Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to "Buprenorphine for the treatment of the neonatal abstinence syndrome"

Contents:

Figure S1. Dose protocol

Identify newborns exposed in utero to opioids

- Maternal history or positive urine drug screen AND/OR
- Positive infant drug screen

Informed consent obtained?

→ **No** → Standard of care monitoring and treatment

Yes ↓

Monitor for signs of neonatal abstinence using Finnegan score.

Three Finnegan scores > 24 or a single score > 12

→ **No** → Monitor for 3 days prior to discharge

Yes ↓

Randomization to treatment allocation

Sum of 3 Finnegan scores > 24 or a single score > 12

OR

Need for rescue dose

→ **No** → Continue double blind treatment. *Sum of 3 Finnegan scores >24 or a single score > 12* OR *Need for rescue dose?* → **Yes**

Yes ↓

Up-titration 25% for buprenorphine/placebo and 20% for morphine/placebo

Maximum dose reached?

Stability for > 2 days without dose advancement?

→ **No** → Monitoring of Finnegan scores on increased dose

→ **Yes** → Phenobarbital 20 mg/kg load with 5 mg/kg/day initiated.

Phenobarbital 2.5 mg/kg when opioid at 50% of maximum dose. Cessation of phenobarbital after three additional opioid wean.

Yes ↓

Wean up to once a day when the sum of the previous three scores is < 18.

Pharmacy notifies team when drug cessation occurs
- Buprenorphine when within 10% of initial dose OR
- Morphine 0.025 mg/kg q 4 hours

Single rescue study drug at previous dose which symptoms controlled

Monitor at least 1 day prior to discharge

↓

Monitor for at least 2 days in an inpatient setting prior to discharge.
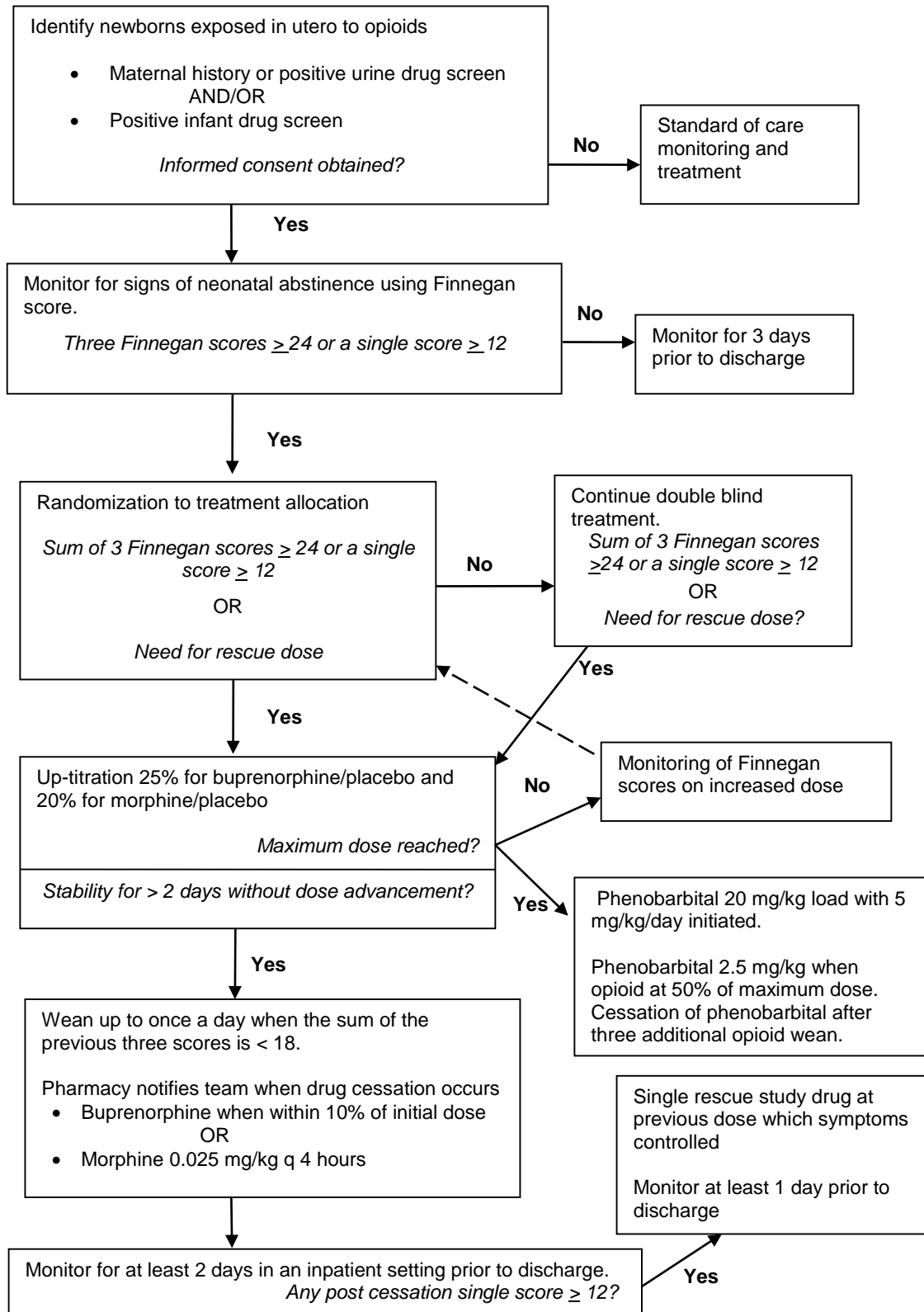*Any post cessation single score > 12?* → **Yes**

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Table S1: MOTHER NAS Scale

Scored Elements	
Signs and Symptoms	*Score*
Crying: Excessive high pitched	2
Crying: Continuous high pitched	3
Sleeps < 1 hours after feeding	3
Sleeps < 2 hours after feeding	2
Sleeps < 3 hours after feeding	1
Hyperactive Moro Reflex	1
Markedly Hyperactive Moro Reflex	2
Mild Tremors: Disturbed	1
Moderate-Severe Tremors: Disturbed	2
Mild tremors: Undisturbed	1
Moderate-Severe Tremors: Undisturbed	2
Increased Muscle Tone	1-2
Excoriation (Indicate specific area):	1-2
Generalized Seizure (or convulsion)	8
Fever > 37.3 C (99.2 F)	1
Frequent Yawning (4 or more successive times)	1
Sweating	1
Nasal Stuffiness	1
Sneezing (4 or more successive times)	1
Tachypnea (Respiratory Rate >60/mm)	2
Poor feeding	2
Vomiting (or regurgitation)	2
Loose Stools	2
Failure to thrive (Current weight > 10% below birth weight 90% BWT=_____ *(record weight in score box 1 x day)*	2
Excessive Irritability	1-3
Total Score	

Table S2: Description of study drug formulation and dosage

	Buprenorphine	Morphine
Active drug solution	0.075 mg/ml buprenorphine in 30% ethanol, with simple syrup	0.4 mg/ml morphine in sterile water
Placebo solution	Sterile water and simple syrup	FD&C Blue #3 in sterile water
Initial daily dose	15.9 mcg/kg/day	0.4 mg/kg/day
Initial unit dose	5.3 mcg/kg q8 hours	0.07 mg/kg q 4 hours
Maximum daily dose	60 mcg/kg/day	1.2 mg/kg/day
Maximum unit dose	20 mcg/kg q8 hours	0.2 mg/kg q 4 hours
Up-titration rate	25%	20%
Maximum # of up-titrations	6	6
Weaning rate	10%	10%
Cessation Dose	Within 10% of starting dose	0.025 mg/kg q 4 hours

Table S3: Descriptive statistics for length of treatment days

Treatment	Strata	Min	Q1	Median	Mean	Q3	Max
Intent to treat population							
Buprenorphine	bottle	3	7	15	18.57	22	67
Buprenorphine	breast	3	12	20	20.92	25	55
Morphine	bottle	13	21	28	32.1	40	67
Morphine	breast	16	23	28	34.22	49	52
Per protocol population							
Buprenorphine	bottle	3	4.75	14.5	14.39	18.75	32
Buprenorphine	breast	3	12	20	20.92	25	55
Morphine	bottle	13	20.75	28	30.75	37.75	67
Morphine	breast	16	22	26	32.75	49.5	52
As treated population							
Buprenorphine	bottle	3	4.75	14.5	14.39	18.75	32
Buprenorphine	breast	3	12	20	20.92	25	55
Morphine	bottle	13	20.75	30	33.54	41.25	67
Morphine	breast	16	23	28	34.22	49	52

Table S4: Descriptive statistics for length of stay days

Treatment	Strata	Min	Q1	Median	Mean	Q3	Max
Intent to treat population							
Buprenorphine	bottle	7	17	21	23.9	27	71
Buprenorphine	breast	7	15.5	26	27.08	37	58
Morphine	bottle	18	28	33	38.52	46	70
Morphine	breast	20	28	32	40.11	57	58
Per protocol population							
Buprenorphine	bottle	7	12	20.5	20	24.75	37
Buprenorphine	breast	7	15.5	26	27.08	37	58
Morphine	bottle	18	27.75	33	37.25	43.75	70
Morphine	breast	20	27.5	31	38.5	57	58
As treated population							
Buprenorphine	bottle	7	12	20.5	20	24.75	37
Buprenorphine	breast	7	15.5	26	27.08	37	58
Morphine	bottle	17	27.75	34.5	39.62	49	71
Morphine	breast	20	28	32	40.11	57	58

Table S5: Estimated coefficients for the post-natal trends in respiratory rates while receiving study drug

Coefficient	Drug	Strata	Estimate	StdErr	95%LCL	95%UCL	P (*)
Intercept	Buprenorphine	bottle	54.3	2.06	50.0	58.5	<.0001
Intercept	Buprenorphine	breast	56.3	2.35	51.5	61.2	<.0001
Intercept	Morphine	bottle	51.9	1.04	49.8	54.0	<.0001
Intercept	Morphine	breast	48.8	1.63	45.5	52.2	<.0001
Linear	any	bottle	-0.114	0.031	-0.179	-0.048	0.002
Linear	any	breast	0.015	0.048	-0.087	0.118	0.76

(*) p-value for testing the null hypothesis that corresponding coefficient is zero.
Variance component estimates with Wald tests, based on 14,332 observations in 58 subjects:
Random effect in intercept: 61.4, SE=18.5, p<0.001 (Buprenorphine); 18.9, SE=5.8, p<0.001 (Morphine)
Random effect in linear coef.: 0.20, SE=0.08, p=0.004 (Buprenorphine), 0.01, SE=0.006, p=0.045 (Morphine),
Residual: 140.8, SE=1.7, p<0.0001.

Table S6: Estimated coefficients for the weight change trends while receiving study drug

Coefficient	Drug	Strata	Estimate	StdErr	95%LCL	95%UCL	P (*)
Intercept	Buprenorphine	0	-36.2	33.8	-103.2	30.7	0.29
Intercept	Buprenorphine	1	-292.9	27.9	-349.2	-236.5	<.0001
Intercept	Morphine	0	-180.3	22.4	-225.5	-135.1	<.0001
Intercept	Morphine	1	-201.5	36.4	-274.7	-128.4	<.0001
Linear	Buprenorphine	0	-95.5	11.9	-118.8	-72.2	<.0001
Linear	Buprenorphine	1	-6.5	5.6	-17.6	4.7	0.25
Linear	Morphine	0	-13.0	3.4	-19.8	-6.2	0.000
Linear	Morphine	1	-25.4	6.2	-37.8	-13.1	<.0001
Quadratic	Buprenorphine	0	11.27	1.48	8.36	14.17	<.0001
Quadratic	Buprenorphine	1	3.59	0.39	2.82	4.35	<.0001
Quadratic	Morphine	0	3.11	0.21	2.71	3.52	<.0001
Quadratic	Morphine	1	4.73	0.42	3.90	5.56	<.0001
Cubic	Buprenorphine	0	-0.37	0.07	-0.51	-0.23	<.0001
Cubic	Buprenorphine	1	-0.10	0.01	-0.12	-0.07	<.0001
Cubic	Morphine	0	-0.07	0.01	-0.08	-0.06	<.0001
Cubic	Morphine	1	-0.14	0.01	-0.16	-0.11	<.0001
Quartic	Buprenorphine	0	0.0043	0.0012	0.0020	0.0066	0.000
Quartic	Buprenorphine	1	0.0008	0.0001	0.0006	0.0010	<.0001
Quartic	Morphine	0	0.0005	0.0000	0.0004	0.0006	<.0001
Quartic	Morphine	1	0.0012	0.0001	0.0010	0.0015	<.0001

(*) p-value for testing the null hypothesis that corresponding coefficient is zero.
Variance component estimates with Wald tests, based on 1077 observations in 58 subjects:
Random effect in intercept: 5943, SE=2039, p=0.002 (Buprenorphine); 6481, SE=2068, p<0.001 (Morphine)
Random effect in linear coef.: 106.5, SE=50.3, p=0.017 (Buprenorphine), 70.5, SE=27.7, p=0.005 (Morphine),
Residual: 1663, SE=83, p<0.0001.

Table S7: Post-natal mean change from the birth weight (g)
The mean weight change was significantly different between treatment groups only at week 1 (7 days post-natal) but not at 2-4 post-natal weeks.

Day	Drug	Mean	95%LCL	95%UCL	p-value
7	Buprenorphine	-231.2	-275.9	-186.5	<.0001
14	Buprenorphine	36.7	-43.5	117.0	0.34
21	Buprenorphine	380.0	245.1	514.9	<.0001
28	Buprenorphine	685.9	471.2	900.6	<.0001
7	Morphine	-166.6	-209.9	-123.3	<.0001
14	Morphine	59.1	-4.9	123.1	0.07
21	Morphine	349.6	256.5	442.8	<.0001
28	Morphine	618.7	488.6	748.9	<.0001
7	Morphine vs. BUP	64.5	3.7	125.4	0.04
14	Morphine vs. BUP	22.4	-76.8	121.5	0.65
21	Morphine vs. BUP	-30.4	-187.7	127.0	0.69
28	Morphine vs. BUP	-67.2	-307.4	173.1	0.56

BUP = buprenorphine

Table S8: Estimated coefficients for post-natal heart rates trends while receiving study drug

Coefficient	Drug	Strata	Estimate	StdErr	95%LCL	95%UCL	P (*)
Intercept	Buprenorphine	bottle	129.02	2.28	124.39	133.65	<.0001
Intercept	Buprenorphine	breast	143.15	2.44	138.15	148.15	<.0001
Intercept	Morphine	bottle	136.49	1.49	133.45	139.52	<.0001
Intercept	Morphine	breast	135.52	2.35	130.74	140.30	<.0001
Linear	Buprenorphine	bottle	2.14	0.24	1.66	2.61	<.0001
Linear	Buprenorphine	breast	0.71	0.19	0.32	1.09	0.001
Linear	Morphine	bottle	0.97	0.08	0.80	1.13	<.0001
Linear	Morphine	breast	0.80	0.13	0.54	1.05	<.0001
Quadratic	Buprenorphine	bottle	-0.047	0.008	-0.062	-0.032	<.0001
Quadratic	Buprenorphine	breast	-0.014	0.003	-0.019	-0.008	<.0001
Quadratic	Morphine	bottle	-0.015	0.002	-0.018	-0.012	<.0001
Quadratic	Morphine	breast	-0.013	0.002	-0.018	-0.008	<.0001

(*) p-value for testing the null hypothesis that corresponding coefficient is zero.
Variance component estimates with Wald tests, based on 14,409 observations in 58 subjects:
Random effect in intercept: 59.0, SE=19.15, p=0.001 (Buprenorphine); 34.3, SE=10.9, p<0.001 (Morphine)
Random effect in linear coef.: 0.21, SE=0.09, p=0.013 (Buprenorphine), 0.035, SE=0.017, p=0.020 (Morphine),
Residual: 270.6, SE=3.2, p<0.0001.

Table S9: Mean post-natal heart rates while receiving study drug
Though the quadratic functions had significantly different coefficients by drug and feeding stratum, the mean heart rates at 1-4 post-natal weeks were not significantly different between treatment groups.

Day	Drug	Mean	95%LCL	95%UCL	p-value
7	Buprenorphine	145	141	148	<.0001
14	Buprenorphine	150	146	154	<.0001
21	Buprenorphine	153	147	158	<.0001
28	Buprenorphine	152	145	159	<.0001
7	Morphine	142	139	144	<.0001
14	Morphine	146	143	148	<.0001
21	Morphine	148	145	152	<.0001
28	Morphine	150	146	153	<.0001
7	Morphine vs. BUP	-3.0	-7.3	1.2	0.16
14	Morphine vs. BUP	-4.4	-9.4	0.6	0.08
21	Morphine vs. BUP	-4.1	-10.3	2.1	0.19
28	Morphine vs. BUP	-2.2	-10.1	5.7	0.58

BUP = buprenorphine

Table S10: Thomas Jefferson University Hospital Morphine Protocol

Initial dose:
For three consecutive scores >24 or one score ≥12, start morphine 0.4 mg/kg/day divided every 4 hours (0.07 mg/kg every 4 hours)

Dose Increase:
20% increase per day for scores >24 total on three consecutive measurements or a single score ≥ 12

Rescue Dose
If, between scheduled doses, a child has a single score of ≥ 12, a rescue dose may be administered at the discretion of the treating physician.

Weaning Dose:
- After 48 h of clinical stability, reduce morphine dose by 10% of the total initial dose every 24h
- Reduce dose when the sum of the previous three scores is < 18 and no single score ≥ 8
- Cease therapy when dose is 0.15 mg/kg/day (0.025 mg/kg every 4 hours)
- If inadequate control of symptoms when weaning, administer rescue dose of morphine at current dose level.
- Observe at least 2 days after cessation of therapy.

Adjunctive treatment:
If symptoms not controlled at maximum dose of morphine 1.2 mg/kg/day initiate phenobarbital 20 mg/kg load followed by 5 mg/kg/day.

Phenobarbital Weaning
- When morphine has been weaned to at least 50% of the maximal dose and the sum of the previous three scores is < 18 and no single score is ≥ 8, decrease the phenobarbital dose to 2.5 mg/kg/day.
- The morphine dose will not be changed on the step when phenobarbital is weaned.
- Phenobarbital will be continued for three dose titrations. When the sum of the previous three scores is < 18 and no single score is > 8, discontinue phenobarbital.
- Morphine dose will not be weaned on the step when phenobarbital is discontinued.

DSMB Membership
We thank the service of the following members who served for the entire duration of the trial
Chair: Wade Berrettini
Committee Members: Laura McNicholas, Arzu Onar-Thomas, and John van Den Anker