Day 12 buprenorphine	Day 13 buprenorphine
<b>Case A</b>												
6 AM		90	90	90	90	90						
10 AM							4					
Noon	85 mg/day	120	120	120	120	120		12				
2 PM							4					
4 PM		30	30	30	30	30						
6 PM		90	90	90	90	90						
Midnight		120	120	120	120	120	4					
Total dose		450	450	450	450	450		12				
<b>Case B</b>												
6 AM		60	60	60	60	60	<b>IRM 60</b>	<b>IRM 60</b>				
9 AM		30	30	30	30	30						
10 AM												
Noon	65 mg/day											
2 PM		120	120	120	120	120	4					
4 PM		30	30	30	30	30	4(1415)					
6 PM		60	60	60	60	60	2					
8 PM							2					
9 PM		30	30	30	30	30	2					
10 PM												
11 PM												
Midnight		120	120	120	120	120	<b>IRM 120</b>					
Total dose		450	450	450	450	420	16					16



**TABLE 3.** Daily average and peak subjective and objective withdrawal assessments

		SOWS average peak		Himmelsbach average peak		Pupil diameter average peak (mm)	
<b>Case A</b>							
Methadone	Day 1	10.5	16	3.7	6	3.2	3.5
	Day 2	10.0	22	3.2	5	3.0	3.4
Morphine	Day 3	3.8	15	2	5	3.6	4.3
	Day 4	0	0	2.3	5	3.4	3.7
	Day 5	0	0	3.7	6	3.5	3.8
	Day 6	0	0	1.8	4	3.4	3.5
	Day 7	3.6	7	1.7	3	3.3	3.5
Buprenorphine	Day 8	7.3	16	4.5	5	3.4	3.6
	Day 9	18.6	32	3.6	5	3.4	4.0*
<b>Case B</b>							
Methadone	Day 1	3.0	6	3.7	4	3.5	4.0
	Day 2	3	11	4.2	7	3.0	4.1
Morphine	Day 3	2.5	5	3.7	5	2.9	3.4
	Day 4	1.5	3	2.8	4	3.0	3.5
	Day 5	2.8	4	2.7	5	3.3	3.5
	Day 6	2.0	3	2.0	2	3.0	3.5
	Day 7	0.2	1	1.6	3	3.4	3.6
Buprenorphine	Day 8	24.0	54	6.6	12	3.7	4.4
	Day 9	9.8	19	4	5	3.6	4.6
Methadone	Day 10	6.8	19	3.5	4	3.4	4.3
	Day 11	0	0	2	2	3.4	3.4
	Day 12	0	0	2	2	3.7	3.7
<b>Case C</b>							
Methadone	Day 1	1.3	2	2.3	3	3.8	3.9
	Day 2	2.7	11	2.2	4	4.2	4.4
Morphine	Day 3	2.3	3	1.7	3	4.4	4.8
	Day 4	2.3	3	1.8	3	4.3	4.7
	Day 5	1.0	1	1.5	3	4.3	4.4
	Day 6	1.4	2	1.0	2	4.2	4.4
	Day 7	8.0	12	3.0	6	4.2	4.7
Buprenorphine	Day 8	6.2	14	3.2	6	4.5	4.8
	Day 9	19.0	19	3.0	5	3.8	3.8
	Day 10	15.5	20	4.0	5	3.8	4.0
	Day 11	10.0	17	4.0	6	3.6	3.8
	Day 12	9.5	15	4.0	5	3.6	3.9
Methadone	Day 13	10.5	22	3.2	5	3.9	4.3
	Day 14	1.0	1	4	4	3.6	3.6
<b>Case D</b>							
Methadone	Day 1	2	3	0.3	1	5.0	5.7
	Day 2	1.4	2	0	0	5.0	5.7
Morphine	Day 3	0	0	1.2	2	4.9	5.3
	Day 4	0	0	0.8	2	4.8	5.6
	Day 5	0.5	2	1.5	3	5.3	5.7
	Day 6	0	0	1.2	2	5.1	5.3
	Day 7	0.4	2	1.0	2	5.3	5.4
Buprenorphine	Day 8	2.4	10	1.6	4	5.7	6.4
	Day 9	2.9	15	2.4	4	5.0	5.4
	Day 10	1.3	3	2.7	4	5.1	6.0

*(Continued)*

TABLE 3. Continued

		SOWS average peak		Himmelsbach average peak		Pupil diameter average peak (mm)	
Methadone	Day 11	0	0	2.5	5	5.0	5.2
	Day 12	0	0	1.0	2	5.3	5.7
	Day 13	0	0	5.0	5	6.5	6.5

\*Data confounded by heroin and cocaine use.

*Note:* SOWS items included anxiety, yawning, perspiring, eyes tearing, nose running, goose flesh, shaking, hot flashes, bones and muscle ache, restlessness, nausea, vomiting, muscle twitch, stomach cramps, need to shoot up now. Objective signs of opioid withdrawal included lacrimation 0=none, 1=manually induced tearing of the eye, and 2=spontaneous tearing of the eye; rhinorrhea 0=none, 1=watery sound when sniffing in either nostril, and 2=spontaneous runny nose; perspiration 0=none, 1=can palpate sweat on skin, and 2=observe sweat without even touching participant; piloerection 0=none, 1=can feel bumps after manually stimulating skin, and 2=spontaneous gooseflesh; bowel sounds 0=none, 1=no more than one sound every 15 sec, and 2=more than one sound every 15 sec; yawning 0=none, 1=one yawn during observation period, and 2=two or more yawns during observation period; restlessness 0=none, 1=one behavioral sign, and 2=two or more behavioral signs.

### Transition to Buprenorphine

At 6 AM on day 8, an IRM dose was administered. At noon, a 4 mg buprenorphine dose was given. At 2 PM, Case B reported increasing withdrawal and that her dose was too low. SOWS and Himmelsbach scores were increased. At 2:15 PM, 4 mg of buprenorphine was administered. From 4 PM to 10 PM, four additional 2 mg doses were given. The total daily dose of buprenorphine on day 8 was 16 mg. At 9 PM, a panic attack was diagnosed, and 50 mg hydroxyzine was administered successfully to alleviate symptoms. Peak withdrawal occurred at 11 PM (SOWS score 54, Himmelsbach score 12). At this time, she vomited and was agitated. Two 60 mg IRM doses given thirty minutes apart alleviated her symptoms, and she slept from 1 AM to 7:30 AM. On day 9, withdrawal subsided. IRM 60 mg was given at 6 AM. SOWS and Himmelsbach scores decreased throughout the day. After receiving a split 16 mg dose of buprenorphine she reported being comfortable. Fetal assessments were normal (see Table 4). On day 10 at 5 AM, Case B reported that her dose was adequate. At 9:30 AM, she withdrew from the study and was returned to methadone due to anxiety over feeling different on the buprenorphine.

### Summary

The withdrawal demonstrated during the transition to buprenorphine was either precipitated or spontaneous withdrawal. The suppression by doses of IRM on days 8 and 9 and suppression by buprenorphine on day 9 suggest spontaneous withdrawal. Subsequently, a split dose procedure was used on day 1 of transition six hours after the last IRM dose.

### Case C

#### Methadone Baseline Observations

During methadone, she reported no discomfort and exhibited little withdrawal (see Table 3). Concomitant medications included Maalox<sup>®</sup>, Milk of Magnesia, and Fleets enema<sup>®</sup> from days 4–9.

### Transition to IRM

IRM 360 mg per day (equivalent to 60 mg methadone) was given. During transition to IRM, no significant withdrawal was observed. Fetal ultrasound on day 6 was normal (see Table 4). On day 7, Case C complained of nausea and increased withdrawal, accompanied by elevations in SOWS and Himmelsbach scores. She refused PRN IRM medication during this period.

### Transition to Buprenorphine

On day 8, the final 90 mg of IRM dose was administered at 6 AM. Buprenorphine 6 mg was administered at noon and again at 2 PM. At 5 PM, mild withdrawal was reported and observed. At 6 PM, a PRN dose of 30 mg IRM relieved her symptoms, and she slept from 11 PM to 7 AM. On day 9 at 8:30 AM, she began vomiting, which was suspected to be due to withdrawal. She vomited her 30 mg IRM given at 9 AM. At 9:15 AM, a morphine injection 10 mg was administered due to continued nausea. Over the next three hours, two additional 10 mg morphine IM injections and two doses of compazine 25 mg were administered for nausea and withdrawal symptoms. Symptoms abated. At noon 12 mg buprenorphine was given. At 2:30 PM, 50 mg diphenhydramine was administered for extreme restlessness and two additional oral PRN doses of IRM were given during the afternoon. At 11 PM, she was given 6 mg buprenorphine, and she refused fetal assessments. She slept from 10:30 PM to 2 AM. On day 10 at 2 AM and 6 AM, PRN 30 mg doses of IRM were administered. She complained of slight nausea accompanied by a temperature elevation of 99.3°F. She reported upper right quadrant pain and white stools. Right upper quadrant tenderness was observed. A presumptive diagnosis of cholelithiasis (gallstones) was made. Prior to dosing with 16 mg buprenorphine and 25 mg prochlorperazine for nausea, intravenous fluids were started. She reported withdrawal. The fetal assessment was normal (see Table 4). Her withdrawal lessened over the afternoon, but peaked again just prior to her 11 PM 4 mg

**TABLE 4.** Fetal ultrasound assessments during transition

Case	Screening, stabilized on methadone	Baseline, two days of methadone	Day 6 (four days of IMR)	Buprenorphine
<b>Case A</b>				
Dose/hrs post-dose	85 mg/2 hrs	85 mg/2 hrs	450 mg/2 hrs post-1200 dose	12 mg/4 hrs
Fetal weight	1486 gms 3'4" (37%),			
Heart rate (bpm)/rhythm	normal	normal	150 bpm,	170 bpm
Amniotic fluid index level (mm)	133 mm	92 mm	119 mm	68 mm*
Fetal movement	decreased	decreased	normal	normal
<b>Case B</b>				
Dose/hrs post-dose	65 mg/2 hrs	65 mg/2 hrs	450 mg/2 hrs post-1200 dose	4 mg/2 hrs
Fetal weight	751 gms 1'10" (57%),			
Heart rate (bpm)/rhythm	133 bpm	130 bpm	normal	135 bpm
Amniotic fluid index (mm)	111 mm	112 mm	113 mm	normal
Fetal movement	normal	decreased	normal	normal
<b>Case C</b>				
Dose/hrs post-dose	65 mg/2 hrs	65 mg/2 hrs	360 mg/2 hrs post-1200 dose	16 mg/2 hrs
Fetal weight	615 gms 1'5" (45%)			
Heart rate (bpm)/rhythm	130 bpm	130 bpm	normal	130 bpm
Amniotic fluid index (mm)	normal	126 mm	normal	125 mm
Fetal movement	normal	normal	normal	normal
<b>Case D</b>				
Dose/hrs post-dose	50 mg/2 hrs	50 mg/2 hrs	330 mg/2 hrs post-1200 dose	8 mg/2 hrs
Fetal weight	518 gm 1'2" (55%)			
Heart rate (bpm)/rhythm	normal	140 bpm	144 bpm	156 bpm
Amniotic fluid index (mm)	138 mm	normal	142 mm	normal
Fetal movement	normal	normal	normal	normal

\*Diagnosed with having anhydramnios and fetal tachycardia attributed to dehydration and cocaine use and was found to be positive for opiates and cocaine; normal heart rate is 120–160 bpm.

Note: All fetuses were deemed anatomically normal.

Fetal weight was calculated only at screening using Hadlock's formula.<sup>17</sup> Fetal heart rate was considered normal if it was between 120–160.<sup>18</sup> Amniotic fluid index (AFI) involves dividing the maternal abdomen into four quadrants using the umbilicus and linea nigra as the horizontal and vertical reference points. Holding an ultrasound transducer perpendicular to the floor, the vertical diameter of the largest pocket of amniotic fluid is identified and measured. The numbers from each quadrant are added together and the sum is the AFI. Decreased amniotic fluid is defined by an AFI less than or equal to 5 cm and increased amniotic fluid is an AFI greater than or equal to 24 cm.<sup>19</sup>

dose of buprenorphine. On day 11, she began vomiting, which was unaffected by a 20 mg buprenorphine at noon or a 4 mg dose at 10 PM. A preliminary report of an abdominal sonogram suggested "sludge" in the biliary tree. On day 12, Case C continued to complain of nausea without vomiting. Intravenous fluids were discontinued because she was able to eat and drink. She was dosed with 20 mg buprenorphine at noon. Her withdrawal scores indicated moderate withdrawal throughout the day (see Table 3). On day 13, she was without nausea and vomiting with no objective signs of withdrawal. On day 14, Case C again vomited. The possibility of hepatitis or gall bladder disease led to her termination from the study. She was subsequently

returned to methadone and transferred to obstetrics for continued care.

### Summary

In retrospect, Case C exhibited nausea and vomiting prior to the transition to buprenorphine. Clinically, the nausea and vomiting was judged more intense than that of opioid withdrawal and was not accompanied by other withdrawal signs or symptoms. Similar episodes of nausea and vomiting were reported 1–3 months prior to admission and again following a return to stabilization on methadone. The withdrawal observations in this case were confounded with an underlying and probably

unrelated medical condition. The continued use of divided doses of buprenorphine along with the availability of IRM for breakthrough withdrawal appeared to be of benefit. Case C's responses led to a modification of the dosing protocol. The new planned protocol, intended to make the transition more comfortable, was to administer the same targeted daily buprenorphine dose in evenly divided doses every six hours with continued availability of PRN IRM.

#### Case D

##### *Methadone Baseline Observations*

There were no complaints or signs or symptoms of withdrawal, and fetal assessments were normal while being maintained on 50 mg/day methadone (see Table 4). Concomitant medications included Milk of Magnesia on day 4 and acetaminophen on day 5. All medications continued until day 9.

##### *Transition to IRM*

Case D was given IRM between 330–360 mg per day (equivalent to 55–60 mg methadone) (see Table 2). During the IRM transition, Case D took all daily PRN IRM doses. She showed no withdrawal or adverse effects and fetal ultrasound was normal (see Table 4).

##### *Transition to Buprenorphine*

Starting at noon on day 8, Case D was transitioned to buprenorphine 4 mg administered every six hours (see Table 2). On day 8 following buprenorphine administration, she took two 30 mg PRN IRM doses. Severe constipation was treated with docusate sodium, Fleets enema<sup>®</sup>, warm compresses, and hot liquids. On day 9, she reported anxiety and missed the “numbing” feeling of methadone. She attributed the feelings of loss of control and nervousness to the emergence of suppressed trauma experiences and feelings. No withdrawal was reported or observed. Fetal ultrasound was normal (see Table 4). On day 10, she reported no withdrawal but felt that buprenorphine made her feel “spacy”. She withdrew from the study and was returned to methadone.

##### *Summary*

Administration of buprenorphine 4 mg every six hours for 48 hours resulted in a smoother transition from methadone to IRM to buprenorphine. Early symptoms of breakthrough withdrawal appeared to respond to IRM. No withdrawal symptoms were associated with additional doses of buprenorphine given after the IRM. This dosing protocol appeared to be effective in making the transition from methadone through IRM to buprenorphine. However, because of the lack of numbing subjective effects produced by methadone that were liked by this subject and the reported “spacy” feeling during the buprenorphine transition, the subject withdrew from

buprenorphine. It is possible that the addition of the IRM could have precipitated the spacy feeling.

## DISCUSSION

The transition from opioids such as heroin and morphine to buprenorphine is accomplished with fewer complaints of dysphoria and withdrawal than transition from methadone to buprenorphine. The hypothesis of this exploratory study is that a five-day interval of IRM would make the transition from methadone to buprenorphine more like that from heroin to buprenorphine. The results of these cases show that transition from methadone to IRM produced minimal discomfort and behavioral changes attributed to withdrawal. This required multiple daily doses of morphine to be administered to maintain a single daily dosing with methadone. The total daily dose of IRM was approximately six times the single daily stabilizing dose of methadone. The subsequent transition from IRM to buprenorphine produced discomfort and behavioral disruption that was attributed to withdrawal. To attempt to minimize the discomfort, additional manipulations were performed. The dose of buprenorphine was administered in divided doses, doses of buprenorphine were increased rapidly,<sup>13</sup> and additional doses of oral IRM were administered in addition to the buprenorphine. None of these manipulations resulted in patients continuing on buprenorphine maintenance. Except for Case D, the buprenorphine dosing protocol used does not support the concept that a five-day administration of a short-acting opiate will increase the tolerability of the transition from methadone to buprenorphine.

One explanation for these observations is based upon the known time course of methadone withdrawal and previous observations. Withdrawal from oral methadone is first observed between 24–48 hours following the last administered dose. Maximum withdrawal intensity is seen starting on day 3 and does not decrease until the third week.<sup>16</sup> This suggests that morphine suppresses methadone withdrawal, but that the five-day administration of IRM did not alter the methadone withdrawal time course. The failure of buprenorphine to suppress withdrawal could be related to its interaction with methadone, which may be distinct from its interaction with IRM.

If this theory is correct, it would suggest that IRM would have to be administered longer, perhaps up to four weeks, between methadone and buprenorphine so that any residual methadone withdrawal had sufficient time to dissipate. The major difficulty in transitioning patients was the appearance of seemingly mild withdrawal signs and symptoms that lead to behavioral disruptions and anxiety. Based upon available measures, the transition had little if any effect on the fetus. Medical records show all neonates were born well after study completion and had outcomes typical of this population.

Another explanation is that the dose and frequency of buprenorphine was not adequate to suppress withdrawal during transition. During the transition to buprenorphine, the ideal protocol would minimize  $C_{\max}$  and maximize  $C_{\min}$ . The former would reduce the likelihood of precipitating withdrawal with buprenorphine, while the latter would reduce the likelihood of observing a spontaneous withdrawal due to achieving inadequate plasma levels. Initial induction and transition studies utilized a single daily dose based on the "methadone" model of treatment.<sup>20</sup> In this study, the subjective reports of withdrawal symptoms over the 24 hr dosing interval decreased as the dose was increased over three days. Buprenorphine steady-state plasma level is achieved in approximately five half-lives (ie, 3–8 days). During this period, the time that trough blood levels are below the threshold for withdrawal suppression, estimated to be  $> 0.7 \text{ ng/ml}$ ,<sup>21</sup> must be minimized. Thus, dose and dose frequency of buprenorphine prior to achieving this steady-state therapeutic trough level could be critical during the first few days of buprenorphine dosing if this theory is correct. Case D would appear to support this theory.

Conclusions from this exploratory study are limited. A sample size of four patients, all with confounding medical and psychiatric issues, may not be indicative of results with all opioid-dependent, pregnant patients. The procedures and results provide valuable clinical information for future investigations to improve the comfort of the transfer from methadone to buprenorphine.

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