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Association of *OPRM1* and *COMT* Single-Nucleotide Polymorphisms With Hospital Length of Stay and Treatment of Neonatal Abstinence Syndrome

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Abstract

Importance—Neonatal abstinence syndrome (NAS) caused by in utero opioid exposure is a growing problem; genetic factors influencing the incidence and severity have not been previously

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examined. Single-nucleotide polymorphisms (SNPs) in the μ-opioid receptor (*OPRM1*), multidrug resistance (*ABCB1*), and catechol-o-methyltransferase (*COMT*) genes are associated with risk for opioid addiction in adults.

Objective—To determine whether SNPs in the *OPRM1*, *ABCB1*, and *COMT* genes are associated with length of hospital stay and the need for treatment of NAS.

Design, Setting, and Participants—Prospective multicenter cohort study conducted at 5 tertiary care centers and community hospitals in Massachusetts and Maine between July 2011 and July 2012. DNA samples were genotyped for SNPs, and then NAS outcomes were correlated with genotype. Eighty-six of 140 eligible mother-infant dyads were enrolled. Infants were eligible if they were 36 weeks' gestational age or older and exposed to methadone or buprenorphine in utero.

Main Outcomes and Measures—Primary outcome measure was length of hospital stay, with between-group differences expressed as β and calculated with linear regression models. Secondary outcome measures included need for any medical treatment for NAS and treatment with 2 or more medications.

Results—Infants with the *OPRM1* 118A>G AG/GG genotype had shortened length of stay (β = −8.5 days; 95% CI, −14.9 to −2.1 days; *P* = .009) and were less likely to receive any treatment than AA infants (48% vs 72%; adjusted odds ratio, 0.76; 95% CI, 0.63–0.96; *P* = .006). The *COMT* 158A>G AG/GG genotype was associated with shortened length of stay (β = −10.8 days; 95% CI, −18.2 to −3.4 days; *P* = .005) and less treatment with 2 or more medications (18% vs 56%; adjusted odds ratio, 0.68; 95% CI, 0.55–0.86; *P* = .001) than the AA genotype. Associations with the *ABCB1* SNPs were not significant.

Conclusions and Relevance—Among infants with NAS, variants in the *OPRM1* and *COMT* genes were associated with a shorter length of hospital stay and less need for treatment. These preliminary findings may provide insight into the mechanisms underlying NAS.

In the past decade, there has been a significant increase in opioid use during pregnancy, estimated to affect 5.6 per 1000 births.[1,2] Neonatal abstinence syndrome (NAS) is a disorder composed of a constellation of signs and symptoms involving dysfunction of the nervous system, gastrointestinal tract, and respiratory system because of in utero drug exposure or iatrogenic withdrawal after postnatal use of drugs for pain control and sedation. The incidence of NAS has tripled in the past decade, affecting 60% to 80% of infants born to mothers receiving methadone or buprenorphine.[1,3] Although clinical factors, including maternal smoking, psychiatric medications, and breastfeeding, can affect the incidence and severity of NAS, to our knowledge contributing genetic factors influencing NAS have not been previously identified.[3–5]

Opioid addiction is highly heritable (≥70%), according to adult twin studies.[6] Polymorphisms in the μ-opioid receptor (*OPRM1*), multidrug resistance *(ABCB1*), and catechol-O-methyltransferase (*COMT*) genes have been associated with variability in adult opioid dependence. *OPRM1* encodes the μ-opioid receptor affecting opioid efficacy, dependence, and tolerance. The *OPRM1* 118A>G single-nucleotide polymorphism (SNP) has a minor allele frequency of 12% to 15% in whites and has been associated with an increased risk for addictive behaviors and variations in response to opioid medications.[7–10]

Morphine and methadone are substrates of the P-glycoprotein transporter 170, which is encoded in the *ABCB1* gene that regulates opioid absorption, distribution, and elimination.[8,9] The *ABCB1* 2677G/T/A, 1236C>T, and 3435C>T SNPs are highly prevalent (40%–50% in whites) and have been associated with methadone requirements in adults.[10–12] Catechol-o-methyltransferase is a key enzyme that metabolizes catecholamines in the nervous system and has been linked to substance abuse.[13] The *COMT* 158A>G SNP has a minor allele frequency of approximately 50% in whites and has been associated with responses to pain and morphine dosing requirements in adults.[10,13–15]

The objective of this study was to determine whether genomic variations in the *OPRM1, ABCB1,* and *COMT* genes are associated with length of hospital stay (LOS) and the need for treatment of NAS.

METHODS

Participants and Study Design

Infants of 36 weeks' gestational age or older were enrolled from Tufts Medical Center (Boston, Massachusetts), affiliated hospitals in the Boston area (Brockton Hospital, Melrose Wakefield Hospital, and Lowell General Hospital), and Eastern Maine Medical Center (Bangor, Maine) if they were exposed to maternal methadone (Tufts and Eastern Maine Medical Center) or buprenorphine (Tufts) in utero for at least 30 days, as documented in the maternal obstetric records. Participants were enrolled between July 2011 and July 2012. Mothers were recruited in the third trimester or upon admission to the labor and delivery unit. One infant was excluded because of a severe medical problem that prolonged hospitalization and affected the need for opioid medications. All mothers whose infants participated were also enrolled in the study. The study was approved by the institutional review boards of all sites and written informed consent was obtained from all participants.

To obtain a DNA sample, cord blood (PAXgene Blood DNA tube), maternal peripheral blood, or a saliva sample (Oragene OG-500 or OG-250 DNA collection kit with CS-1 sponges) was collected from all participants.[16,17] Baseline characteristics were collected from the infant's chart, including birth demographics, medical diagnoses, and NAS outcome measures. Maternal records were reviewed to obtain information, including obstetric complications, use of tobacco or psychotropic medications, and substance abuse treatment during pregnancy. Race and ethnicity as defined by the maternal participants was also collected because response to narcotics, the development of addiction, and genetic variations vary according to ethnicity.

Infants were treated according to institutional NAS treatment protocols. All infants were scored every 3 to 4 hours with a modified Finnegan NAS severity scoring system (MOTHER NAS Scale), which was performed in an identical fashion at all sites[3,18] and is a standardized 21-item checklist of the most frequently observed withdrawal symptoms, with a range of scores between 0 and 42. Infants with 3 consecutive scores of 8 or more or 2 consecutive scores of 10 or more began receiving first-line therapy, which was neonatal morphine solution (0.5–1.0 mg/kg/d) or methadone (0.5–1.0 mg/kg/d). If the infant reached the maximum recommended dose of morphine or methadone and still had 2 to 3 consecutive

scores of 8 or more, then second-line therapy was initiated with phenobarbital or clonazepam. Infants were weaned from morphine, methadone, and clonazepam as inpatients and monitored for 48 hours before discharge home. Phenobarbital weaning was completed on an outpatient basis.

Laboratory Methods

All DNA samples were sent to the Tufts Medical Center Clinical and Translational Research Center Core Laboratory for processing. Blood samples collected in DNA tubes were frozen within 14 days at −70°C until DNA isolation.[16] Salivary specimens were stored at room temperature before DNA extraction.[17] DNA was then isolated and the regions of interest were genotyped for the following 5 SNPs: 118A>G (rs1799971, dbSNP database; assay C_8950074_1) within the *OPRM1* gene; 3435C>T (rs1045642, dbSNP; assay C_7586657 _20), 2677G/T/A (rs 2032582, dbSNP; assays C_11711720C_30 and C_11711720D_40), and 1236C>T (rs1128503, dbSNP; assay C_7586662 _10) within the *ABCB1* gene; and 158A>G (rs4680, dbSNP; assay C_25746809_50) within the *COMT* gene, using established Taqman technology.

Statistical Methods

Genotype frequencies for the infants were summarized and the χ^2 test (goodness of fit) was used to assess for differences from the HapMap CEU database.[10] Each SNP was assessed for Hardy-Weinberg equilibrium. Demographic and clinical information was described for the cohort. NAS outcome measures were LOS (days), maximum modified Finnegan score during the hospitalization, maximum daily dose of morphine or methadone (milligrams), need for any NAS treatment, and need for treatment with 2 or more medications (yes/no). Length of hospital stay was chosen as the primary outcome measure because it reflects the overall severity of NAS (longer LOS is associated with more treatment with 1 or more medications to control symptoms and a longer weaning period) and is routinely used in studies of NAS.

We used the dominant genetic model to assess the association between each SNP and the NAS outcome measures. Homozygotes for the major allele were compared with grouped heterozygotes and homozygotes for the minor allele. Then, in an additive genetic model, the number of minor alleles (0, 1, or 2) was tested for association with the outcome. Because total opioid treatment days correlated strongly with LOS ($r = 0.92$; $P < .001$), opioid days are not reported separately. Independent sample *t* tests or analysis of variance was used to assess for differences in continuous variables; and the χ^2 test (test of independence) for categorical variables. Additive models that were statistically significant were further examined by testing pairwise comparisons and trend. For those outcome measures with $P < .05$ in the bivariable analysis, linear or logistic regression was performed to adjust for demographic and clinical factors that were found to be associated with the outcome at $P < .05$ in bivariable analysis. β Coefficients were derived from linear regression models, representing between-group differences in LOS. The α level (probability of type I error) for genetic association results was set at .01, applying the Bonferroni method to account for the testing of 5 SNPs.

Those SNPs that demonstrated an association with NAS outcomes were then combined in linear and logistic regression models to determine whether there was an additive effect of carrying more than 1 of these minor alleles. Regression analyses were also used to examine whether knowledge of the maternal SNP genotype was associated with infant NAS outcomes. The McNemar test was used to assess the correlation between maternal and infant genotypes. Statistical analyses were performed with R programming (2010).

RESULTS

From the Tufts-affiliated sites, a total of 65 mothers were eligible; 5 refused consent and 9 were missed, leading to an enrollment of 78% (n = 51). At Eastern Maine Medical Center, an estimated 75 mothers were eligible and 47% (n = 35) were enrolled (the remainder were missed). Our total cohort included 86 mother-infant dyads (all singleton pregnancies). Mean birth weight was 3.2 kg (95% CI, 3.1–3.3 kg) and 98% of participants were white (Table 1). Medical and psychiatric comorbidities of the participants are listed in Table 1. Eighty-one (94%) of the mothers were receiving opioid substitution therapy from the first trimester, with 17 (20%) relapsing into illicit drug use during the third trimester. Five of the mothers had gestational diabetes or preeclampsia; none had significant complications during delivery.

Average LOS for all infants was 22.3 days (95% CI, 18.8–25.8 days); for treated infants, 31.6 days (95% CI, 28.2–35.0 days). Fifty-six (65%) of all infants were treated for NAS, and 24% were also treated with phenobarbital (n = 16) or clonazepam (n = 5). NAS outcome measures were not significantly different between the Tufts and Eastern Maine Medical Center sites.

DNA was available for all 86 infants and 79 of the mothers. The genotype frequencies for the infants are shown in Table 2. A genotype was unable to be determined for 1 infant for the *OPRM1*, 2 infants for the *COMT*, and 2 to 4 infants for each of the *ABCB1* SNPs (insufficient sample available). The *OPRM1* 118A>G, *COMT* 158A>G, *ABCB1* 2677G/T/A, and *ABCB1* 1236C>T SNPs demonstrated Hardy-Weinberg equilibrium and were not statistically different from the allele frequencies of the HapMap CEU.[10] A higher allele frequency of the minor T allele for *ABCB1* 3435C>T was found in our population in comparison with the HapMap CEU ($\chi^2 = 6.78$; $P = .03$).

Variables related to NAS severity are shown in Table 3. Breastfeeding demonstrated a consistent association with all outcome measures, with breastfed infants demonstrating decreased LOS (15.8 vs 27.4 days; $P < .001$) and receipt of any medical treatment for NAS (50% vs 77%; $P = .009$). Infants born to mothers who smoked cigarettes had a higher likelihood of receiving 2 or more medications (31% vs 0%; $\chi^2 = 7.88$; $P = .005$). However, cigarette smoking was not found to be significantly related to other NAS severity outcome measures (Table 3). Maternal methadone or buprenorphine dose at delivery did not correlate with any NAS outcome measure.

OPRM1, *COMT*, and *ABCB1* SNP Associations

Infants with the *OPRM1* 118A>G AG or GG genotype had shorter LOS and were significantly less likely to receive any treatment than AA infants in adjusted, but not unadjusted, analyses (Table 4). Maximum Finnegan scores and treatment rates with 2 or more medications were not significantly different. Analyses were adjusted for study site and breastfeeding. The additive model was not applied to *OPRM1* because the minor allele frequency was less than 0.2.

In a dominant model (AA vs AG/GG), infants with the *COMT* AG or GG genotype had shorter LOS compared with those with the AA genotype and less treatment with 2 or more medications in adjusted and unadjusted analyses (Table 5). The maximum Finnegan score did not differ between infants with AA/GG and AA genotypes.

In an additive genetic model for the *COMT* SNP (AA vs AG vs GG), infants with the AG and GG genotypes received 2 or more medications less often than AA infants (AG, 9/46 [20%]; GG, 3/22 [13%]; and AA, 10/17 [56%]; $P = .005$), as seen in the dominant model (eTable 1, available at http://www.jama.com). However, the AG genotype was not significantly different from the GG genotype for any other NAS severity outcome measure.

In bivariable analyses, no NAS severity measure was different according to infant genotype in any of the 3 *ABCB1* SNPs (eTable 2).

Combined Infant *OPRM1* and *COMT* Genotypes

Twenty-three infants had both protective alleles (defined as *OPRM1* and *COMT* AG/GG genotypes), 2 had *OPRM1* only, 45 had *COMT* only, and 15 had neither. Given the findings for the *OPRM1* 118A>G and *COMT* 158A>G SNPs, regression analyses were performed to compare infants who had both protective alleles with those who had the G allele in *COMT* only or in neither SNP. In linear regression adjusted for breastfeeding, LOS was not statistically significantly different for infants with neither allele (β = 13.1 days; 95% CI, 3.2–23.1 days) or *COMT* only (β = 6.7; 95% CI, −1.0 to 14.5) compared with infants with both. In logistic regression adjusted for breastfeeding, the receipt of any NAS treatment was not statistically significantly different when neither protective allele was present (odds ratio = 6.37; 95% CI, 1.40–37.34) or when only *COMT* was present (odds ratio = 3.81; 95% CI, 1.26–12.55).

Maternal *OPRM1* and *COMT* Genotype

In an exploratory model we tested whether maternal *OPRM1* and *COMT* SNP genotypes had any association with any NAS outcome measure. Maternal *O P R M 1* AG/GG genotype in the 118A>G SNP was associated with less receipt of any NAS treatment (40% vs 69%; $P = .04$; adjusted odds ratio = 0.70; 95% CI, 0.54–0.90; $P = .008$) in a model that adjusted for study site and breastfeeding. After adjusting for the infant *OPRM1* genotype, the odds for needing any treatment were no longer statistically significant (odds ratio = 0.74; 95% CI, 0.57–1.02). In a model that adjusted for infant *OPRM1* genotype and breastfeeding, maternal *OPRM1* genotype was not associated with a decrease in LOS (β = −11.0 days; 95% CI, −20.6 to −1.4 days). Infant *OPRM1* genotype was independent of maternal genotype

(McNemar $\chi^2 = 3.37$; $P = .07$) in our cohort, likely secondary to the small sample size. No differences in NAS outcome measures were found according to maternal *COMT* 158A>G genotype.

DISCUSSION

Data indicate that SNPs in the *OPRM1* (118A>G) and *COMT* (158A>G) genes in the infant are associated with NAS, with those with the minor G alleles in these 2 SNPs demonstrating a reduction in LOS and for the receipt of any medical treatment of NAS. Data also suggest that maternal *OPRM1* 118A>G genotype may be associated with neonatal outcome. Given our small sample size, the results of this study should be taken as preliminary, with need for further confirmation of these associations in larger studies.

The *OPRM1* 118A>G SNP causes an amino acid change resulting in a 3-fold increase in binding with β-endorphin.[19] Data from animal models and in vivo studies also indicate that the G allele is associated with a decrease in protein expression and μ-opioid receptor binding.[19–21] In a mouse model, differences in the affective component of morphine withdrawal were observed, depending on SNP genotype.[21] Previous studies have also demonstrated a protective effect of the G allele against nausea and vomiting.[22] Infants with the G allele, a variant known to be associated with adult drug addiction, may have been more tolerant to opioid withdrawal because of decreased opioid receptor binding and increased binding of endogenous β-endorphin. In addition, given that the minor allele frequency is 12% to 15%, if the mother carries at least 1 copy of the G allele, she has a 50% or greater chance of passing along this allele to her infant. Future studies will need to determine whether this SNP is a helpful prenatal predictor of NAS.

Variations in the *COMT* gene have previously been linked with disorders such as schizophrenia, anxiety, and drug abuse.[13] Addictive drugs increase the brain's dopaminergic transmission, with the COMT enzyme playing a crucial role in dopamine inactivation. The *COMT* 158A>G SNP leads to a valine-to-methionine amino acid substitution. The Met-containing enzyme (G allele) demonstrates a 3-to 4-fold reduction in COMT enzyme activity.[23,24] In individuals with the G allele, there is up-regulation of the μ-opioid receptor in various regions of the brain.[24] Previous studies in adult patients with cancer showed that those with the Val/Val (AA) and Val/Met (AG) genotypes required significantly more morphine than those with Met/Met (GG).[14] We postulate that an association exists in infants with the G allele, with shorter LOS and the need for less treatment for NAS because of reduction in COMT enzyme activity, increased level of circulating catecholamines, and improved stress tolerance.

Though we did not see significant results for the 3 *ABCB1* SNPs, this gene remains an important candidate gene for NAS. SNPs in this gene have previously been shown to affect methadone requirements in adults by decreasing P-glycoprotein transporter expression and function.[11,12] Studies in a larger population of infants are necessary to further evaluate the effects of variations in the *ABCB1* gene on NAS.

This study has some limitations. Though the modified Finnegan scoring system is a well-validated tool for evaluating NAS symptoms, it remains somewhat subjective, with significant intraobserver variability. Identical NAS scoring guidelines were used at all study centers. However, there may have been variability in scoring, treatment, and weaning methods among the many physicians and nurses providing care to these infants. The use of expert NAS scorers and supervised treatment protocols is warranted in future studies.

In addition, our primary outcome measure of LOS can be influenced by social determinants such as placement in foster care. However, we demonstrated a strong correlation between LOS and total opioid treatment days ($r = 0.92$) in our cohort, making social factors unlikely to be a significant contributor. We also did not collect data on the cumulative amount of replacement opioids the infants received during the hospitalization, which could serve as an additional outcome measure.

Other limitations to the generalizability of this study include lack of ethnic variability (minor allele frequency can vary according to ethnicity) and the relatively small number of infants, which did not allow for replication of results or full exploration of the additive genetic model. It is possible that the nonsignificance for many of the outcome measures was due to small sample size and lack of statistical power.

To our knowledge, this is the first study to examine the association of genomics with opioid withdrawal in infants and may provide insight into the mechanisms underlying NAS. There is a need for replication of these results before more definitive conclusions can be made of the association between the *OPRM1* and *COMT* variants and NAS.

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Table 1

Maternal and Infant Demographics

	No. (%)
Infants (n = 86)	
Gestational age ≥38 wk	70 (81)
Male	51 (59)
White	84 (98)
Breastfed	38 (44)
Medical comorbidities	
Respiratory	13 (15)
Hypoglycemia	2 (2)
Cow's milk intolerance	7 (8)
Mothers (n = 86)	
Cesarean delivery	31 (36)
HIV positive	2 (2)
Hepatitis C positive	30 (35)
Opioid medication	
Methadone	55 (64)
Dose, mean (95% CI), mg[a]	106.3 (88.5–124.1)
Buprenorphine	31 (36)
Dose, mean (95% CI), mg[a]	15.8 (12.7–18.9)
Smoked cigarettes	67 (78)
Psychiatric diagnoses	
Depression	15 (17)
Bipolar disorder	8 (9)
Anxiety disorder	32 (37)
Benzodiazepines[b]	10 (12)
SSRIs[b]	4 (5)

Abbreviations: HIV, human immunodeficiency virus; SSRI, selective serotonin reuptake inhibitor.

[a] Dose of maternal methadone and buprenorphine at delivery.

[b] Maternal use of benzodiazepines or SSRIs during the third trimester.

Table 2

Infant Genotype Frequencies (N = 86)

Single-Nucleotide Polymorphism	No.	Genotype Frequencies	Allele Frequencies	*P* Value for Hardy-Weinberg
OPRM1 118A>G (rs1799971)	85	AA = 0.71	A = 0.85	.42
		AG = 0.28	G = 0.15	
		GG = 0.01		
ABCB1 3435C>T (rs1045642)	83	CC = 0.26	C = 0.45	.03
		CT = 0.38	T = 0.55	
		TT = 0.36		
ABCB1 2677G/T/A (rs2032582)	82	GG = 0.26	G = 0.48	.28
		GT = 0.44		
		TT = 0.26	T = 0.48	
		AG = 0.04	A = 0.04	
		AA = 0.01		
ABCB1 1236C>T (rs1128503)	84	CC = 0.36	C = 0.59	.65
		CT = 0.46	T = 0.41	
		TT = 0.18		
COMT 158A>G (rs4680)	84	AA = 0.20	A = 0.47	.43
		AG = 0.54	G = 0.53	
		GG = 0.26		

Table 3

Potential Covariates of Neonatal Abstinence Syndrome Severity

Variable	Length of Stay, Mean (95% CI), d	*P* Value	Infants Treated, No. (%)	*P* Value
Methadone (n = 55)	24.2 (19.7–28.7)	.15[a]	38 (69)	.30[b]
Buprenorphine (n = 31)	18.9 (13.2–24.6)		18 (58)	
Methadone maternal dose, mg[c]	*r* = 0.15	.29[d]	Treated: 99.9 (77.4–122.4) vs untreated: 109.0 (84.9–133.1)	.57[a]
Buprenorphine maternal dose, mg[c]	*r* = 0.08	.69[d]	Treated: 15.7 (10.6–20.8) vs untreated: 15.8 (11.5–20.1)	.96[a]
Benzodiazepines				
No (n = 74)	21.1 (17.6–24.6)	.27[a]	47 (63)	.69[b]
Yes (n = 10)	30.1 (13.0–47.2)		7 (70)	
Smoking				
No (n = 19)	18.4 (11.3–25.5)	.22[a]	11 (58)	.45[b]
Yes (n = 67)	23.4 (19.3–27.5)		45 (67)	
Breastfeeding				
No (n = 48)	27.4 (22.5–32.3)	<.001[a]	37 (77)	.009[b]
Yes (n = 38)	15.8 (11.5–20.1)		19 (50)	
Gestational age, wk				
<38 (n = 16)	25.5 (16.0–35.0)	.43[a]	11 (69)	.74[b]
≥38 (n = 70)	21.6 (17.8–25.4)		45 (64)	

First-line neonatal abstinence syndrome treatment

Variable	Length of Stay, Mean (95% CI), d	*P* Value	Infants Treated, No. (%)	*P* Value
Morphine solution (n = 38)	32.6 (28.4–37.0)	.35[a]	NA	
Methadone (n = 18)	29.4 (23.9–34.9)		NA	

Abbreviation: NA, not applicable.

[a] *P* values calculated with 2-sample *t* tests.

[b] *P* values calculated with a χ^2 test of independence.

[c] Dose of maternal methadone and buprenorphine at delivery.

[d] *P* values calculated with the Pearson correlation test.

Table 4

OPRM1 118A>G Dominant Model[a]

Neonatal Abstinence Syndrome Outcome	*OPRM1* AA (n = 60)	*OPRM1* AG/GG (n = 25)	*P* Value for Unadjusted	Adjusted Difference (95% CI)	*P* Value for Adjusted
LOS, mean (95% CI), d	24.1 (19.8 to 28.4)	17.6 (11.2 to 24.0)	.19[b]	β = −8.5 (−14.9 to −2.1)[c]	.009
Infants treated, No. (%)	43 (72)	12 (48)	.04[d]	OR, 0.76 (0.63 to 0.96)	.006
≥2 Medications, No. (%)	12 (28)	4 (16)	.23[d]		
Maximum daily morphine, mean (95% CI), mg	1.79 (1.60 to 1.98)	1.98 (1.71 to 2.25)	.52[b]		
Maximum daily methadone, mean (95% CI), mg	1.76 (1.59 to 1.93)	1.17 (0.87 to 1.48)	.26[b]		
Maximum score, mean (95% CI)[e]	12.0 (11.1 to 12.9)	10.7 (9.5 to 11.9)	.08[b]		

Abbreviations: LOS, length of stay; *OPRM1*, μ-opioid receptor; OR, odds ratio.

[a] Adjusted analyses performed only for our primary outcome measure of LOS and those with $P < .05$. All analyses were adjusted for breastfeeding and study site.

[b] *P* values for unadjusted results were calculated with 2-sample *t* tests.

[c] β Coefficients indicating between-group differences in LOS were calculated with linear regression models.

[d] *P* values for unadjusted results were calculated with a χ^2 test of independence.

[e] Maximum modified Finnegan score during the hospitalization.

Table 5

COMT 158A>G Dominant Model[a]

Neonatal Abstinence Syndrome Outcome	*COMT* AA (n = 16)	*COMT* AG/GG (n = 68)	*P* Value for Unadjusted	Adjusted Difference (95% CI)	*P* Value for Adjusted
LOS, mean (95% CI), d	31.1 (23.5 to 38.7)	20.4 (16.5 to 24.3)	.014[b]	β = −10.8 (−18.2 to −3.4)[c]	.005
Infants treated, No. (%)	14 (87.5)	41 (60.3)	.04[d]	OR, 0.79 (0.69 to 0.99)	.02
≥2 Medications, No. (%)	9 (56.2)	12 (17.6)	.001[d]	OR, 0.68 (0.55 to 0.86)	.001
Maximum daily morphine, mean (95% CI), mg	2.10 (1.63 to 2.57)	1.74 (1.59 to 1.89)	.05[b]		
Maximum daily methadone, mean (95% CI), mg	1.78 (1.36 to 2.20)	1.58 (1.42 to 1.74)	.59[b]		
Maximum score, mean (95% CI)[e]	13.6 (11.6 to 15.6)	11.3 (10.6 to 12.0)	.03[b]	β = −2.3 (−4.0 to −0.5)	.011

Abbreviations: *COMT*, catechol-O-methyltransferase; LOS, length of stay; OR, odds ratio.

[a] Adjusted analyses performed only for our primary outcome measure of LOS and those with $P < .05$. All analyses were adjusted for breastfeeding and study site.

[b] *P* values for unadjusted results were calculated with 2-sample *t* tests.

[c] β Coefficients indicating between-group differences in LOS were calculated with linear regression models.

[d] *P* values for unadjusted results were calculated with a χ^2 test of independence.

[e] Maximum modified Finnegan score during the hospitalization.