Central Nervous System Depression of Neonates Breastfed by Mothers Receiving Oxycodone for Postpartum Analgesia

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Objective To quantify the incidence of central nervous system (CNS) depression in neonates breastfed by mothers medicated with oxycodone as compared with neonates whose breastfeeding mothers used codeine or acetaminophen only.

Study design We retrospectively compared 3 cohorts in 533 breastfeeding mother-infant pairs exposed to oxycodone (n = 139), codeine (n = 210), or acetaminophen only (n = 184). Standardized questionnaires were administered to mothers during the postpartum period to identify maternal and neonatal health outcomes temporally related to analgesia exposure.

Results Maternal exposure to oxycodone during breastfeeding was associated with a 20.1% rate of infant CNS depression (28/139) compared with 0.5% in the acetaminophen group (1/184; $P < .0001$; OR, 46.16; 95% CI, 6.2-344.2) and 16.7% in the codeine group (35/210; $P > .05$; OR, 0.79; 95% CI, 0.46-1.38). Mothers of neonates with symptoms in the oxycodone and codeine cohorts took significantly higher doses of medication compared with mothers of infants with no symptoms in the same cohorts ($P = .0005$ oxycodone; median, 0.4 mg/kg/day; range, 0.03-4.06 mg/kg/day versus median, 0.15 mg/kg/day; range, 0.02-2.25 mg/kg/day; codeine $P < .001$; median, 1.4 mg/kg/day; range, 0.7-10.5 mg/kg/day versus 0.9 mg/kg/day; range, 0.18-5.8 mg/kg/day). Mothers were significantly more likely to experience sedative adverse effects from oxycodone as compared with codeine ($P < .0001$; OR, 17.62; 95% CI, 9.95-31.21).

Conclusion Oxycodone is not a safer alternative to codeine in breastfed infants. *(J Pediatr 2012;160:33-7)*.

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Oxycodone is a semisynthetic opioid commonly used to treat moderate to severe pain postoperatively and in cancer. There is limited information on the excretion of oxycodone into breast milk and the subsequent effects, if any, on the breastfed child.[1] On the basis of a few characteristics of oxycodone, it may be readily transferred into breast milk.[1,2] Oxycodone has high oral bioavailability (60%-87% in adults) and rapid oral absorption.[3,4] It is moderately protein bound (38%-45%) such that there may be sufficient amount of unbound drug in the maternal plasma to be transferred to milk.[5] Oxycodone is a weak base (pKa 8.5).[6] Because breast milk (pH 7.2) is slightly more acidic than plasma (pH 7.4), unbound oxycodone can be subjected to an "ion-trapping" effect.

Because of the recent publicity about neonatal central nervous system (CNS) depression after codeine and breastfeeding,[7] some clinicians are now prescribing oxycodone in place of codeine during the postpartum period. However, like codeine, oxycodone is a substrate for the cytochrome P450 (CYP) 2D6 and 3A4. CYP3A4 produces the major metabolite, noroxycodone via N-demethylation, and CYP2D6 catalyzes O-demethylation producing oxymorphone, which accounts for 10% of the circulating oxycodone metabolites. These metabolites have varying potencies and affinities for the mu opioid receptor. Oxymorphone is 14 times more potent than oxycodone.[8] Its affinity for the mu opioid receptor is 40- and 3-fold higher than oxycodone and morphine, respectively.

The neonatal safety of oxycodone use during breastfeeding has not been established. Thus, it is important to clarify the incidence of neonatal CNS depression. The objectives of this study are to quantify the incidence of CNS depression in neonates breastfed by mothers medicated with oxycodone, to determine whether

CNS	Central nervous system
CYP	Cytochrome P450
PMA	Postmenstrual age

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oxycodone is a safer alternative to codeine, and to identify characteristics of symptomatic cases that may help with clinical management.

Methods

A retrospective study consisting of 3 cohorts (breastfeeding mother-infant pairs exposed to oxycodone, codeine, or acetaminophen only) was conducted, after obtaining research ethics board approval from the Hospital for Sick Children (Toronto, Ontario, Canada). The mother-infant pairs were recruited from the Motherisk Program at the Hospital for Sick Children, a teratology information center that counsels women with evidence-based information about the safety of using medication during pregnancy and breastfeeding.

The files of women who had called to inquire about the safety of acetaminophen only, codeine, or oxycodone during breastfeeding were reviewed.

The acetaminophen-only cohort (n = 590) consisted of mothers who had contacted the Motherisk Program between January 2004 and December 2008 to inquire about the safety of acetaminophen during breastfeeding. In the codeine cohort (n = 681), mothers had contacted Motherisk inquiring about codeine with acetaminophen (for example, Tylenol with codeine T1: acetaminophen 300 mg + codeine phosphate 8 mg; T2: acetaminophen 300 mg + codeine phosphate 15 mg; or most commonly T3: acetaminophen 300 mg + codeine phosphate 30 mg) or codeine alone between January 2004 and December 2008. A subset of the codeine study participants were included in an earlier study by Madadi et al.[9] The oxycodone cohort (n = 289), recruited between January 2007 and October 2010 as a response to the increased prevalence of oxycodone use in the breastfeeding population, consisted of mothers who had asked about oxycodone-acetaminophen (for example percocet: acetaminophen 325 mg + 5 mg oxycodone or 10 mg oxycodone or 20 mg oxycodone) or oxycodone alone during breastfeeding.

Original intake forms from the Motherisk Program contain maternal demographic information (age, parity, gravidity, and weight), infant information (sex, birth weight, birth defects, postmenstrual age [PMA] of child at time of opioid/acetaminophen use), dose of oxycodone/codeine/acetaminophen that had been prescribed, indication, frequency of breastfeeding, and duration of breastfeeding recorded at the time of consultation.

After informed maternal consent, a standardized follow-up questionnaire was administered during a telephone interview to elucidate adverse maternal and neonatal events, with the focus on CNS depression temporally related to either 3 of the drugs according to maternal self-reports and the reversibility of CNS depression on discontinuation of opioid usage or breastfeeding. Infants identified with symptoms of CNS depression (sleepiness/lethargy or not waking up for feeding during the period of drug exposure via breast milk) were classified as "symptomatic." Dose of medication used, frequency of breastfeeding, duration of breastfeeding, supplementation with formula, maternal ethnicity, and maternal adverse effects during medication use were also recorded during this second consultation. Mothers identified as experiencing sedation were also classified as "symptomatic."

We excluded mothers who did not provide consent for the telephone interview, mothers who took other sedative medications beside oxycodone or codeine alone (such as benzodiazepines, skeletal muscle relaxant, and oxycodone and codeine concurrently), and mothers who reported using alcohol or drugs of abuse in late pregnancy or while breastfeeding. We also excluded cases in which CNS anomalies were diagnosed in infants.

The demographic characteristics of the 3 cohort were compared with one-way ANOVA or Kruskel-Wallis when appropriate. Within the oxycodone and codeine group, the symptomatic infants were compared with asymptomatic infants with the Student *t* test or Fischer exact test or nonparametric tests (Mann Whitney or Wilcoxon signed-ranked test) when appropriate. ORs and 95% CIs were calculated.

Results

We examined the files of 1560 women inquiring about oxycodone (n = 289), codeine (n = 681), or acetaminophen only (n = 590). Of these, 533 women were available for follow up (139 in the oxycodone cohort, 210 in the codeine cohort, and 184 in the acetaminophen-only group; **Figure** [available at www.jpeds.com]).

In the codeine group, 65% (137/210) of mothers were taking a combination codeine-acetaminophen product, and the rest were taking codeine alone (73/210). In the oxycodone group, 52.5% (73/139) of mothers were taking a combination oxycodone-acetaminophen product, and the rest were taking oxycodone alone (66/139).

There were no differences in maternal age, ethnic distribution, and infant birth weight in the 3 cohorts (**Table I**). However, maternal weight, parity, and PMA of the infant at the time of drug exposure were significantly different in the 3 cohorts. Further statistical analysis between the oxycodone and codeine cohorts only showed that PMA and parity remained significant (**Table II**; available at www.jpeds.com).

The indication for oxycodone, codeine, and acetaminophen-only use during breastfeeding were significantly different in the 3 cohorts (**Table III**), but not between the oxycodone and codeine cohorts (**Table IV**; available at www.jpeds.com).

In the oxycodone cohort, 20.1% (28/139) of mothers reported neonatal CNS depression compared with only 0.5% (1/184) of mothers in the acetaminophen-only group ($P < .0001$; OR, 46.16; 95% CI, 6.191-344.2) and 16.7% (35/210) of mothers in the codeine group ($P > .05$; OR, 0.7929; 95% CI, 0.4570-1.376). Of the 28 neonates who experienced sedation after being breastfed by an mother medicated with oxycodone, 4 infants were also observed to have "irregular breathing." In addition to death as a result of opioid toxicity in one infant whose mother was taking codeine,[7,9] 4 infants in

Table I. Demographic characteristics of mothers and their infants in the oxycodone, codeine, and acetaminophen-only cohorts

	Oxycodone cohort (n = 139)	Codeine cohort (n = 210)	Aacetaminophen-only cohort (n = 184)	*P* value
Maternal age, years	32.9 (4.6) n_{dcr} = 139	32.7 (4.5) n_{dcr} = 153	32.0 (5.0) n_{dcr} = 173	.18
Maternal weight, kg	73.2 (14.3) n_{dcr} = 139	72.9 (14.7) n_{dcr} = 183	67.9 (13.8) n_{dcr} = 166	<.001
Nulliparous, n (%)	51 (37%) n_{dcr} = 139	107 (60%) n_{dcr} = 179	109 (61%) n_{dcr} = 179	<.0001
Maternal non-Caucasian ethnicity, n (%)	17 (28.7%) n_{dcr} = 139	31 (38.3%) n_{dcr} = 210	46 (25.0%) n_{dcr} = 184	.58*
Infant birth weight, kg	3.37 (0.59) n_{dcr} = 139	3.42 (0.59) n_{dcr} = 207	3.41 (0.58) n_{dcr} = 177	.76
Infant PMA, weeks†	53.6 (32.9) n_{dcr} = 138	53.9 (16.4) n_{dcr} = 165	53.9 (13.3) n_{dcr} = 181	.0012

n_{dcr}, number of responses per discriptor.
Maternal-infant pair characteristics, mean (SD).
*For dichotomous variables, the Fisher exact test was used to compare the contingencies; $P < .05$ denotes statistical significance.
†Age of infants at the time of oxycodone/codeine/acetaminophen-only exposure and breastfeeding.

the codeine cohort were taken to the emergency department for symptoms of lethargy.

Oxycodone-medicated mothers of symptomatic infants took significantly higher doses of oxycodone than mothers of asymptomatic infants (median, 0.4 mg/kg/day; range, 0.03-4.06 mg/kg/day; $P = .005$ versus median, 0.15 mg/kg/day; range, 0.02-2.30 mg/kg/day). However, all mothers received doses that fell within the recommended range (not exceeding 40 mg/day; **Table V**; available at www.jpeds.com). Symptomatic infants breastfed by mothers medicated with oxycodone had significantly longer consecutive hours of uninterrupted sleep per day than asymptomatic infants (median, 5 hours/day; range, 3-24 hours/day; $P = .0216$ versus median, 4 hours/day; range, 1-21 hours/day). Similarly, in the cohort receiving codeine, mothers of symptomatic infants took significantly higher codeine doses than mothers of asymptomatic infants (median, 1.4 mg/kg/day; range, 0.7-10.5 mg/kg/day versus median, 0.9 mg/kg/day; range 0.18-5.8 mg/kg/day; $P < .001$; **Table VI**). Maternal reports of resolution of neonatal symptoms when maternal narcotics or breastfeeding ceased were also documented. Thirty-eight of 39 and 30 of 35 mothers reported reversibility of neonatal symptoms on cessation of oxycodone and codeine or breastfeeding, respectively.

Mothers medicated with oxycodone and codeine with symptomatic babies were significantly more likely to experience CNS depression themselves (26/28 maternal CNS depression with symptomatic infant versus 66/111 maternal CNS depression with asymptomatic infant, $P < .001$; OR, 8.864; 95% CI, 2.002-39.240 in oxycodone cohort; 15/35 maternal CNS depression with symptomatic infant versus 6/175 maternal CNS depression with asymptomatic infant, $P < .001$; OR, 21.1; 95% CI, 7.4-60.6 in codeine cohort).

Mothers medicated with oxycodone were more likely to experience CNS depressive adverse effects compared with mothers taking codeine (92/139 in oxycodone cohort versus 21/210 in codeine cohort; $P < .0001$; OR, 17.62; 95% CI, 9.95-31.21). In addition to experiencing lethargy, a proportion of mothers in the oxycodone and codeine cohorts experienced other adverse effects, such as nausea, vomiting, constipation, dizziness, weakness, and confusion (**Table VII**).

Table III. Maternal indications for oxycodone, codeine, or acetaminophen-only

	Oxycodone* n_{dcr} = 139	Codeine† n_{dcr} = 210	Acetaminophen only n_{dcr} = 184	*P* value
Cesarean delivery	30	60	9	<.0001
Vaginal/episiotomy	1	7	10	.0673
Headache/migraine	6	14	62	<.0001
Dental/minor surgery	38	65	8	<.0001
Chronic disease	10	10	10	.614
Cold/cold-related pain	0	0	47	–
Other	37	45	24	.1046
Unknown	8	9	14	.3719

n_{dcr}, number of responses per discriptor.
*A total of 52.5% (73/139) of mothers were prescribed a combination oxycodone-acetaminophen product.
†A total of 65% (137/210) of mothers were prescribed a combination codeine-acetaminophen product.

Discussion

After a fatal case in a breastfed infant exposed to codeine through breast milk,[7] both the US Food and Drug Administration and Health Canada published warnings indicating that codeine use in breastfeeding may not be safe for infants.[10,11] As a result, some institutions are now replacing codeine with oxycodone for postpartum pain relief. However, Seaton et al detected oxycodone in breast milk from all mothers taking any dose of oxycodone.[1] The levels of oxycodone in breast milk strongly correlated with plasma levels, suggesting that oxycodone persisted in the breast milk of some mothers. Therefore, it is important to address the neonatal safety of oxycodone during breastfeeding.

In this study, we compared the maternal reports of CNS depression in breastfed infants exposed to oxycodone with those in infants who were exposed to codeine or acetaminophen alone. Our analysis reveals several important features of this potentially fatal adverse reaction: the maternal self-report of

Table VI. Characteristics of symptomatic versus asymptomatic mother-infant pairs within the oxycodone and codeine cohorts

	Oxycodone cohort			Codeine cohort		
	Symptomatic (n_{total} = 28)	Asymptomatic (n_{total} = 111)	*P* value	Symptomatic (n_{total} = 35)	Asymptomatic (n_{total} = 175)	*P* value
Maternal dose (mg/kg/day)*	0.4 (0.03-4.1) n_{dcr} = 28	0.15 (0.02-2.3) n_{dcr} = 111	<.001	1.4 (0.7-10.5) n_{dcr} = 25	0.9 (0.2-5.8) n_{dcr} = 67	<.001
Infant PMA (weeks)†	47.6 (16.1) n_{dcr} = 28	55.2 (35.9) n_{dcr} = 111	.456	52.0 (15.0) n = 35	54.2 (16.6) n = 130	.439
Breastfeeding duration (days breastfed with concurrent maternal medication consumption)	18 (24) n_{dcr} = 28	11 (24) n_{dcr} = 111	.051	7 (1-180) n_{dcr} = 34	4 (1-247) n_{dcr} = 157	.12
Frequency of breastfeeding (number of feeds /day)	7.5 (3.0) n_{dcr} = 28	7.8 (2.7) n_{dcr} = 111	.514	8 (2.88) n_{dcr} = 29	7 (2.65) n_{dcr} = 166	.12
Formula supplementation	13 (46.4%) n_{dcr} = 28	52 (46.8%) n_{dcr} = 111	.483‡	20 (64.5%) n_{dcr} = 31	89 (55.6%) n_{dcr} = 160	.298‡
Hours slept by infant	5 (3-24) n_{dcr} = 28	4 (1-21) n_{dcr} = 111	.022			

n_{total}, number of total responses; n_{dcr}, number of responses per descriptor.
Maternal-infant pair characteristics, mean (SD), and median (range) as appropriate.
*Maternal dose was within recommended adult dose of 5 or 10 mg oxycodone every 6 hours.[13]
†Age of infants at the time of oxycodone/codeine/acetaminophen-only exposure and breastfeeding.
‡For dichotomous variables, the Fisher exact test was used to compare the contingencies; $P < .05$ denotes statistical significance.

neonatal CNS depression is higher in neonates breastfed by mothers mediated with oxycodone than in infants breastfed by mothers medicated with acetaminophen. Maternal oxycodone use is associated with a similar incidence of neonatal CNS depression as compared with codeine and should not be considered to be a safe alternative for codeine during breastfeeding. Symptomatic infants of mothers medicated with oxycodone were sleeping longer than asymptomatic infants. In most cases of CNS depression in the oxycodone and codeine cohort, the parents reported dramatic neonatal improvement when exposure of the opioid ceased. There was a dose-response relationship with mothers of symptomatic infants having consumed on average 50% more oxycodone and codeine per kg of maternal body weight. However, some mothers reported neonatal CNS depression when they were consuming as little as 0.03 mg/kg of oxycodone daily. Furthermore, there was a trend for mothers of symptomatic infants of using oxycodone or codeine for longer periods than mothers of asymptomatic infants. Our findings suggest that maternal CNS depression is a strong predictor of neonatal CNS depression for both oxycodone and codeine. When clinicians observe maternal CNS depression, they need to monitor the child for it as well. Finally, mothers medicated with oxycodone were more likely to experience CNS depressive adverse effects in addition to other adverse effects known to be associated with opioid use compared with mothers taking codeine.

Table VII. Maternal adverse event reported with oxycodone or codeine use during breastfeeding

	Oxycodone (n = 139)	Codeine (n = 139)
Sedation*	92 (%)	21 (%)
Other concomitant adverse events		
Nausea	19 (21)	4 (19)
Vomiting	8 (8.6)	2 (9.5)
Constipation	23 (25)	13 (62)
Dizziness	23 (25)	6 (29)
Weakness	8 (8.6)	6 (29)
Confusion	1 (1)	0 (0)
Rash	0 (0)	2 (9.5)

*Of the proportion of mothers who reported experiencing adverse effects with oxycodone or codeine medication, all listed sedation as an adverse event. All other adverse effects with oxycodone or codeine medication occurred in conjunction with sedation. Mothers were significantly more likely to experience sedative adverse effects from oxycodone as compared with codeine ($P < .0001$; OR, 17.62; 95% CI, 9.95-31.21).

Several differences in the 3 cohorts in this study need to be highlighted. First, maternal indications for receiving acetaminophen or opioids were different in the cohorts. This is reflective of the general practice of prescribing opioids for pain relief after caesarian delivery or episiotomy in Canada. Therefore, questions related to comparative efficacy among codeine, oxycodone, and acetaminophen cannot be addressed by this study. Second, with sequential statistical analysis, mothers in the codeine group were found to be significantly more likely than mothers in the oxycodone group to be first-time mothers. Arguably, the inexperience of first-time mothers may lead to hypervigilance and increased anxiety, which could translate to increased reporting of CNS depressive symptoms. Although we observed a similar incidence of neonatal CNS depression between oxycodone and codeine, parity could have biased these results, causing over-reporting of CNS depression in the codeine group. Third, infants who were exposed to oxycodone via breast milk were slightly younger in the oxycodone group as compared with the codeine and acetaminophen groups. Pharmacodynamic modeling has revealed that compromised neonatal opioid clearance capacity (which is closely related to age) may predispose infants to CNS depressive adverse effects when exposed to maternal opioids.[12] However, within the oxycodone group, there was no difference in PMA between symptomatic infants and asymptomatic infants.

The major limitation of this study was its retrospective nature, and thus the potential for recall bias was introduced. Furthermore, the population of mothers interviewed were

self-selected because they took the initiative to call the Motherisk Program and ask for safety advice. It is possible that these women may have exhibited increased vigilance in monitoring their infants for symptoms of adverse drug reaction than the general population, but this increased attention would also likely improve recall of the event. The control group or acetaminophen cohort was deemed critical to account for non-specific features that may resemble neonatal CNS depression especially when they are based on maternal reports. In accordance, there is only one maternal-positive report of infant CNS depression when a mother was breastfeeding and consuming acetaminophen alone.

In conclusion, maternal consumption of oxycodone is associated with an increased risk of CNS depression in the breastfed infant, such that 1 in 5 breastfed infants with mothers medicated with oxycodone experienced symptoms of CNS depression. Therefore, replacement of codeine by oxycodone during breastfeeding cannot be assumed to be safe for the child and the mother. In the future, prospective and pharmacogenetic studies are needed to investigate other factors related to maternal oxycodone use and neonatal CNS depression. ■

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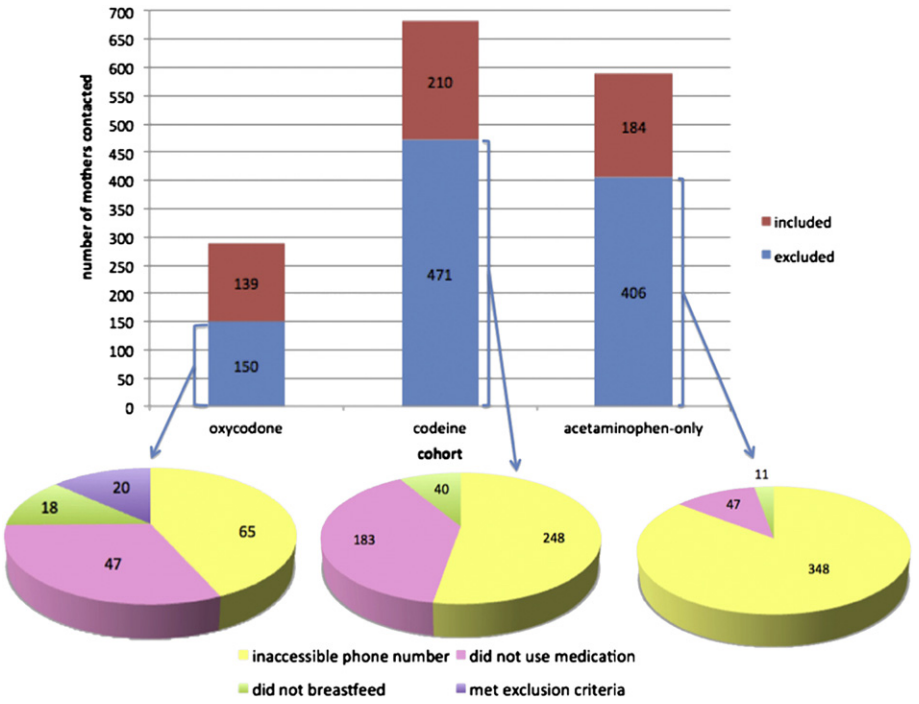

Figure. Reasons for excluding patients who had inquired about acetaminophen-only, oxycodone, or codeine.

Table II. Demographic characteristics of mothers and neonates in oxycodone and codeine cohorts

	Oxycodone cohort (n = 139)	Codeine cohort (n = 210)	*P* value
Maternal age, years	32.9 (4.6) n_{dcr} = 139	32.7 (4.5) n_{dcr} = 153	.65
Maternal weight, kg	73.2 (14.3) n_{dcr} = 139	72.9 (14.7) n_{dcr} = 183	.81
Nulliparous, n (%)	51 (37%) n_{dcr} = 139	107 (60%) n_{dcr} = 179	<.0001
Maternal non-Caucasian ethnicity, n (%)	17 (28.7%) n_{dcr} = 139	31 (38.3%) n_{dcr} = 210	.58*
Infant birth weight, kg	3.37 (0.59) n_{dcr} = 139	3.42 (0.59) n_{dcr} = 207	.24
Infant PMA, weeks	53.6 (32.9) n_{dcr} = 138	53.9 (16.4) n_{dcr} = 165	.02

n_{dcr}, number of responses per descriptor.
Maternal-infant pair characteristics, mean (SD).
*For dichotomous variables, the Fisher exact test was used to compare the contingencies; $P < .05$ denotes statistical significance.

Table IV. Indication for using oxycodone and codeine

	Oxycodone cohort n_{dcr} = 139	Codeine cohort n_{dcr} = 210	*P* value
Cesarean delivery	30	60	.17
Vaginal/episiotomy	1	7	.15
Headache/migraine	6	14	.48
Dental/minor surgery	38	65	.55
Chronic disease	10	10	.36
Other	37	45	.30
Unknown	8	9	.61

n_{dcr}, number of responses per descriptor.

Table V. Oxycodone dosing regimen[13]

	Naïve patients	Patients receiving alternative opioid	Use with non-opioid medication
OxyIR	5 or 10 mg every 6 hours	Determine total daily dosage of present analgesic, calculate approximate daily oral oxycodone dosage to provide equivalent analgesia*	Non-opioid medication may be continued; when discontinuing non-opioid, should increase opioid dose to compensate
OxyContin	10 or 20 mg every 12 hours		
Percocet (5 mg oxycodone + 325 mg acetaminophen	1 tablet every 6 hours†		
Percocet-demi (2.5 mg oxycodone + 325 mg acetaminophen)	1 to 2 tablets every 6 hours		
Supeudol	5 or 10 mg every 6 hours		

Individual dosing requirement vary considerably on the basis of each patient's age, weight, severity, cause of pain, and medical and analgesic history.
*Treat appropriate pain with only one opioid at a time.
†May occasionally be necessary to exceed usual recommended dose in cases of more severe pain or tolerance.