Received: 14 January 2021 | Revised: 19 April 2021 | Accepted: 2 May 2021

DOI: 10.1111/cts.13074

ARTICLE

Pharmacometric dose optimization of buprenorphine in neonatal opioid withdrawal syndrome

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Funding information
This investigator-initiated study was supported by an unrestricted grant from Chiesi.

Abstract

Results from Blinded Buprenorphine OR Neonatal morphine solution (BBORN), a previous phase III trial in infants with neonatal opioid withdrawal syndrome (NOWS), demonstrated that sublingual buprenorphine resulted in a shorter duration of treatment and shorter length of hospital stay than the comparator, oral morphine. Objectives of Buprenorphine Pharmacometric Open Label Research study of Drug Exposure (BPHORE), a new trial with buprenorphine in a similar population, were to (1) optimize initial dose, up-titration to achieve symptom control and weaning steps of pharmacologic treatment and (2) investigate safety of the revised regimen. A pharmacodynamic model linked buprenorphine exposure to NOWS symptom scores. Adaptive dose regimens were simulated using BBORN results to compare dosing regimens for times to stabilization, weaning, and cessation. A clinical trial using model informed doses (BPHORE), was conducted. Simulations indicated benefits in time to stabilization and weaning when up-titration rates increased to 30%. Stabilization time was not greatly impacted by the starting dose. Time to wean and time to cessation were dose dependent. A weaning rate of 25% shortened time to cessation. Ten infants were enrolled in BPHORE using buprenorphine starting dose of 24 μg/kg/day, 33% titration, and 15% wean rate. Five subjects required adjuvant therapy. Half-maximal effective concentration (EC_{50}) values indicated maximum buprenorphine doses did not generate maximal effect size, suggesting potential efficacy of a further increased dose if a goal was to reduce the use of adjunct agents. Simulations indicated that further benefits can be gained by increasing starting doses of buprenorphine and increasing wean rates. Use of a model-based analysis to provide focused guidelines for care can be used with goals of reducing treatment time and hospital stays in infants with NOWS.

[Correction added on 23 December 2021, after first online publication: The surname of the author Gagan Kaushal was misspelled and has been corrected in this version.]

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Buprenorphine has demonstrated efficacy for the pharmacologic treatment of neonatal opioid withdrawal syndrome (NOWS).

WHAT QUESTION DID THIS STUDY ADDRESS?

The study sought to explore a variety of buprenorphine dose regimens using modeling and simulation. A revised dose approach was explored in an open label clinical trial.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The study explored the exposure response of buprenorphine in controlling the symptoms of NOWS. The exposure response relationship was described.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The model of buprenorphine response will allow the optimization of dose regimens that may reduce the length of pharmacologic treatment and length of stay for infants treated for NOWS.

INTRODUCTION

Pharmacotherapy with an opioid is the standard of care in infants for whom supportive nonpharmacologic approaches do not control infant withdrawal symptoms in those exposed to opioids in utero.[1] The ideal pharmacologic agent has not been established.[2] Meta-analysis[3] has suggested buprenorphine may have a potential efficacy advantage over morphine or methadone for the neonatal opioid withdrawal syndrome (NOWS, also known as neonatal abstinence syndrome) based upon randomized controlled trials[4] and use in a treatment paradigm.[5] The dose used in the initial clinical trial[6] was extrapolated from adults and critically ill neonates,[7] with subsequent use in neonates informing only minor empiric dose adjustment.[8] A population pharmacokinetic-pharmacodynamic (PK-PD) model[9,10] based upon data from clinical trials conducted at Thomas Jefferson University defined covariates associated with buprenorphine drug disposition. Drug effect was linked to measures of patient outcome, including the MOTHER neonatal abstinence syndrome (NAS) scores (an instrument based upon the Finnegan score that overlaps most elements used to assess symptom severity). The time to control symptoms was affected by buprenorphine exposure and modeled as an indirect response. Variability in exposure was largely governed by differences in individual estimates of apparent clearance (CL/F). Variability in response was largely governed by differences in individual estimates of apparent clearance of buprenorphine (CL/F, interindividual variability = 72.3% coefficient of variation [CV]).[9,10] We used this model to simulate dose regimens that would optimize buprenorphine exposure to minimize withdrawal symptoms. An adaptive dose simulation uses the same population and characteristics as a completed study but is used to test variations in the study protocol to optimize treatment and guide future studies. As in the study, simulated doses could be adapted at the time the score was collected to maximize individual patient response to therapy. A prospective, single arm study with doses based on these simulations was conducted, with a goal of updating the existing model with more robust data. The optimized buprenorphine dose regimen was designed to favor reduced length of pharmacologic treatment and hospital stay, measured by three end points: time to stabilization (TTS), time to wean (TTW), and time to cessation (TTC). This study did not seek to revise the previously generated PK model but focused on assessing a revised PD model.

METHODS

Clinical trials

The current study was based on data generated in the blinded phase III trial study, **B**linded **B**uprenorphine **OR** **N**eonatal morphine solution (BBORN; NCT01452789), which compared the length of pharmacologic treatment using sublingual buprenorphine or oral morphine solution to treat NOWS. In this study, buprenorphine exposures ranged from undetectable (lower limit of quantification [LLQ] = 0.1 ng/ml) to 0.6 ng/ml and the median length of treatment was 15 days in the buprenorphine group, compared to 28 days for infants who were treated with the morphine solution. Additional details of this study can be found in the study by Kraft.[4] This study was used to generate the PK and PD data model[9] that informed

simulations performed in this report, which were then used to inform the dosing regimen for the subsequent **B**uprenorphine **Ph**armacometric **O**pen Label **R**esearch study of Drug **E**xposure (BPHORE) trial.

BPHORE was a dose exploration trial (NCT03608696) conducted at Thomas Jefferson University. The primary objective was to leverage the results of the BBORN trial using a model-based approach to recommend a dosing regimen that would optimize buprenorphine exposure in infants with a goal of reducing treatment duration and hospital stay. Secondary objectives were examination of safety and efficacy of this revised regimen. Inclusion criteria were largely consistent with previous buprenorphine clinical trials[4,6,8] of infants greater than 36 weeks gestation without concurrent medical issues. Unlike our previous clinical trials, infants with multiple exposures to psychotropic drugs, including benzodiazepines, were included in the BPHORE trial. Patient flow is listed in Supplementary Figure S1. The dose regimen used in the BPHORE trial is compared to the BBORN in Supplementary Table S1. The dosing algorithm and dose adjustments are provided in Figure 1. Both trials used the MOTHER NAS scoring instrument. All opioid exposed neonates roomed in with their mothers. Nonpharmacologic care, including promotion of breastfeeding, swaddling, rocking, and low stimulation environment where used. A modified NAS (MNAS) scoring was performed every 3–4 hours. Consented infants with increasing NOWS severity requiring pharmacologic treatment were allocated to the study regimen. The study was approved by the Thomas Jefferson University Institutional Review Board.

Clinical data used in model-based analysis

The BBORN dataset was used to develop the PD model to simulate scenarios and select the optimal dosing regimen for BHORE (Figure 2). The BPHORE dataset was used to validate the simulations and recommend further changes to buprenorphine dosing recommendations for infants with NOWS. All study data used for analysis were assembled and formatted using version 3.2 or above of R.[11] Twenty-eight subjects from the BBORN study who received buprenorphine were used in the estimation-simulation dataset. The demographics of this study subset are shown in Supplementary Table S2. Phenobarbital was used as adjuvant therapy if the withdrawal symptoms were not controlled at the maximum dose of buprenorphine (60 μg/kg/day in the BBORN study). PK observations were excluded from the modeling dataset if they were below the limit of quantification or if phenobarbital was administered concurrently. With these exclusions applied, there were 117 buprenorphine concentrations and 3609 observations of MOTHER NAS scores from the BBORN study. The mean (SD) concentration of buprenorphine across subjects was 0.249 ng/ml (0.101).

For the BPHORE study, 10 subjects were used to compare the PD observations to the simulations. There was no formal power calculation. There were 48 buprenorphine concentrations and 908 observations of MOTHER NAS scores. The same criteria for data exclusion were applied for both studies, except the maximum dose before phenobarbital was administered was 75 μg/kg/day in

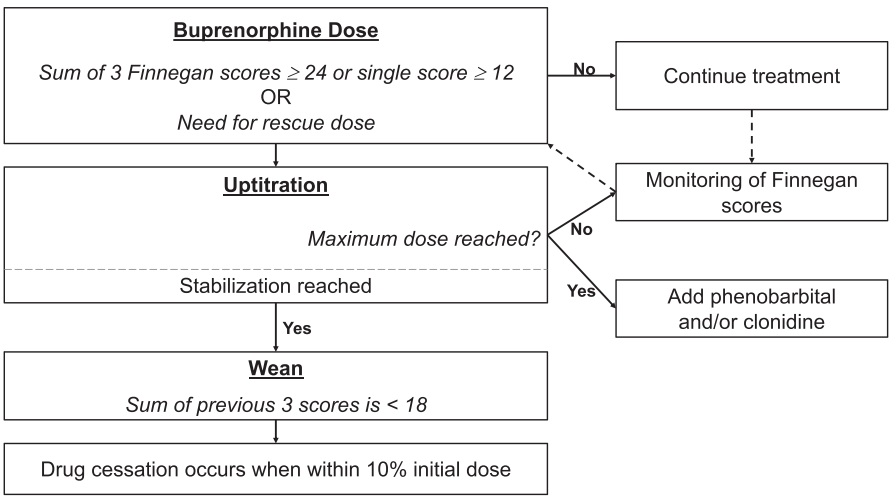

FIGURE 1 Dosing algorithm used in Blinded Buprenorphine OR Neonatal morphine solution (BBORN) and Buprenorphine Pharmacometric Open Label Research study of Drug Exposure (BPHORE) trials

FIGURE 2 Clinical data used in model-based analysis for BBORN (Blinded Buprenorphine OR Neonatal morphine solution) and BPHORE (Buprenorphine Pharmacometric Open Label Research study of Drug Exposure) studies

BPHORE. Phenobarbital was the primary adjuvant therapy. Clonidine was used as an additional adjuvant therapy if stabilization was not reached after adding phenobarbital. For BPHORE PK samples, the limit of quantification of buprenorphine was 0.05 ng/ml. Quantitation of buprenorphine in basified plasma was carried out using butyl chloride extraction (1:3 ratio for plasma to butyl chloride-acetonitrile [4:1] mix) using D4-buprenorphine as internal standard.[12] Samples were dried, reconstituted in 3:7 (water: acetonitrile), and subjected to liquid chromatography mass spectroscopy (Thermo Orbitrap High Resolution Mass spectrometry coupled with Dionex 3000 HPLC system) using isocratic runs on C18 reverse phase column. The calibration curve with linear coefficient r^2 greater than 0.99, was established in the range of 0.05 to 3 ng/ml. The mean (SD) concentration of buprenorphine across subjects in BPHORE was 0.275 ng/ml (0.243).

Model development

A population PK-PD model using data from the BBORN trial has been published by members of our group.[9] The PK model from this publication was leveraged to re-work the PD portion of the model toward the goal of having an equally predictive model describing the changes in MOTHER NAS scores that resulted from changes in buprenorphine exposure using fewer parameters. Individual-level random effects for PK model parameters CL/F, Vc/F, and Vp/F were used to predict individual exposures for subjects in BBORN. Model estimation was performed using NONMEM software system (version VII, level 4.4; ICON Development Solutions, Hanover, MD, USA) with the PREDPP model library and NMTRAN subroutines. The model was validated by evaluating precision around parameter estimates, verifying parameter estimates were reasonable and by visual diagnostics (population and individual prediction plots, residual plots, and visual predictive check). For the visual predictive check, 500 simulations from the PD model were performed and plotted with observed data. If model performance was adequate, plots of observed MOTHER NAS scores over time would be encompassed by simulated 95% prediction intervals.

Adaptive dose simulations

The PD model was developed from BBORN data and simulations from this model were used to explore variations in dosage regimens. Keeping the rules for up- and down-titrations and those for stopping treatment (based on observed MOTHER NAS score) the same as BBORN (Figure 1), other aspects of the clinical trial design were investigated through simulation and are summarized in Table 1. Simulations performed using the mrgsolve package in R (version 0.10.4)[13] generated Monte Carlo replicates ($n = 300$) of the BBORN dataset (sample times and covariates) using PD parameters from the final model. Only aspects of the different scenarios, such as starting dose, titration, and weaning rates, were modified from the BBORN dataset of sample times and covariates. Additive residual variability, drawn from a normal distribution (NID[0,σ^2]) was also applied to simulated MOTHER NAS scores. End points were defined as follows (and shown in Figure 3):

- TTS: Time from first dose until maximum dose was reached.
- TTW: Time from first dose until weaning (weaning was defined as down titration as a result of the sum of the three previous MOTHER NAS scores being less than 18 and no up-titrations within 48 h).
- TTC: Time from start of weaning until the last dose was administered.

Results of the simulations were represented using the survival package in R (version 3.2–3),[14] which fits

TABLE 1 Model simulation scenarios

Parameter	Simulation scenarios
Starting dose	0.1, 0.5, 1, 5.3, 8, 10, and 15 μg/kg
Up-titration	25%, 30%, 50%
Weaning	10%, 15%, 25%

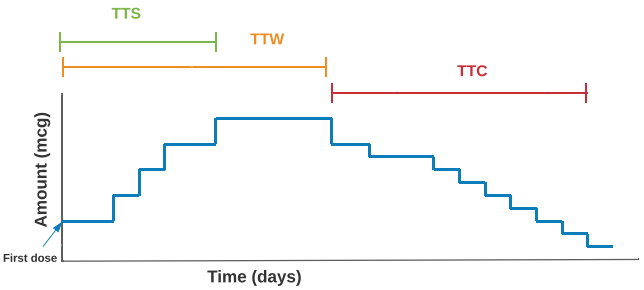

FIGURE 3 Graphical depiction of endpoints investigated in adaptive dose simulations. Time to stabilization (TTS) is the time from first dose until maximum dose was reached. Time to wean (TTW) is the time from first dose until weaning (weaning was defined as down titration as a result of the sum of the 3 previous MOTHER neonatal abstinence syndrome (NAS) scores being less than 18 and no up-titrations within 48 h) and can only be reached if stabilization is reached, first. Time to cessation (TTC) is the time from start of weaning until dose was within 10% of initial dose and can only be reached if time to wean ()TTW is reached, first

Kaplan-Meier curves to time-to-event data, stratified by dose. The events were achievement of stabilization, weaning, or cessation of treatment. This method of comparing simulation scenarios was selected because, depending on the scenario, a simulated subject may not reach the given end point within the time the same observed subject was on study in BBORN. In this case, the simulated event would be right-censored. Although every effort was made to recreate the clinical paradigm with the adaptive simulations, there were some aspects of the BBORN trial that were not incorporated into the simulations. For one, it was not possible to simulate effects of any of the adjuvant therapies. Thus, for the purposes of comparing simulation scenarios (starting doses, titration, and wean rates), the maximum buprenorphine dose limitation was not imposed. In addition, the weaning rules stated that only one down-titration could occur within a 24 h period (see Figure 1); this was also not enforced in the simulations and a subject could theoretically have up to three down-titrations in 1 day. Rescue dosing (defined in the dosing schema as dosing buprenorphine less 8 h apart if the MOTHER NAS score was greater than 12) was incorporated into the simulation and could occur within 4 h of a regular q8 dose.

RESULTS

Model development and adaptive dose simulations

The PD model used in the simulations was modified from Moore,[9] in order to describe changes in MOTHER NAS scores as a continuous end point, and took the following structure form:

$$\mathrm{NOWST} = \mathrm{NOWSMAX} * \exp(-\mathrm{NOWSM} * \mathrm{PNA})$$

$$\mathrm{EFFECT}_{\mathrm{drug}} = \mathrm{EMAX} * \mathrm{C2}/(\mathrm{EC50} + \mathrm{C2}) + 1$$

$$\frac{d\mathrm{NOWS}}{dt} = K_{\mathrm{in}} * (1 + \mathrm{NOWST}) - K_{\mathrm{out}} * \mathrm{NOWS} * \mathrm{EFFECT}_{\mathrm{drug}}$$

$$\mathrm{NOWS}_0 = K_{\mathrm{in}} * (1 + \mathrm{NOWST})/K_{\mathrm{out}},$$

Where NOWST represents the natural improvement of withdrawal symptoms with postnatal age (PNA) and NOWSM is the rate of improvement proportional to PNA, $\mathrm{EFFECT}_{\mathrm{drug}}$ is the buprenorphine effect, which follows indirect response dynamics with EMAX representing the maximal drug effect, C2 the buprenorphine concentration and EC50 the concentration of buprenorphine, which elicits half of the maximal effect on NOWS scores. $\frac{d\mathrm{NOWS}}{dt}$ is the rate of change in NOWS scores, with rate constants K_{in} and K_{out} and NOWS_0 is the initial condition for the rate of change in NOWS severity scores assessed by the MOTHER NAS tool.

The final PD model parameters used for simulations are shown in Supplementary Table S3. All the fixed effects were estimated with good precision. The random effects on NOWSMAX and NOWSM were poorly estimated (having 95% confidence interval [CI], which encompasses zero). This is likely because of sparse data used to estimate the PD effects. Kaplan-Meier curves were generated for the simulated TTS and TTW at different starting dose levels and for different rates of titration. These results at the 25% titration rate are shown in Figures 4 and 5. The table below the figure summarizes the estimated cumulative probability of stabilization and weaning events, stratified by starting dose. A summary of TTS, TTW, and TTC, in days, across different simulation scenarios is shown in Table 2. For a subject to have reached the end of treatment (cessation) by the clinical definition in the BBORN trial, the subject had to wean to a level within 110% of starting dose (in other words, cessation is the time at which dose is < initial dose*1.1). Simulations were performed comparing TTC for different starting doses and wean rates. Time-to-event curves showing results of simulations with different starting doses at the 10% wean rate are shown in Figure 6. The table below the figure summarizes the estimated cumulative probability of cessation stratified by starting dose.

Recommendation for BPHORE study based on adaptive trial simulations and results for efficacy

The adaptive dose simulations indicated there would be a benefit of an up-titration rate of at least 30% and a wean rate as high as 25% (Table 2, Figures 4–6). The starting buprenorphine dose had a greater impact on weaning and cessation times than on time to stabilization. Simulations indicated that a starting dose of 15 mcg/kg q8 h could shorten treatment duration by 2–3 days due to cumulative benefits on TTW and TTC. However, the data that was informing the model and from which simulations were derived (BBORN trial) had a maximum buprenorphine dose of 60 μg/kg/day (20 μg/kg q8) and adjunct therapy was used if this dose was reached before stabilization. In order to guide dose optimization under these dosing limitations, a summary of simulation records that were censored (if subject was up-titrated to the maximum dose before the end point was reached, within the time course in the observation dataset, the simulation record for the end point was censored) was

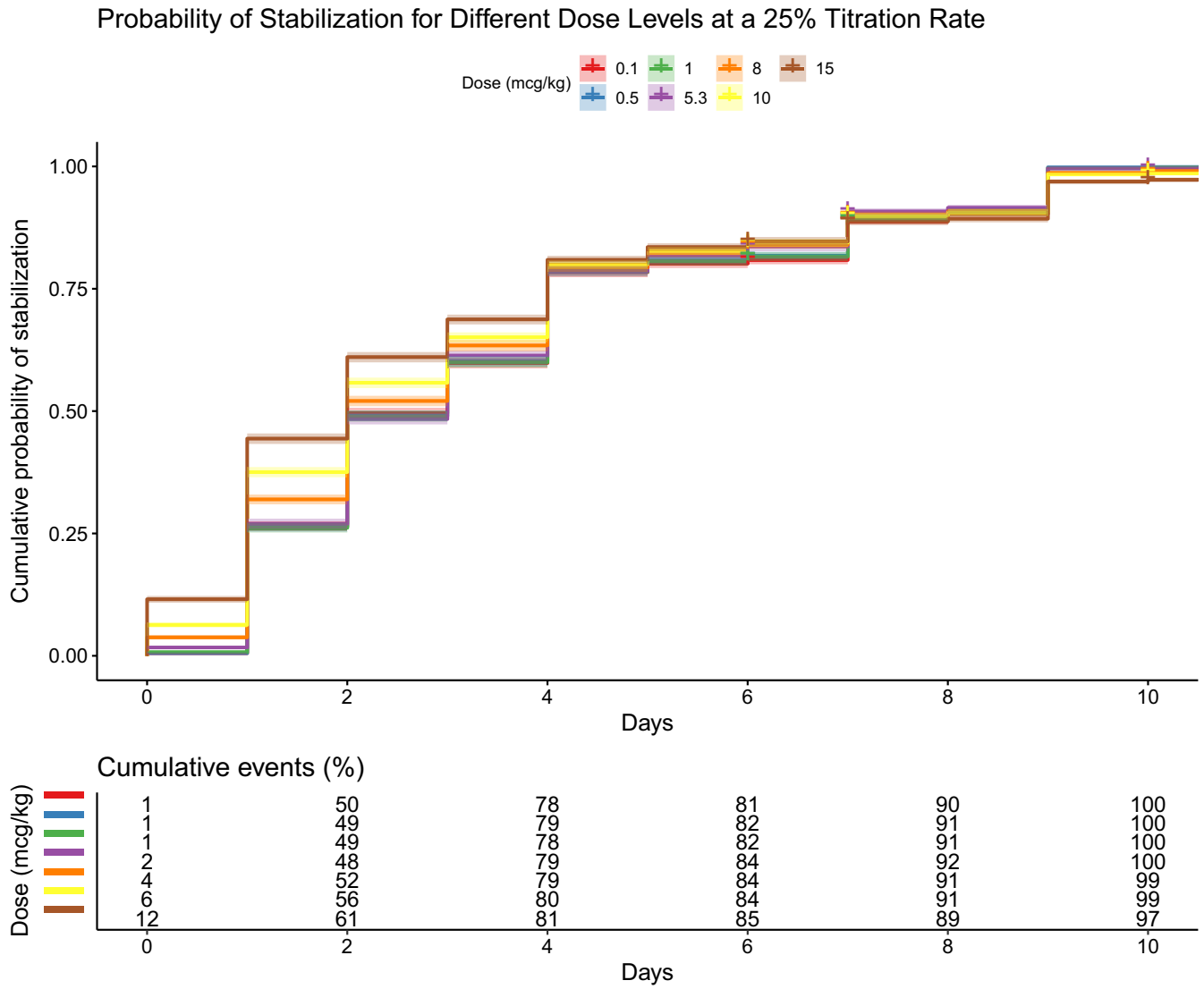

FIGURE 4 Kaplan-Meir plots for simulated time to event time to stabilization (TTS) are shown at different initial dose levels and at a 25% up-titration rate. + denotes censoring. The table below the plot summarizes the estimated percentage of patients who have not reached stabilization stratified by starting dose

summarized and compared to the observed percentage of subjects in BBORN who were also censored (either received adjunct therapy or left the study prematurely). This summary (Supplementary Table S4) demonstrates the simulations are aligned with observed data in terms of the proportion of subjects that reached the maximum dose of buprenorphine. In future studies, if reaching 60 mg/kg/day buprenorphine and using adjunct therapy is no concern, simulations support use of a high starting dose, high titration rate, and high weaning rate. If it is in the patient's best interest to rely on buprenorphine and this maximum dose is imposed, the simulations support either a starting dose around 1 (and use of any titration rate tested here and a high wean rate) or a starting dose between 5.3 and 8 mg/kg and up-titration rate less than 50%. These differences in optimal treatment with a maximum dose imposed must be considered in future study designs.

From the results of the simulations a starting dose of 8 μg/kg q 8 h was selected for the BHORE study, along with rates for up-titration and weaning of 33% and 15%, respectively. Although the simulations indicated further benefit by using a higher starting dose, a more modest dose increase relative to the starting dose in BBORN was selected out of an abundance of caution in the neonatal population and the smaller incremental benefit at higher simulated doses. Compared to the previous up-titration rate of 25% and down-titration rate of 10% used in BBORN and our clinical care protocol, the dosing protocol used in BPHORE utilized the larger titration steps for more rapid stabilization and bigger weaning steps to

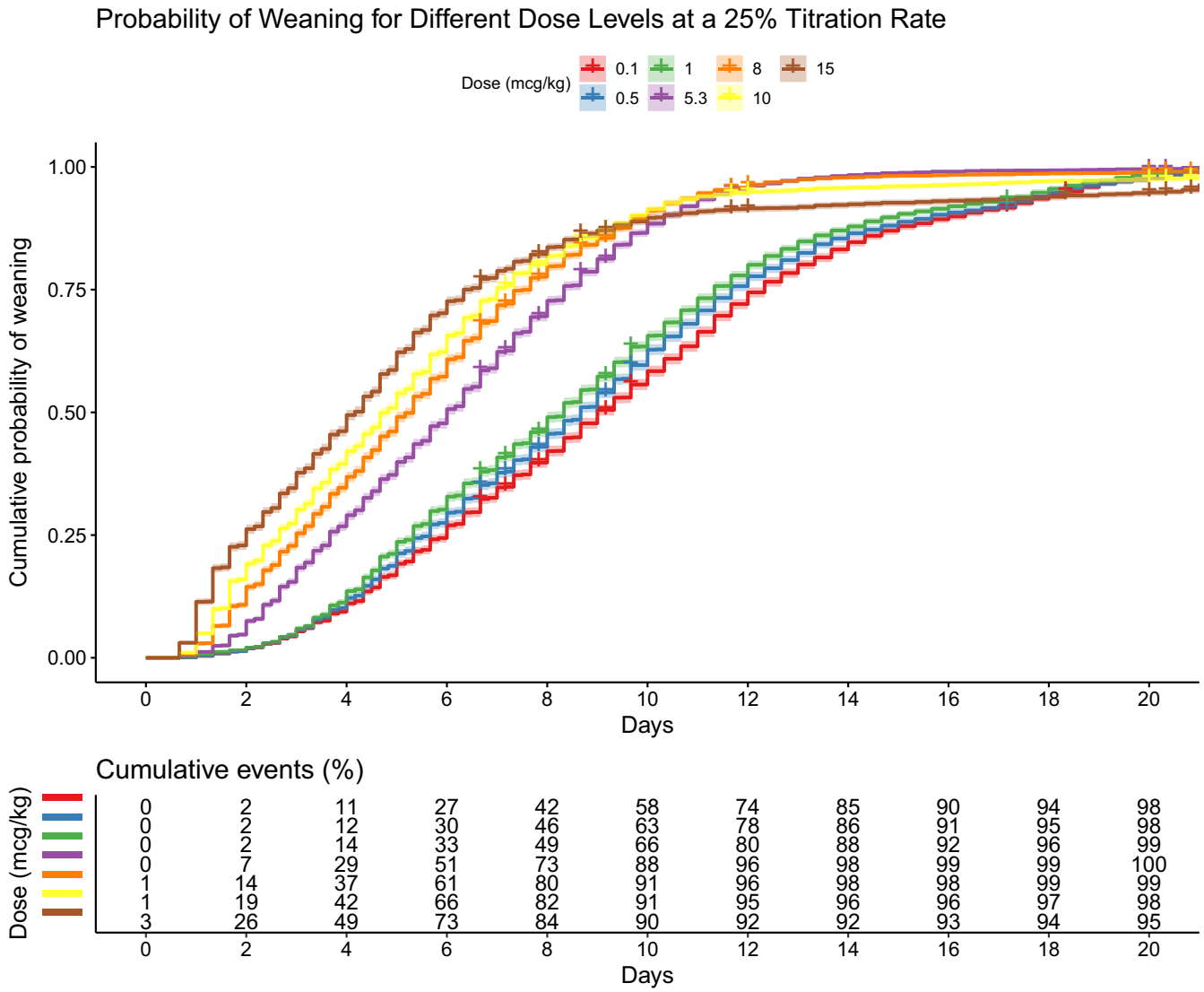

FIGURE 5 Kaplan-Meir plots for the simulated time to event time to wean (TTW) are shown at different initial dose levels and at a 25% up-titration rate. "+" denotes censoring. The table below the plot summarizes the estimated percentage of patients who have not reached weaning stratified by starting dose

shorten treatment time. The use of a relatively low initial dose was chosen to minimize opioid exposure in those who ultimately would have control of symptoms at lower exposure. The maximum dose of buprenorphine that could be reached before adjunct therapy was needed was increased to 75 μg/kg/day. Observed lengths of treatment (TTW + TTC) were calculated for BBORN and BPHORE studies. These were compared to a simulation (using the same methodology as the adaptive dose simulations, but instead using the specific dosing protocols from BBORN and BPHORE) in which individuals were censored if the maximum buprenorphine dose was reached prior to the end point. For the BBORN study, the observed median (95% CI) length of treatment in days calculated by adding median TTW and median TTC was 23.8 (15.7 and 43.7, respectively); and simulated was 20.5 (17.9 and 23.1, respectively). For BPHORE, the observed length of treatment for those only treated with buprenorphine was 16.8 (13.0 and 33.9, respectively); and simulated was 13.1 (6.66 and 30.3, respectively). For purposes of comparison, these results do not include those treated with adjunctive phenobarbital or clonidine.

BPHORE clinical trial results for safety

Nineteen patients had consent provided. Of these, nine did not have signs or symptoms of NOWS sufficiently severe to warrant pharmacologic treatment (Figure 1). Demographics of 10 treated subjects, length of drug treatment, and length of stay by individual are listed in

TABLE 2 Simulated stabilization, weaning and cessation times (days) for probability level of at least 50% by initial dose and up-titration and wean rates

	Titration rate (%)			Wean rate (%)		
Dose	**25**	**30**	**50**	**10**	**15**	**25**
Time to stabilization (days)						
0.1	2.7	1.7	2			
0.5	2.7	1.7	2			
1	2.7	1.7	2			
5.3	2.7	1.7	2.3			
8	2.3	1.7	2			
10	2	1.5	2			
15	1.7	1.3	1.7			
Time to weaning (days)						
0.1	9	9	9			
0.5	8.7	8.7	8.7			
1	8.3	8.3	8.3			
5.3	6	6	6.3			
8	5.3	5	5.3			
10	4.8	4.7	5			
15	4.2	4.2	4.3			
Time to cessation (days)						
0.1				22.7	19	15.3
0.5				21.7	18.3	15
1				21	17.3	14
5.3				15	1.7	10
8				12.7	10.7	8.7
10				12	10	8
15				10	8.3	6.7

Note: The observed time to stabilization, time to wean, and time to cessation in the Blinded Buprenorphine OR Neonatal morphine (BBORN) trial (dose = 5.3 μg/kg, 25% titration level, and 10% wean level) at the same probability was 4.92, 9.37 and 19.8 days, respectively.

Supplementary Table S5. There were two adverse events during the study. One infant developed a grade 1 rash graded as unlikely related to buprenorphine. The rash resolved despite continued dosing of buprenorphine. A second infant had a grade 2 seizure graded as unlikely related to buprenorphine and due to underlying severe NOWS symptoms complicated by selective serotonin reuptake inhibitor (SSRI) withdrawal. At the time of the event, there were significantly elevated MOTHER NAS scores, uncontrollable tremors, and multiple episodes of emesis requiring multiple rescues and increased doses of study drug. During a phenobarbital loading dose for NOWS, the infant had two episodes of extensor posturing with apnea leading to cyanosis consistent with clinical diagnosis of seizure. C-reactive protein was normal, and lactate was elevated with mild metabolic acidosis. Following the phenobarbital infusion, the infant calmed and there were no additional seizures identified by continuous video electroencephalography (EEG) monitoring, although severe tremors continued consistent with SSRI withdrawal.

DISCUSSION

Optimized treatment for NOWS starts with maximizing nonpharmacologic measures. Adequate symptom control of NOWS promotes growth, fosters maternal bonding, and minimizes the amount of pharmacologic treatment. Model-based approaches are increasingly brought to bear in the quest to optimize treatment for NOWS.[15–17] Challenges include dynamic drug disposition and elimination in the first days of life and PK variability for commonly used pharmacologic agents.[18] The biology of opioid withdrawal is not fully understood in newborns, and there is not general agreement on instruments to measure disease severity nor the severity of disease that should prompt use of pharmacologic therapy or accepted clinical trial end points.[19] Understanding these challenges, we sought to (1) build on prior work describing buprenorphine PK exposure in infants with control of NOWS symptoms, (2) simulate optimized dose regimens, (3) test these revised dose regimens, and (4) feed these data back into the PK-PD model for use in future work. Specifically, we leveraged clinical trial data from a phase III trial, BBORN, and used a model-based approach to recommend a dosing regimen for BPHORE, a subsequent trial in a similar population. The PD model provided a good description of the efficacy data from BBORN, as determined by the following diagnostics:

1. All fixed effect parameters in the model were estimated with good precision (no 95% CI encompassing zero) and comparable to previously reported estimates. Some random effects had less precision, likely because of the sparse data in BBORN (N = 28). The EC50 in this analysis was estimated at 0.942 ng/ml (95% CI 0.870–1.01), which is comparable to what was previously reported in the literature. The reported EC50 in Moore[9] was 0.509 ng/ml, whereas Mizuno[17] reported an EC50 of 0.766 (95% CI 0.467–1.17) using an indirect response model but not an EMAX model. The slightly larger estimate in our analysis may indicate that buprenorphine exhibits physiologic responses even at relatively low exposures and the maximum effect of buprenorphine on NOWS scores had not been reached in BBORN. This is in agreement with effects of buprenorphine seen in adults where relief of withdrawal symptoms occurs at serum concentrations

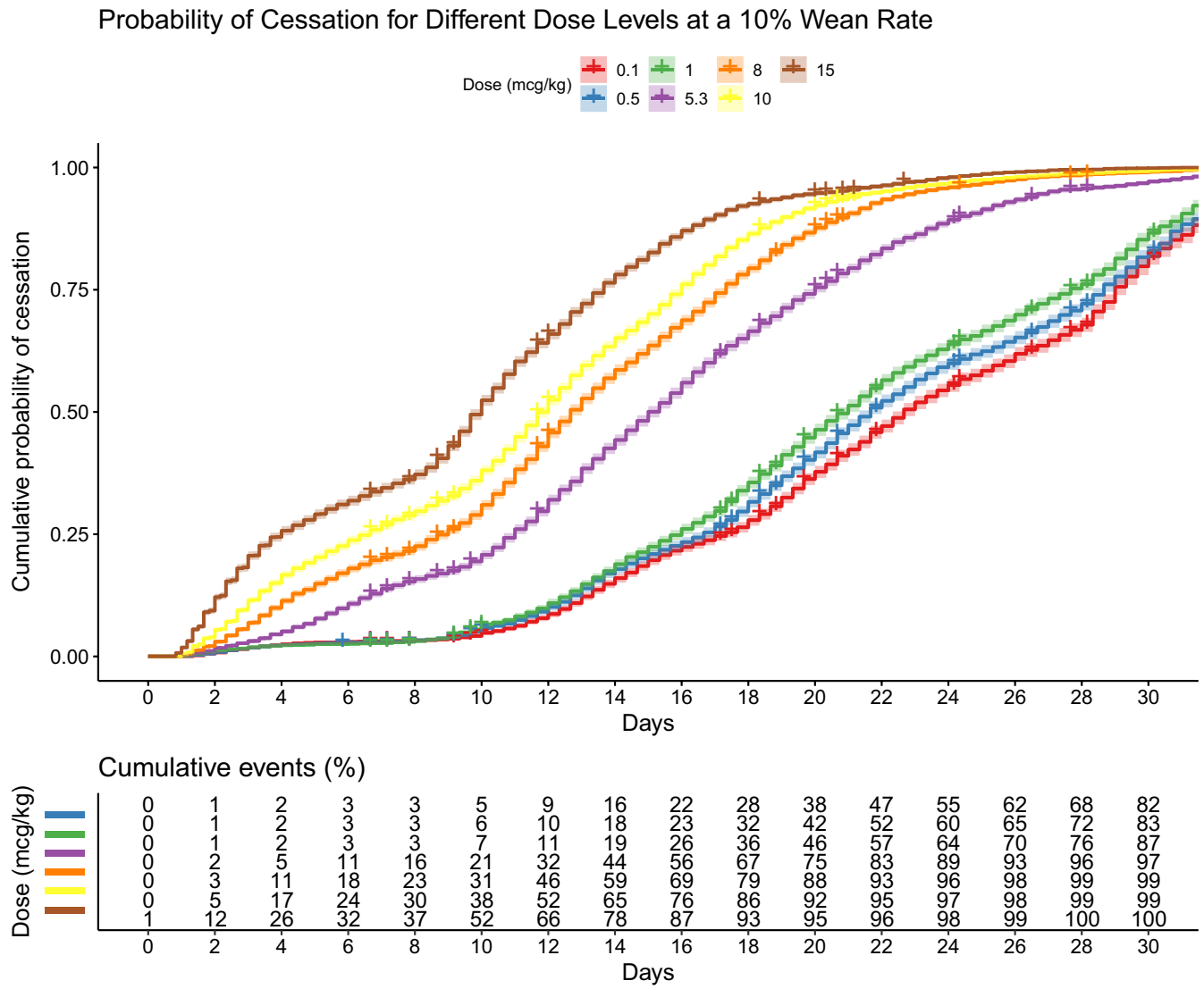

FIGURE 6 Kaplan-Meir plots for the simulated time to event time to cessation (TTC) are shown at different dose levels and at a 10% weaning rate. "+" denotes censoring. The table below the plot summarizes the estimated percentage of patients who have not reached cessation stratified by starting dose

of 0.7–1 ng/ml, with 50%–60% occupancy at the μ opioid receptor, depending on the region of the brain. At concentrations of about 2.5 ng/ml, greater than 80% of receptors are occupied.[20]

2. Diagnostic plots and visual protective checks demonstrated good model performance (Supplementary Figure S2 to Figure S4). The model tended to slightly underpredict higher scores at baseline (Supplementary Figure S2, right panel), which may be a result of the range of predicted scores being constrained by initial conditions in the model.

The BPHORE trial was a small, single arm, uncontrolled trial. This design and lack of a concurrent control group makes it difficult to assess the revised dose schema on the end points of length of treatment. A challenge we faced was that the group of infants seen in this trial appeared to have more severe disease than those in the BBORN trial. Half required treatment with phenobarbital, compared to only 15% in BBORN. One third of the infants in BPHORE required two adjuncts (phenobarbital and clonidine), whereas none did in BBORN. This may be driven by maternal methadone dose.[21] The median maternal dose for the eight infants with this exposure in BPHORE was 158 mg (38–400 mg; Table S5) compared to 130 mg (25–265 mg) for BBORN infants ($n = 33$). BPHORE infants who required phenobarbital had a median maternal methadone dose of 300 mg compared to 70 mg for those who did not require adjunct therapy. Additionally, more BPHORE infants had polysubstance exposures, including benzodiazepines, that were specifically excluded in the BBORN trial. This may

account for the overall differences in length of treatment for BPHORE (22.9 days) compared to that in BBORN (15 days). The difference in length of treatment should be viewed carefully, because there was no control group in BPHORE that would provide some read out of the severity of disease of the population during the conduct of BPHORE (October 2018 to June 2019) compared to BBORN (October 2011 to June 2016). Another possibility is that given the smaller sample size (10 vs. 63 enrolled infants in BPHORE and BBORN, respectively), there was a distribution of sicker infants into the study population of BPHORE by chance. One complication of having a cohort that had more severe disease, is that the linking of buprenorphine PK exposure to symptom control is not possible when an adjunct drug, such as phenobarbital, is used and is influencing the PD measure (MOTHER NAS scores). The model examined the impact of the exposure of only buprenorphine on disease symptoms. Because adjunct therapy impacted the NOWS scores in a way that could not be accounted for or simulated without PK concentrations of these drugs, those observations in infants who received phenobarbital or clonidine were censored. Last, it is possible that the updated dosing regimen may have been causal in the differences in the short-term outcomes noted between the BBORN and BPHORE populations. The effective exposure of buprenorphine required to control symptoms is dynamic, as the natural history of NOWS in each infant will peak and then decline. A dosing regimen would ideally be able to react to symptom scores and provide an optimized dose. NOWS is a complicated disease for which the biologic basis is only partially understood, and the inherent variability in individual patient presentations, responses, and impact of unmeasured covariates may push the limits of the possible with modeling approaches.

Other shortcomings of the simulations, or ways in which the simulations could not completely mimic reality, were clinical restrictions on weaning and some deviation from the dose adjustment protocol that may have occurred at the discretion of the treating physician or reflect missed opportunities by the clinical team. This was very uncommon in BBORN and BPHORE, but if this occurred it represented a variation from the rules the model assumed were followed exactly. These factors may explain why simulations of BBORN were more optimistic (the model predicted at least 50% probability of reaching TTS was about 3 days; observed was closer to 5 days, the model predicted TTW was 6 days; observed was over 9 days, and model predicted TTC was 15 days; observed was almost 20 days). When censoring for maximum buprenorphine dose was imposed in the simulations, they were much closer to the observed.

The maximum dose was increased in the BPHORE study to 75 μg/kg/day, compared to 60 μg/kg/day used in BBORN, and titration rate increased from 25% to 30%. Because both starting dose and titration rate were also increased, there was a greater likelihood of reaching the maximum dose more quickly. The simulations suggested that increasing the maximum dose, as well as both the starting dose and the wean rate may shorten treatment times. The estimated EC50 is over 0.9 ng/ml and average concentrations were 0.249 and 0.272 ng/ml for BBORN and BPHORE, respectively. This suggests the current dose range results in concentrations that are on the linear part of the exposure-response curve and not close to the maximum. With this in mind, raising the maximum dose beyond 75 μg/kg/day widens the window of opportunity to be able to see more beneficial effects of buprenorphine as a phenobarbital sparing approach. A caveat is that there is a delay between exposure and effect (described by an indirect response model) so the response rate of an infant may also contribute to the need for adjuvant therapy. The primary dose-dependent safety concern with all opioids is respiratory depression. This is much less of an issue with buprenorphine, which as a partial agonist has ceiling effects at higher concentrations. Indeed, fatal overdose from buprenorphine in adults is very uncommon unless it is taken with sedative hypnotics that work by a different receptor (like benzodiazepines or alcohol). Children under 3 years may be more susceptible than adults to respiratory depression.[22,23] However, whereas a measurable, but nonclinically significant decrease in respiratory rate with morphine (a full agonist at the μ opioid receptor) has been noted in NOWS treatment, this has not been the case in infants treated with buprenorphine.[4] Sublingual buprenorphine used in neonates contains alcohol 30% w/v absolute amount ingested per patient is small with levels undetected or below LLQ in 50%.[24] In all cases, alcohol was below the American Academy of Pediatric guideline for safe administration of alcohol-containing medications.[25] There were no safety issues identified in BPHORE with the use of a higher maximum dose of buprenorphine. This is not surprising, and indeed respiratory depression is not an issue in the treatment of NOWS in a controlled inpatient setting, even when using full agonists, as control of withdrawal symptoms long precedes respiratory depression.

The current study examined only the relationship between buprenorphine exposure and control of NOWS symptoms. In our analysis, there were no changes to the PK model published in our earlier work. Although long-term neurodevelopmental outcomes have been explored in some clinical trials as secondary end points,[26] our investigation was confined to short-term end points due to the difficulty of conducting such studies and expected

large amount of variability in a small population. Future goals will be an updated PK model examining buprenorphine, norbuprenorphine, and glucuronidated buprenorphine measured in urine. This will further characterize the variability in exposure in the neonatal population. If a maximum buprenorphine dose will be imposed in future studies, it would be worthwhile to characterize the PK of adjuvant therapies (phenobarbital and clonidine) and optimize combination therapy. Phenobarbital is an inducer of CYP3A,[27] the enzyme, which also metabolizes buprenorphine. The impact of phenobarbital on buprenorphine clearance in neonates is not defined.[28] CYP3A7 has only minor impact on buprenorphine metabolism,[29] but this may come to prominence in the neonate due to low 3A4 expression.[30] If phenobarbital is routinely dosed with buprenorphine at higher doses of buprenorphine than have been studied, it would be pertinent to understand any drug-drug interactions (DDIs) at therapeutic doses of both therapies. Although NOWS is less common in premature infants, modeling of glucuronidation changes in this population could identify optimized doses for these infants and extend use earlier than 36 weeks. Buprenorphine is metabolized in humans by a combination of phase I and phase II reactions.[31] The influence of maturation on glucuronidation capacity in newborns, including pre-terms, infants, and children under the age of 3 years, has been studied using morphine and its major metabolites as a model drug.[32] Formation clearances of morphine to its glucuronides and elimination clearances of the glucuronides are primarily influenced by bodyweight. Additionally, a PNA of less than 10 days was identified as a factor affecting the formation clearance to the glucuronides. In the PK model, PNA was a covariate on buprenorphine clearance, indicating as postnatal age increased (up to about 20 days) so did elimination of buprenorphine, possibly due to the ontogeny of buprenorphine glucuronidation.[10] Future work also includes investigating the impact of dosing intervals via simulation and evaluating whether an initial period of q4 dosing would also shorten treatment duration. In efforts to shorten hospital stays, future studies may include transitioning earlier to outpatient if an adequate daily dose is given and adhered to. The time at which a neonate can effectively transition to outpatient can also be explored through simulation, as fewer dose administrations would be desirable in this paradigm. By leveraging data from two clinical trials (one used to develop a model and one used to validate) we have shown that adaptive dose simulations can provide effective dosing recommendations with buprenorphine. There is an unmet clinical need to standardize the assessment and management of infants with NOWS toward reduction of treatment time and hospital stays and there is evidence that implementation of focused guidelines for care does this.[33] We have demonstrated how model-based analysis can provide valuable support for further distillation of these guidelines.

CONCLUSIONS

In this analysis, clinical end points (target buprenorphine concentration, TTS, TTW, and TTC) in the BBORN trial were investigated by adaptive model simulations. In the simulations, TTS was largely independent of buprenorphine starting dose but was improved by increasing the titration rate from 25% to 30%. Further increases in titration rate did not shorten TTS. TTW was dependent on starting dose, and, like TTS, could be improved by increasing the upward titration rate from 25% to 30% but further increases did not shorten TTW. TTC was dependent on both starting dose and wean rates with the maximum reduction of TTC estimated at a starting dose of 15 μg/kg q8 h (daily dose 45 μg/kg/day) and wean rate of 25%.

When the simulations were censored if the simulated subject had titrated up to the maximum daily dose (60 μg/kg/day), most of the subjects reached the maximum buprenorphine dose and needed adjunct therapy at starting dose levels of 5.3 μg/kg and an up-titration rate of 50% prior to weaning. Based on favorable simulated efficacy advantages, combined with a conservative approach to the rate of dose increase and ability to titrate before reaching maximum dose, a starting dose of 8 μg/kg q8 h, an up-titration rate of 33% and a wean rate of 15% was selected for the phase II trial (BPHORE) using the same MOTHER NAS score cutoff points for dose adjustment, as used in BBORN.

Comparing total length of treatment between BPHORE simulated and observed indicated that the simulation was well-aligned with what was observed. Furthermore, in BPHORE, five subjects out of 10 required phenobarbital, of which three required both phenobarbital and clonidine because these subjects reached the maximum dose of buprenorphine before reaching stabilization, which was a trend also supported by the simulation. In terms of achieving the objective of shortening treatment duration, the BPHORE dose regimen performed well in the simulations and is a reasonable regimen to use with buprenorphine, in light of practical and safety considerations. Simulations indicated higher initial doses (10 or 15 μg/kg q 8 h) would lead to shorter treatment times but would potentially overtreat some infants who would otherwise have had adequate control on the lower dose of 8 mcg/kg. Although an up-titration rate of 50% may provide quicker control of symptoms in some infants, the concern of overtreatment identified with a higher initial dose is also present. The

simulations do support consideration for larger weaning dose reductions, which could shorten treatment time. Model and simulation-based approaches for optimal dosing regimen cannot identically replicate an observed trial where patient variability and clinician discretion in dosing decisions and dose regimen cannot always be precisely replicated. In addition, this investigation was small and appeared to have patients with more severe NOWS. These limitations aside, adaptive dose simulations can be useful in guiding dose regimens for planned trials in pediatric populations.

ACKNOWLEDGEMENT

The authors thank Massimo Cella, PhD for his review of a draft of this manuscript.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

R.E.B. and W.K.K. wrote the manuscript. W.K.K., N.Z., R.E.B., and S.A.J. designed the research. W.K.K. and S.A.J. performed the research. R.E.B., A.R., W.K.K., and G.K. analyzed the data. N.Z. and M.G. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Eudy-Byrne R, Zane N, Adeniyi-Jones SC, et al. Pharmacometric dose optimization of buprenorphine in neonatal opioid withdrawal syndrome. *Clin Transl Sci*. 2021;14:2171–2183. https://doi.org/10.1111/cts.13074