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Clonidine as an Adjunct Therapy to Opioids for Neonatal Abstinence Syndrome: A Randomized, Controlled Trial

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Abstract

Objective—To determine if oral clonidine would reduce the duration of opioid detoxification for neonatal abstinence syndrome.

Methods—Infants with intrauterine exposure to methadone or heroin and neonatal abstinence syndrome (2 consecutive modified Finnegan scores of ≥ 9) were enrolled at 2 hospitals during 2002–2005 and followed until final hospital discharge. All enrolled infants (80) received oral diluted tincture of opium according to a standardized algorithm and were randomly assigned to receive oral clonidine (1 $\mu\text{g}/\text{kg}$ every 4 hours) (40 infants) or placebo (40 infants). Primary outcome was duration of opioid therapy. Secondary outcomes included the amount of opium required to control symptoms, number of treatment failures, and differences in blood pressure, heart rate, and oxygen saturation.

Results—The median length of therapy was 27% shorter in the clonidine group (11 [95% confidence interval: 8–15 days]) than in the placebo group (15 days [95% confidence interval: 12–17 days]). In the clonidine group, 7 infants required restarting opium after initial discontinuation versus none in the placebo group, with the total length of treatment/observation remaining significantly less in the clonidine group. Higher dosages of opium were required by 40% of the infants in the placebo group versus 20% in the clonidine group. Treatment failures occurred in 12.5% of the infants in the placebo group versus none in the clonidine group. Hypertension, hypotension, bradycardia, or desaturations did not occur in either group. Three infants in the clonidine group died as a result of myocarditis, sudden infant death syndrome, and homicide, all after hospital discharge and before 6 months of age.

Conclusions—In this randomized, double-blind trial, adding clonidine to standard opioid therapy for detoxification from in utero exposure to methadone or heroin reduced the duration of pharmacotherapy for neonatal abstinence without causing short-term adverse cardiovascular outcomes. A larger trial is indicated to determine long-term safety.

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Keywords

infants; opioid withdrawal; clonidine; tincture of opium

What's Known on This Subject

Little is known about alternative detoxification strategies for the infant with severe NAS. Clonidine has been used to detoxify adults with opioid dependency.

What This Study Adds

This study is the first randomized, placebo-controlled trial using clonidine as adjunct therapy for NAS. It adds an alternative treatment paradigm for these infants.

Neonatal Abstinence Syndrome (NAS) occurs in 55% to 94% of infants born to substance-dependent women.^{1–4} Clinical features include neurologic hyperexcitability (insomnia, irritability, hypertonia, hyperreflexia, tremors, and seizures), enteric symptoms (vomiting, diarrhea, feeding disturbances), and sympathetic/parasympathetic dysregulation (sweating, fever, tachypnea, and congestion). Holding, swaddling, and minimal stimulation may alleviate mild and nonprogressive withdrawal, but may be insufficient for severe NAS.^{5–7}

Treatment for severe NAS includes pharmacotherapy,^{8–10} the goals of which are to ameliorate hyperactivity and autonomic instability and to promote normal patterns of sleeping, feeding, and weight gain. Pharmacotherapy is most often performed in an inpatient setting,^{9,11–13} prolonging hospitalization.

Clonidine, an α_2 -adrenergic receptor agonist, is used to ameliorate opiate withdrawal symptoms in older children and adults.^{14,15} However, little is known about its efficacy and safety in treating infants with NAS. We hypothesized that clonidine (in combination with an opioid) would ameliorate withdrawal more rapidly than an opioid alone.

Methods

Study Subjects and Design

After institutional review board approval and written parental consent, this study was conducted at 3 Baltimore hospitals (Johns Hopkins Hospital [JHH], Johns Hopkins Bayview Medical Center [JHBMC], and Mt Washington Pediatric Hospital) from March 2002 through December 2005. All study infants were born at JHH or JHBMC and were either discharged to home or transferred to the Center for Neonatal Transitional Care at Mt Washington Pediatric Hospital for extended hospitalization. Of 221 eligible infants, 80 (36%) were randomly assigned to 2 treatment groups (Fig 1), which represented 80% (80 of 98) of the infants enrolled. Reasons for nonenrollment included (1) infant-mother dyad participation in another study, (2) starting an infant on diluted tincture of opium (DTO) before enrollment, (3) study staff unavailability to enroll infants, and (4) maternal refusal. Reasons for maternal refusal included (1) negative maternal experience with the sedating effects of clonidine and (2) desire not to involve infant in research or expose infant to “additional drugs.”

The study was a prospective, block-randomized, double-blind, placebo-controlled trial of clonidine and diluted tincture of opium (clonidine/DTO) versus opium alone (placebo/DTO) to treat infants with NAS. Infants were potentially eligible for inclusion between 0 and 14 days of age if they were prenatally exposed to opioids and developed moderate to severe NAS (2

consecutive modified Finnegan scores (MFSs)¹⁶ of ≥ 9) requiring pharmacotherapy. Infants were excluded for (1) gestational age of <35 weeks, (2) intrauterine growth retardation (birth weight below the 5th percentile), (3) congenital anomalies, (4) illness requiring oxygen, intravenous fluids, or medications, and (5) breastfeeding (possible confounder of breast milk opioids).

Infants were stratified before randomization to the hospital of birth and maternal methadone use. Urine toxicology was performed on each infant-mother dyad at the time of delivery, and a detailed drug history was obtained from each mother at the time of enrollment. Eligible patients were randomly assigned by the research pharmacist into 2 strata by a computerized random list in blocks of 4. Investigators, parents, and caretakers were blinded to group allocations until the study was completed.

Protocol

Enrolled infants were randomly assigned to receive either clonidine/DTO or placebo (isotonic saline)/DTO. A clear, colorless, liquid formulation of clonidine was diluted 1:10 in saline in the research pharmacy. Study infants received oral clonidine 1 $\mu\text{g}/\text{kg}$ every 4 hours or an equal volume of placebo. DTO was given as a 1:25 dilution, 0.4 mg/mL (morphine equivalent [ME]). The dose of clonidine (6 $\mu\text{g}/\text{kg}$ per day) used in this study was based on the only published report by Hoder et al¹⁷ who used clonidine (3–5 $\mu\text{g}/\text{kg}$ per day divided every 4–6 hours) in 7 newborns with NAS, our previous experience using open-label clonidine (6–12 $\mu\text{g}/\text{kg}$ per day divided every 4–6 hours) in 8 infants with intractable NAS, and input and then approval from the US Food and Drug Administration.

The dosing algorithm to guide the escalation and deescalation of DTO was used at all 3 sites. All infants were started on 0.2 mL DTO (0.08 mg ME) orally every 4 hours. NAS symptoms were uncontrolled if there were 2 consecutive MFSs of ≥ 9 . DTO was incrementally escalated to 0.3, 0.4, and 0.5 mL every 4 hours, then to 0.5, 0.7, and 0.9 mL every 3 hours, until withdrawal symptoms (MFS < 9) were controlled. Clonidine/placebo dose was based on measurement of weight (mL/kg) and maintained at that dose.

When symptoms were controlled (mean daily MFS < 9), infants were continued on clonidine/placebo and the DTO dose that controlled symptoms for at least 48 hours. Afterward, DTO was deescalated by increments of 0.05 mL per dose, for each 24-hour period. For example, an infant receiving 0.4 mL of DTO every 4 hours, whose symptoms were controlled for 48 hours, would then receive DTO 0.35 mL every 4 hours for 24 hours, with a reduction of 0.05 mL every 24 hours thereafter. If there were 2 consecutive MFSs of ≥ 12 during deescalation, the last previous DTO dose that controlled symptoms (MFS < 9) was resumed, with continuation of the protocol. Infants with 2 consecutive MFSs of ≥ 9 on the highest dose (0.9 mL every 3 hours) were defined as treatment failures, withdrawn from the treatment algorithm, and continued NAS management was at the discretion of the clinical care team. However, total opioid dose, length of treatment, MFSs, and vital signs were still collected, and follow-up calls were made to caregivers for 6 months after discharge. All infants were included in the intention-to-treat analysis.

Vital signs (temperature, heart rate, respiratory rate, oxygen saturation, blood pressure) were monitored; weights, input, and outputs were measured daily and the MFS was calculated every 3 to 4 hours. Infants were examined by a physician or neonatal nurse practitioner daily. Blood pressure was measured every 4 hours for the first 48 hours on and after stopping clonidine or placebo; otherwise, it was measured every 12 hours. Hypotension was defined as blood pressure below the 5th percentile. Rebound hypertension was defined as an increase of blood pressure above the 95th percentile of age-specific norms. Oxygen saturations $\leq 95\%$ were

considered abnormal. Infants were removed from the study if they had an illness necessitating transfer to the NICU.

Outcome Measures

The primary outcome was the total duration of pharmacotherapy for NAS. Secondary outcomes included the amount of DTO required to treat the NAS (with or without clonidine), treatment failure (>0.9 mL of DTO every 3 hours), seizures, weight gain, blood pressure, heart rate, and hemoglobin saturation measured by pulse oximetry.

Statistical Analysis

Before the study, the mean duration of treatment for NAS at the participating centers was 13 days (SD: 5). To demonstrate 25% reduction in the primary outcome with a power of .8 and a 2-tailed α value of .05, 40 infants were needed for each group. All 80 infants were included in the primary intention-to-treat analysis.

Unless otherwise indicated, for descriptive statistics, means and SDs are reported for normally distributed data and medians and interquartile ranges for nonnormally distributed data. Ninety-five percent confidence intervals (CIs) are also reported. Log-rank test is reported for time-dependent outcome data. Fisher's exact test is reported for categorical variables.

Continuous variables were analyzed by using an independent-samples t test for between group comparisons and a paired-samples t test for within group comparisons corrected for multiple comparisons. Continuous variables following nonnormal distributions were analyzed by using the Mann-Whitney U test. All tests were 2-sided with a statistical significance of $P < .05$. All data analyses were performed with SPSS 15 (SPSS Inc, Chicago, IL) and Prism 4.0 (GraphPad Software, Inc, San Diego, CA). The data and safety monitoring board reviewed the data in blocks of 20 patients enrolled, meeting 4 times during the course of the study. No early stopping rules were implemented because of the small sample size.

Results

Patient Characteristics

Forty infants each were assigned to the clonidine/DTO and the placebo/DTO groups. Both groups were similar with regard to maternal and infant demographic factors. Infants in the clonidine/DTO group were lower in average birth weight (mean: 2864 g [SD: 365] vs 3047 g [SD: 395]; $P = .03$) (Table 1). Of the infants, 89% were exposed to methadone, 69% to heroin, and 61% to cocaine plus an opiate during pregnancy. Of the infant-mother dyads, in both groups 3 of 40 either had a positive urine toxicological screen for benzodiazepines at time of delivery or a history of exposure during pregnancy. Exposure to sertraline or paroxetine occurred in 3 of 40 and 6 of 40 in the clonidine/DTO and placebo/DTO groups, respectively. Prenatal exposure to opiates was comparable in both groups as was maternal length of opiate dependency, maternal opiate dose at delivery, and number of mothers enrolled in a methadone treatment program (Table 2).

Primary Outcomes

For the clonidine/DTO group, the median length of therapy was 27% shorter than for the placebo/DTO group (11 days [95% CI: 8–15] vs 15 days [95% CI: 13–17]), with a range of 4 to 28 and 4 to 100 days (log-rank; $P = .02$, Fig 2), respectively. Although birth weight between the 2 groups differed, weight at the start of treatment did not. We used a symptom-based dosing algorithm for DTO, but both groups received the same dose of DTO/kg at the start of therapy. Infants prenatally exposed to methadone had a median length of treatment 3 times that of infants exposed to heroin alone (15 days [95% CI: 12–18] for methadone versus 5 days [95% CI: 4–

6] for heroin, log-rank; $P = .005$). When considering only infants exposed to methadone, clonidine was associated with a shorter length of therapy (12 days [95% CI: 9–16] for clonidine/DTO versus 17 days [95% CI: 11–22] for placebo/DTO, log-rank; $P = .01$). Nine infants in the placebo group had a length of treatment of ≥ 28 days (median: 32 [range: 29–100]), and all were treated with methadone. At the time of delivery, 5 of 9 and 3 of 9 infant-mother dyads had positive toxicology for heroin and cocaine, respectively, and 1 of 9 of the mothers was on Klonopin and Zoloft.

Secondary Outcomes

There was no difference in maximum weight loss or the time to reach the nadir of weight loss between the 2 groups (Table 3). The total dose (mean [SD]) of DTO required for the clonidine/DTO and placebo/DTO groups was 19.4 (20.1) mL, 7.7 (8.0) mg ME and 47.9 (89.2) mL, 19.2 (3.3) mg ME, respectively. Overall, the clonidine group needed less DTO/kg per day of treatment than the infants in the placebo group ($P < .03$, analysis of variance; Fig 3); the divergence occurred after the fifth day of treatment (Fig 3).

Five of the 80 infants failed treatment (required ≥ 0.9 mL of DTO every 3 hours). Treatment failures occurred on days 2, 3, 5, 7, and 16, all in the placebo/DTO group (Table 4). Three infants in the placebo/DTO group experienced seizures versus none in the clonidine/DTO group. Diagnosis of seizures was made by the clinical care team; all infants received an electroencephalogram after phenobarbital was administered and no infant had an abnormal electroencephalogram. Seven infants, all in the clonidine/DTO group, rebounded (increasing MFS, necessitating restarting DTO within 12–48 hours after stopping), but most infants were then weaned from DTO within 2 to 5 days (Table 4). Despite the inclusion of these additional days of treatment, the median length of treatment for the clonidine/DTO group was still less than for the placebo/DTO group (Fig 2; $P = .02$, log-rank test).

Blood pressures and heart rates were statistically lower in the clonidine/DTO group but remained in the normal range for newborns,¹⁸ and no infant required intervention for lower blood pressures. The maximum differences in systolic, diastolic, and mean arterial pressures were greatest at 24 and 48 hours after starting the protocol (Table 5). In the 48 hours after discontinuing the study drug, the clonidine/DTO group had a mean increase in systolic blood pressure from 81 (8) to 86 (6) mm Hg (Table 5). The clonidine/DTO group had a higher heart rate of 145 (10) versus 140 (9) beats per minute in the placebo/DTO group, which occurred 48 hours after starting the protocol. No difference in heart rate was observed 48 hours after stopping clonidine (Table 5).

Safety and Toxicity

Hypertension, hypotension, bradycardia, or hemoglobin desaturation were not observed during the study.

One infant (79C) in the clonidine/DTO group developed supraventricular tachycardia (SVT) at 5 days of age, 3 days after discontinuing clonidine, requiring 1 dose of adenosine, without recurrence. The infant was discharged from the hospital without additional treatment.

Three infants, all in the clonidine/DTO group, died within 2 months of life, all after discharge from the hospital. The causes of death were myocarditis, SIDS, and homicide (methadone overdose), confirmed by autopsy. These infants died at (1) 50 postnatal days (6 days after discharge and 44 and 23 days after clonidine and DTO were discontinued, respectively), (2) 32 postnatal days (23 days after discharge), or (3) 52 postnatal days (22 days after discharge). All deaths were reported as serious adverse events to the Food and Drug Administration and

the Data Safety and Monitoring Board, which deemed the deaths not likely attributed to clonidine exposure, and the study was allowed to continue.

Discussion

Multiple drug classes (opioids, benzodiazepines, barbiturates, and phenothiazines) have been used alone or in combination to manage NAS in infants born to drug addicted mothers.^{9,19} However, this is the first randomized, controlled trial of clonidine²⁰ and the largest prospective double-blind, randomized trial of any kind in this patient population. Our findings that clonidine in combination with DTO stabilized and detoxified infants with moderate to severe NAS more rapidly than DTO alone confirms the findings of a previously published, small, open-label study in neonates¹⁷ and validates by using α_2 -adrenergic receptor agonists in the management of opioid withdrawal symptoms.

Clonidine has successfully been used to treat the symptoms of opioid (and other drug) withdrawal in older children²¹ and adults.^{22–24} Being a central α_2 -adrenergic receptor agonist acting at presynaptic receptors in the midbrain and medulla, clonidine inhibits sympathetic outflow by decreasing central catecholamine release, leading to reduced blood pressure and heart rate.^{25,26} Clonidine is well absorbed after oral and transdermal administration, is highly lipid soluble, and readily distributes in the central nervous system.²⁷ Adverse effects include hypotension, rebound hypertension, atrioventricular block, and bradycardia. Concurrent use of β -blockers increases adverse events in adults,²⁸ and toxicity can result from accidental ingestion by children.^{29–31}

The transient decrease in blood pressure when starting clonidine/DTO and increase after stopping it was within the range of blood pressure norms for term infants.¹⁸ The differences in blood pressure between the 2 groups may have been directly related to clonidine or attributed to better early control of NAS. Rebound of symptoms of NAS was limited to the clonidine/DTO group (Table 4) and was controlled with small amounts of opioid for a short period. It is unclear if rebound was due to withdrawal from clonidine, DTO, or both. A 2-step reduction of the clonidine dose over 48 hours or weaning of opioids before stopping clonidine may result in fewer rebound events.

The 4 serious adverse events (1 episode of SVT and 3 deaths) all occurred in the clonidine/DTO group and happened after discontinuation of clonidine. The SVT episode occurred 3 days after stopping clonidine and was successfully treated with adenosine; it did not recur. Clonidine has been used to treat cardiac dysrhythmias³² and is associated with elevations of blood pressure and heart rate after abrupt discontinuation in children³³ and adults,³⁴ but has only caused SVT in 1 adult with severe heart and renal failure.³⁵ Although we think it unlikely, we cannot say with certainty that stopping clonidine caused the single episode of SVT in this otherwise healthy infant. Furthermore, whether clonidine contributed to the 3 deaths caused by myocarditis, SIDS, and homicide is not known.

This study was not designed to detect differences in lengths of hospitalization, because hospitalization may be prolonged and discharge delayed even after pharmacotherapy is no longer required in this population. In agreement with other reports,³⁶ methadone exposure was associated with longer pharmacotherapy for NAS than heroin exposure alone; clonidine shortened the length of treatment of methadone-exposed infants.

Interpretation of our results is limited by the small number of patients, which limited the statistical power to determine the true assessment of the effect of clonidine on short- and long-term adverse events. The short-term follow-up precluded assessment of long-term neurodevelopment. Although the study sample was diverse in gender, ethnicity, and exposure

to methadone and heroin, the small number of hospitals in a limited geographic area limits broad generalization of our findings.

Because the pharmacokinetics of clonidine in newborn infants was not available to us at the time of this trial, we chose the dose of 1 $\mu\text{g}/\text{kg}$ every 4 hours on the basis of the study of Hoder et al,¹⁷ our experience using clonidine in 8 infants with intractable NAS, and guidance of the Food and Drug Administration who granted the physician-sponsored investigational new drug to perform this trial. As part of the trial, population pharmacokinetics were performed and will be reported in a separate manuscript. The clonidine formulation (100 $\mu\text{g}/\text{mL}$, diluted to 5 $\mu\text{g}/\text{mL}$) administered orally in this study is commercially available for epidural injection; it was selected to ensure accurate dosing as opposed to a suspension made from tablets (0.2 mg).³⁷ A clonidine transdermal patch is available (in 3 concentrations) but can have problems with bioavailability resulting in nonuniform dosing and has been associated with toxicity in infants.³⁸

Dexmedetomidine has 8 times the affinity for the α_2 -adrenergic receptor than clonidine and is approved for short-term sedation for adults. Its effective sedative, analgesic, and anxiolytic properties without respiratory depression are desirable properties³⁹ also for infants,⁴⁰ but randomized trials are essential to demonstrate its efficacy and safety.

The American Academy of Pediatrics recommends DTO for treatment of severe NAS, although diluted morphine is frequently used and has similar efficacy.⁴¹ Clonidine, when used in combination with intravenous opioids, reduces total opioid use in infants.⁴² Thus, clonidine is likely to be effective when combined with oral morphine. For infants requiring >0.5 mL of DTO or 0.2 mg ME every 4 hours, we added clonidine to facilitate NAS symptom control and weaning of the opioid.

Conclusions

This prospective, double-blind, randomized, controlled trial supports the efficacy of clonidine in treating moderate to severe NAS in term newborns prenatally exposed to opioids. In conjunction with DTO, clonidine reduces the length of pharmacotherapy without adverse cardiovascular events. A larger trial is indicated to assess long-term safety.

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Kim; and the study was supervised by Drs Agthe and Gauda. Drs Gauda, Agthe, and Kim had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Abbreviations

NAS

neonatal abstinence syndrome

MFS

	modified Finnegan score
DTO	diluted tincture of opium
ME	morphine equivalent
SVT	supraventricular tachycardia
JHH	Johns Hopkins Hospital
JHBMC	Johns Hopkins Bayview Medical Center
CI	confidence interval

Figure 1.
Patient randomization. One patient received the initial 3 doses as clonidine instead of the study drug (placebo).

Figure 2.

Kaplan-Meier curve showing the effect of clonidine on days of DTO treatment for infants with NAS (log-rank; $P = .02$). The graph also includes the total length of DTO treatment for infants who rebounded who were assigned to the clonidine group.

Figure 3. Effect of clonidine on the amount of DTO (mL/kg) needed to control symptoms of NAS (mean $\pm$ SEM) ($P = .03$, analysis of variance, Bonferroni multiple comparisons). Placebo group, dashed line with circles; clonidine group, straight line with squares.

Table 1

Demographics of Study Participants

Infant Characteristic ^a	Clonidine/DTO Group (N = 40)	Placebo/DTO Group (N = 40)
Birth weight, mean (SD), g	2864 (365)	3047 (395) ^a
Weight at the start of treatment, mean (SD)	2749 (358)	2881 (411)
Gestational age, mean (SD), wk	38.5 (1.5)	38.9 (1.7)
Race or ethnic group, n (%)		
Black	19 (47.5)	13 (32.5)
White	21 (52.5)	27 (67.5)
Male gender, n (%)	19 (47.5)	18 (45)
Study site, n (%)		
JHH	20 (50)	20 (50)
JHBMC	20 (50)	20 (50)
Prenatal exposure, n (%)		
Methadone	36 (90)	35 (87.5)
Heroin	26 (65)	29 (72.5)
Other exposures, n (%)		
Cocaine	25 (62.5)	24 (60)
Tobacco smoke exposure	36 (90)	35 (87.5)
Age at start of treatment, mean (SD), d	2.3 (1.6)	2.0 (0.9)
MFS at start of treatment, mean (SD)	12 (3)	12 (3)

^aBirth weight: $P = .03$; otherwise, no statistically significant differences between groups.

Table 2**Maternal Demographics**

Maternal Characteristic ^a	Clonidine/DTO Group (N = 40)	Placebo/DTO Group (N = 40)
Age, mean (SD), y	30.6 (6.2)	31.8 (5.3)
Duration of opioid dependency, mean (SD), y	8.3 (5)	7.7 (5)
Enrollment in methadone program, n (%)	35 (87.5)	30 (75)
Methadone, mean (SD), mg		
Last dose before delivery	74.8 (43.2)	74 (28.7)
Maximum dose during pregnancy	90.1 (30)	79.1 (26.1)
Epidural or spinal anesthesia, n (%)	27 (67.5)	28 (70)
Delivery, n (%)		
Vaginal	26 (65)	33 (82.5)
Cesarean	14 (35)	7 (17.5)

^aThere were no statistically significant differences between groups.

Table 3**Treatment Outcomes**

Variable and Outcome	Clonidine/DTO Group (N = 40)	Placebo/DTO Group (N = 40)	P
Total daily DTO dose, mL			
Mean (SD)	19.4 (20.1)	47.9 (89.2)	.36 ^a
Median (range)	12.0 (3.8–93)	19.4 (2.8–517)	
Total daily ME dose, mg			
Mean (SD)	7.7 (8.0)	19.2 (3.3)	.36 ^a
Median (range)	4.8 (1.5–37.5)	7.7 (1.1–207)	
Maximum weight loss, mean (SD), % of birth weight	−6.91 (3.0)	−7.79 (3.6)	.21 ^b
Time to weight nadir, mean (SD), d	4.2 (2.8)	4.4 (2.3)	.73 ^b
Proportions of infants			
Required ≥0.5 mL of DTO every 4 h, n (%)	8 (20)	16 (40)	.09 ^c
Seizures, n (%)	0	3 (7.5)	.24
Treatment failure, n (%)	0	5 (12.5)	.05

^aMann-Whitney *U* test, clonidine/DTO group versus placebo/DTO group.

^bIndependent-samples *t* test.

^cFisher's exact test.

Table 4
Treatment Course for Infants in the Clonidine/DTO Group Who Rebounded

Study Identification	Duration of Initial Treatment With DTO, d	Maximum DTO Dose During Initial Therapy, mL Every 4 h	Hours Between Stopping DTO and Resuming DTO, h	Duration of Therapy After Restarting DTO, d	Maximum Dose After Restarting DTO, mL Every 4 h	Prenatal Methadone Exposure Maximum Dose, mg/d
15C	11	0.3	52	2	0.10	75
24C	7	0.3	28	5	0.10	50
26C	6	0.2	48	15	0.10	60
35C	6	0.2	22	2	0.10	65
38C	8	0.2	24	4	0.10	90
66C	19	0.5	36	4	0.05	150
74C	7	0.3	24	3	0.05	120

Table 5
Heart Rate and Blood Pressure Measurements

	Clonidine (N = 40)	Placebo (N = 40)	Difference, Mean (95% CI)
Heart rate, mean (SD), beats per min			
HR: baseline on	144 (7)	146 (9)	1.7 (−2.3 to 4.7)
HR: 24-h on treatment	141 (11) ^a	145 (10)	4.0 (−0.6 to 8.6)
HR: 48-h on treatment	140 (9) ^b	145 (10)	4.7 (0.46 to 8.9)
HR: baseline off	147 (11)	150 (8)	3.9 (−0.5 to 8.2)
HR: 24-h off treatment	149 (10)	153 (8) ^a	4.8 (0.8 to 8.8)
HR: 48-h off treatment	152 (10) ^b	153 (9)	1.4 (−2.9 to 5.6)
Blood pressure, mean (SD), mm Hg			
Systolic: baseline on	75 (8)	74 (11)	−1.0 (5.2 to 3.3)
Systolic: 24-h on treatment	75 (7)	80 (6) ^c	5.2 (2.3 to 8.1)
Systolic: 48-h on treatment	75 (6)	80 (7) ^c	4.7 (1.9 to 7.5)
Systolic: baseline off	81 (8)	85 (7)	3.7 (0.15 to 7.2)
Systolic: 24-h off treatment	81 (8)	85 (8)	4.2 (0.7 to 7.8)
Systolic: 48-h off treatment	86 (6) ^b	87 (8)	1.1 (−2.0 to 4.2)
Diastolic: baseline on	43 (8)	42 (10)	−1.1 (5.2 to 2.9)
Diastolic: 24-h on treatment	42 (7)	45 (9)	3.3 (−0.3 to 6.9)
Diastolic: 48-h on treatment	42 (6)	47 (8) ^b	4.4 (1.1 to 7.6)
Diastolic: baseline off	43 (7)	45 (8)	1.8 (−1.7 to 5.3)
Diastolic: 24-h off treatment	45 (8)	44 (7)	−0.7 (−4.1 to 2.7)
Diastolic: 48-h off treatment	46 (8) ^b	46 (9)	0.4 (−3.2 to 4.1)
MAP: baseline on	55 (6)	53 (8)	−2.1 (−5.5 to 1.2)
MAP: 24-h on treatment	55 (5)	58 (7) ^c	3.3 (0.5 to 6.1)
MAP: 48-h on treatment	55 (5)	59 (7) ^c	4.0 (1.4 to 6.6)
MAP: baseline off	57 (5)	60 (7)	3.1 (0.2 to 5.9)
MAP: 24-h off treatment	59 (6) ^b	60 (5)	1.5 (−1.2 to 4.1)
MAP: 48-h off treatment	61 (6) ^c	60 (6)	−1.2 (−4.0 to 1.5)

Variations in heart rate and blood pressure are shown before starting (on) or stopping (off) clonidine or placebo and at the 24- and 48-hour following periods, respectively. A paired-samples *t* test was used for within-treatment-group comparisons at baseline versus 24 hours and baseline versus 48 hours. HR indicates heart rate; MAP, mean arterial pressure.

^a Statistically significant at the .05 level.

^b Statistically significant at the .01 level.

^c Statistically significant at the .001 level.