PREVALENCE OF CYP2D6-METABOLISM-DEPENDENT OPIOID ANALGESICS AMONG POSTPARTUM PATIENTS

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Abstract

Background: The question is whether postpartum patients can be exclusively managed on cytochrome-P450-family-2-subfamily-D-member-6 (CYP2D6)-metabolism-independent drug forms because their plasma concentrations after oral administrations will be more uniform and predictable as compared to plasma concentrations after CYP2D6-metabolism-dependent oral drugs varying from one extreme of non-efficacious concentrations (among the poor metabolizers) to other extreme of dangerous concentrations (among the ultra-rapid metabolizers).

Objectives: The current retrospective study was designed with primary goal to ascertain the prevalence of CYP2D6-metabolism-dependent codeine, hydrocodone and oxycodone oral forms' usage among postpartum patients as compared to CYP2D6-metabolism-independent morphine and hydromorphone oral forms' usage.

Materials and Methods: Electronic medical records (EMR) were accessed for patients aged 18 years and above who were admitted to the two dedicated-exclusive postpartum floors during one-year period (July 2013 to June 2014). The pharmacy department accessed its database to tabulate the list of postpartum patients who were billed for oral analgesics and antiemetics for the same one-year period.

Results: While only one patient had received oral morphine and oral hydromorphone, 532 postpartum patients (13%) were administered codeine alone or in combination with other oral opioids during their hospital stay and a total of 1680 postpartum patients (41%) were administered CYP2D6-metabolism-dependent opioids (codeine, and/or hydrocodone, and/or oxycodone) out of the total 4063 patients admitted to postpartum floors during the one year period (July 2013-June 2014). Among the abovementioned 1680 postpartum patients, only 509 patients (30%) had documented co-administrations of antiemetics wherein oral hydrocodone administration (41%), oral oxycodone administration (40%), combination oral opioid administration (33%) and oral codeine administration (5%) demonstrated the descending order of likelihood for co-administration of antiemetics.

Conclusion: The CYP2D6-metabolism-dependent opioids use as analgesics among postpartum patients was very commonly prevalent during 2013-2014 at the author's institute.

Keywords: Postpartum Period; Breast Feeding; Cytochrome P-450 CYP2D6; Codeine; Hyrocodone; Oxycodone.

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Introduction

Pain, a very common symptom among postpartum patients,[1] is often managed with non-steroidal anti-inflammatory drugs because common opioid analgesics and their metabolites are secreted in human milk and may have safety concerns for the breastfed infants.[2-3] However, sometimes during inpatient stay and/or at discharge to home, postpartum patients may be prescribed opioid analgesics for management of severe postpartum pain (after normal/instrumental vaginal delivery or cesarean section). Herein, breast feeding may NOT be advisable among post-partum patients if their pain management (inpatient or outpatient) warrants oral opioids such as codeine because the genetic variability of cytochrome-P450-family-2-subfamily-D-member-6 (CYP2D6) can lead to ultra-rapid metabolism of codeine and its conversion into dangerous levels of active drug morphine in 1-2% patients.[4] As similar to codeine, ultra-rapid metabolism due to genetic variability of CYP2D6 has been documented with hydrocodone conversion to active metabolite hydromorphone and oxycodone conversion to active metabolite oxymorphone.[5-9] Probability of central nervous system depression (sedation) in breastfed neonates has been estimated to be 17%-20% with maternal consumption of codeine or oxycodone.[10] Essentially, the question is whether postpartum patients can be exclusively managed on CYP2D6-metabolism-independent drug forms (morphine and hydromorphone) because their plasma concentrations (and consequent transfer into breast-milk with exposure to breastfed infants) after their oral administrations will be more uniform and predictable as compared to plasma concentrations (and consequent transfer into breast-milk with exposure to breastfed infants) after CYP2D6-metabolism-dependent oral drugs varying from one extreme of non-efficacious concentrations (among the poor metabolizers) to other extreme of dangerous concentrations (among the ultra-rapid metabolizers).

Henceforth, the current retrospective study was designed with primary goal to ascertain the prevalence of CYP2D6-metabolism-dependent codeine, hydrocodone and oxycodone oral forms' usage among postpartum patients as compared to CYP2D6-metabolism-independent morphine and hydromorphone oral forms' usage.

Materials and Methods

After Institutional Review Board approval for retrospective study with waived consent designed to decipher prevalence with cross-sectional analysis, electronic medical records (EMR) were accessed for patients aged 18 years and above who were admitted to the two dedicated-exclusive postpartum floors during one-year period (July 2013 to June 2014). The pharmacy department accessed its database to tabulate the list of postpartum patients who were billed for oral codeine (in all forms), oral hydrocodone (in all forms), oral oxycodone (in all forms), oral morphine (in all forms) and oral hydromorphone (in all forms) for the same one-year period. Similarly, a tabulated list was generated for the antiemetics' usage (ondansetron, metoclopramide, promethazine and prochlorperazine in all forms) among the postpartum floors' patients for the same one-year period. The hospital's costs of medications, patients' charges for the medications and patients' age were recorded. For calculating morphine milligram equivalents (MME), Centers for Disease Control and Prevention (CDC) recommended MME conversion factor was utilized for calculations (codeine:0.15, hydrocodone:1, oxycodone:1.5, morphine:1, and hydromorphone:4).[11] The daily doses of the opioids prescribed at discharge to home and patients' plans about breastfeeding were extracted from EMR among these patients, as documented during their inpatient stay or at the time of discharge. Finally, the total postpartum patients' census for this period for these postpartum floors was extracted by business systems applications tools/services.

Statistical Analysis

Based on the postpartum floors' one-year census, the prevalence was planned to be deduced for CYP2D6-metabolism-dependent analgesics (codeine, hydrocodone and oxycodone) oral use and their costs among the postpartum patients as compared to the prevalence of CYP2D6-metabolism-independent analgesics (morphine and hydromorphone) oral use and their costs among postpartum patients. Prevalence of concurrent antiemetics use among postpartum patients was planned to be compared among postpartum

patients receiving CYP2D6-metabolism-dependent analgesics vs. postpartum patients receiving CYP2D6-metabolism-independent analgesics. Chi Square test (Fisher Exact Tests) for proportions' comparisons and analysis of variance (ANOVA) for means' comparisons were planned to be used with p-value of <0.05 as statistically significant.

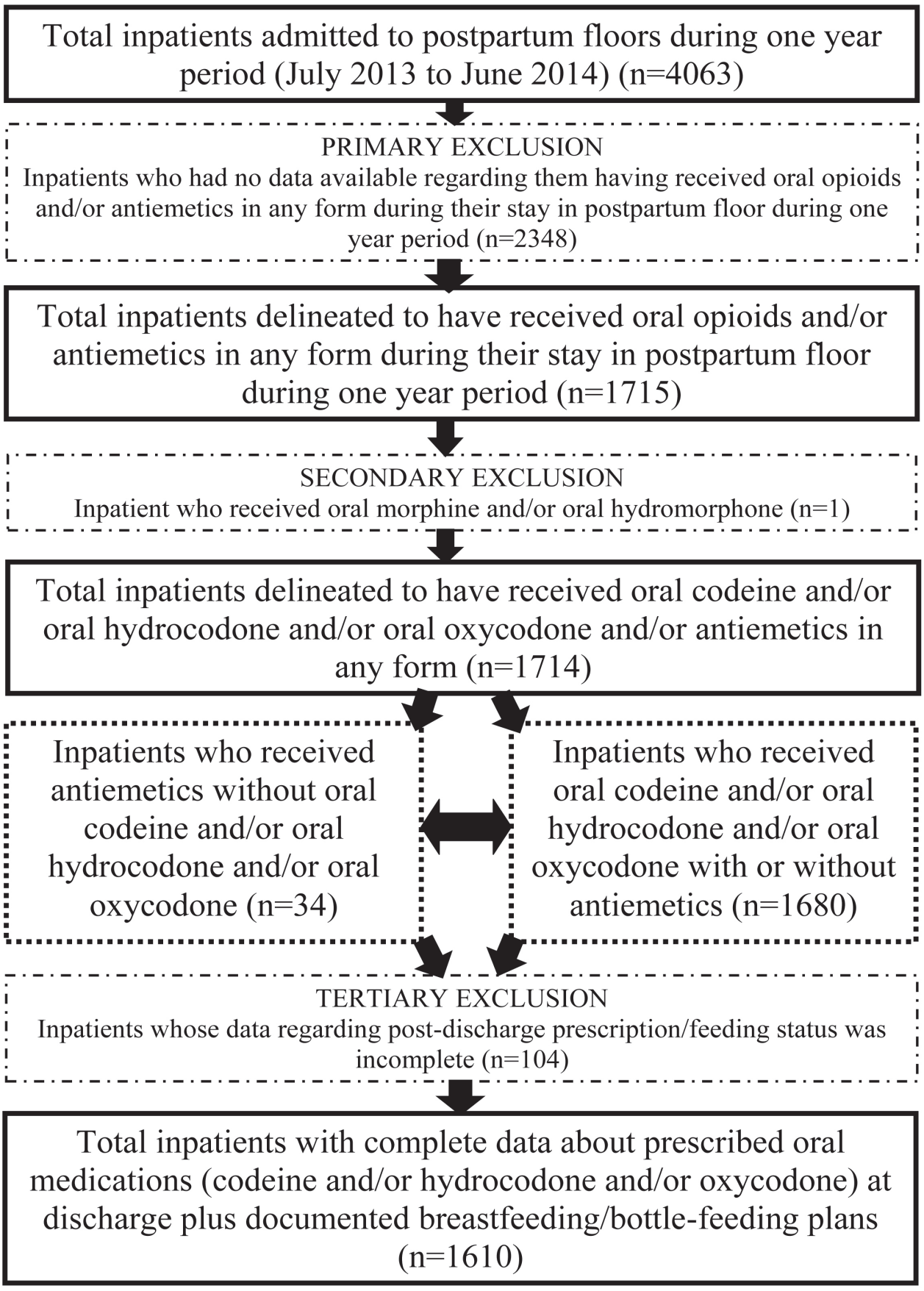
Results

A total of 1,715 patients were delineated among whom only one patient had received oral morphine and oral hydromorphone. Henceforth, only 1,714 patients' data was analyzed who all received oral codeine and/or oral hydrocodone and/or oral oxycodone and/or antiemetics (ondansetron, metoclopramide, promethazine, prochlorperazine) in any form during their inpatient stay at the postpartum floors. There were 34 patients who received antiemetics despite the absence of co-administrations of oral codeine/hydrocodone/oxycodone; these 34 patients may be representing the antiemetic usage with intravenous forms of opioids (intravenous morphine or intravenous hydromorphone) and rare oral/sublingual forms of opioids (methadone/buprenorphine) which were neither reviewed nor analyzed during this study. Among the remaining 1,680 patients who received either only oral codeine (n=479) or only oral hydrocodone (n=1109) or only oral oxycodone (n=10) or combination of any of the abovementioned three (n=82), only 509 patients (30%) had documented co-administrations of antiemetics wherein oral hydrocodone administration (41%), oral oxycodone administration (40%), combination oral opioid administration (33%) and oral codeine administration (5%) demonstrated the descending order of likelihood for co-administration of antiemetics. Patients' demographics, medications' total doses administered during their hospital stay, administered medications' costs to the hospital and corresponding medications' charges billed to the patients are detailed in Table 1. It can be seen that 532 postpartum patients (13%) were administered codeine alone or in combination with other oral opioids during their hospital stay and a total of 1,680 postpartum patients (41%) were administered CYP2D6-metabolism-dependent opioids (codeine, and/or hydrocodone, and/or oxycodone) out of the total 4,063 patients admitted to postpartum floors during the one year period (July 2013-June 2014). The details are in the consort diagram (Figure 1).

Table 1
Patients Demographics, Opioid Doses, Hospital Costs and Patient Charges Data

Medication Received Alone or In Combination With Others As Inpatient	Patients' Age in years (Mean ±SD)	Medication Dose (in mg) Received By The Patients As Inpatient (Mean ±SD)	Medication Costs (in US Dollar) To The Hospital For The Inpatient (Mean ±SD)	Medication Charges (in US Dollar) For The Patients As Inpatient (Mean ±SD)
Codeine (n=532)	27.5 ±5.8	169.7 ±121.9	1 ±0.7	21.8 ±14.4
Hydrocodone (n=1191)	27.3 ±6	90.6 ±47.7	3.4 ±1.9	37.7 ±20.9
Oxycodone (n=40)	27.7 ±5	91.1 ±119.5	3.9 ±7.4	55.1 ±71.2
Ondansetron (n=504)	27.6 ±6.1	5 ±2.7	0.6 ±0.3	11.2 ±5.2
Metoclopramide (n=9)	30.3 ±4.8	32.2 ±27.7	0.3 ±0.2	17.4 ±15
Promethazine (n=65)	28.1 ±5.9	29.2 ±13.7	0.8 ±0.5	15.6 ±27.9
Prochlorperazine (n=7)	31.3 ±5.6	10 ±0	2.1 ±1.6	23.2 ±12.8

Fig. 1


Total inpatients admitted to postpartum floors during one year period (July 2013 to June 2014) (n=4063)
PRIMARY EXCLUSION
Inpatients who had no data available regarding them having received oral opioids and/or antiemetics in any form during their stay in postpartum floor during one year period (n=2348)
Total inpatients delineated to have received oral opioids and/or antiemetics in any form during their stay in postpartum floor during one year period (n=1715)
SECONDARY EXCLUSION
Inpatient who received oral morphine and/or oral hydromorphone (n=1)
Total inpatients delineated to have received oral codeine and/or oral hydrocodone and/or oral oxycodone and/or antiemetics in any form (n=1714)
Inpatients who received antiemetics without oral codeine and/or oral hydrocodone and/or oral oxycodone (n=34)
Inpatients who received oral codeine and/or oral hydrocodone and/or oral oxycodone with or without antiemetics (n=1680)
TERTIARY EXCLUSION
Inpatients whose data regarding post-discharge prescription/feeding status was incomplete (n=104)
Total inpatients with complete data about prescribed oral medications (codeine and/or hydrocodone and/or oxycodone) at discharge plus documented breastfeeding/bottle-feeding plans (n=1610)

Patients' discharge medications as corresponding to their inpatient medications are detailed in Table 2 along with the subdivision of postpartum patients in terms of documented plans for breastfeeding their infants. Due to incomplete data about prescribed medications at discharge and/or missing data about breastfeeding status of the postpartum patients and/or documented prescriptions for other opioids with or without oral codeine/hydrocodone/oxycodone, Table 2 includes only 1,610 patients data (32 inpatients who received antiemetics only, 1,082 inpatients who did not need antiemetics' co-administration with oral codeine/hydrocodone/oxycodone, and 496 inpatients who received antiemetics along with oral codeine/hydrocodone/oxycodone). Interestingly, while deciphering Table 2 data, it can be seen that among patients who were discharged without oral opioids, only 54% were documented to be planning for breastfeeding their infants as compared to patients who were discharged on CYP2D6-metabolism-dependent oral opioids wherein as many as 58% were documented to be planning for breastfeeding their infants. Essentially, as compared to 2011 breastfeeding rates data wherein 79% mothers in the United States (U.S.) breastfed their infants,[12] the current retrospective study data based on EMR documentations suggest that during 2013-2014, at least 57% of postpartum patients (n=1,610) were breastfeeding or considering to breastfeed their infants. Additionally, overall 71% of postpartum patients (n=1,610) were prescribed CYP2D6-metabolism-dependent oral opioids at the time of discharge from the hospital; and patients who as inpatients received CYP2D6-metabolism-dependent oral opioids along with antiemetics were most likely (92%) to be discharged on CYP2D6-metabolism-dependent oral opioids as compared to the inpatients who did not receive antiemetics with CYP2D6-metabolism-dependent oral opioids (62%) or the inpatients who received antiemetics in the absence of CYP2D6-metabolism-dependent oral opioids (19%).

Discussion

The key findings of this study were that during 2013-2014, (a) almost none of the patients received CYP2D6-metabolism-independent oral opioids, oral morphine or oral hydromorphone, during their postpartum stay at our hospital; (b) CYP2D6-metabolism-dependent oral opioids were the chosen medications for administration in more than 40% postpartum patients complaining about pain; (c) codeine use was common (>10%) among our postpartum patients; (d) compared to postpartum patients receiving other CYP2D6-metabolism-dependent oral opioids, postpartum patients who received hydrocodone also received antiemetics more commonly during their hospital stay; and (e) irrespective of whether our postpartum patients received CYP2D6-metabolism-dependent oral opioids or not, breastfeeding rate among our postpartum patients was more than 50% although it was lower than national breastfeeding rates which had been reported to be almost 80%.

Although the author was inspired in 2014 when the author realized a seven years older public health advisory by U.S. Food & Drug Administration (FDA) issued on August 17, 2007 cautioning about risks of CYP2D6-metabolism-dependent codeine use among mothers,[13-14] the current study was designed three years prior to both FDA drug safety communication issued on April 20, 2017 recommending against use of codeine in breastfeeding patients and the American College of Obstetricians and Gynecologists (ACOG) practice advisory issued on April 27, 2017 in regards to preferring CYP2D6-metabolism-independent oral morphine/hydromorphone compared to CYP2D6-metabolism - dependent codeine/ hydrocodone/ oxycodone among breastfeeding mothers.[15-16] However, the study could not be complete until 2018. Therefore, although CYP2D6-metabolism-dependent opioids are the only or almost only oral opioids that were being prescribed among postpartum patients during 2013-2014 at the author's institute, the current study needs a follow up study to ascertain whether the scenario has changed after 2017 FDA drug safety communication or 2017 ACOG practice advisory. It will be also interesting to gauge the effects of CDC guideline,[17] that has been recently reinforced by multiple new legal statutes,[18] for keeping prescribed opioid dosages below 90 MME/day (preferably below 50 MME/day) while being prescribed for less than 7 days (preferably for less than 3 days) in the case of acute pain patients which most of the postpartum patients are. Although as of now, the 2017 ACOG practice advisory stands

Table 2 (a)
Morphine Milligram Equivalent Prescribed At Postpartum Patients' Discharge

Prescribed Opioid At Discharge In Breast-Feeding vs. Bottle-Feeding Patients	Number of Patients	Median(Range) Morphine Milligram Equivalents' Total Daily Dose Post Hospital Discharge	Postpartum Patients Who As Inpatient Received Oral Codeine Only (n)	Postpartum Patients Who As Inpatient Received Oral Hydrocodone Only (n)	Postpartum Patients Who As Inpatient Received Oxycodone Only (n)	Postpartum Patients Who As Inpatient Received Combination of Oral Opioids (n)
PATIENTS WHO RECEIVED ORAL OPIOIDS WITH ANTIEMETICS AS INPATIENT						
No Opioids Prescribed At Discharge						
Breast-Feeding	23	-	9	11	0	3
Bottle-Feeding	15	-	2	12	1	0
Oral Codeine Prescribed At Discharge						
Breast-Feeding	6	31.5 (27)	4	0	0	2
Bottle-Feeding	4	45 (27)	3	0	0	1
Oral Hydrocodone Prescribed At Discharge						
Breast-Feeding	257	60 (160)	3	246	0	8
Bottle-Feeding	176	75 (150)	1	170	0	5
Oral Oxycodone Prescribed At Discharge						
Breast-Feeding	4	75 (30)	0	0	0	4
Bottle-Feeding	2	157.5 (225)	0	0	2	0
Combination of Oral Opioids Prescribed At Discharge						
Breast-Feeding	6	100.5 (78)	0	3	0	3
Bottle-Feeding	3	126 (95.4)	0	3	0	0
PATIENTS WHO RECEIVED ONLY ANTIEMETICS AS INPATIENT						
No Opioids Prescribed At Discharge						
Breast-Feeding	14	-	-	-	-	-
Bottle-Feeding	12	-	-	-	-	-
Oral Hydrocodone Prescribed At Discharge						
Breast-Feeding	3	90 (45)	-	-	-	-
Bottle-Feeding	3	90 (0)	-	-	-	-

Table 2 (b)
Morphine Milligram Equivalent Prescribed At Postpartum Patients' Discharge

Prescribed Opioid At Discharge In Breast-Feeding vs. Bottle-Feeding Patients	Number of Patients	Median(Range) Morphine Milligram Equivalents' Total Daily Dose Post Hospital Discharge	Postpartum Patients Who As Inpatient Received Oral Codeine Only (n)	Postpartum Patients Who As Inpatient Received Oral Hydrocodone Only (n)	Postpartum Patients Who As Inpatient Received Oxycodone Only (n)	Postpartum Patients Who As Inpatient Received Combination of Oral Opioids (n)
PATIENTS WHO RECEIVED ORAL OPIOIDS WITHOUT ANTIEMETICS AS INPATIENT						
No Opioids Prescribed At Discharge						
Breast-Feeding	217	-	172	43	0	2
Bottle-Feeding	190	-	156	23	1	10
Oral Codeine Prescribed At Discharge						
Breast-Feeding	45	27 (99)	44	0	0	1
Bottle-Feeding	34	27 (54)	28	3	0	3
Oral Hydrocodone Prescribed At Discharge						
Breast-Feeding	325	60 (160)	2	310	1	12
Bottle-Feeding	253	60 (175)	3	238	0	12
Oral Oxycodone Prescribed At Discharge						
Breast-Feeding	6	78.8 (45)	0	0	3	3
Bottle-Feeding	3	60 (45)	0	0	0	3
Combination of Oral Opioids Prescribed At Discharge						
Breast-Feeding	6	121.5 (63)	0	6	0	0
Bottle-Feeding	3	90 (138)	0	0	0	3

withdrawn in favor of aggressive measures shifting gears for the postpartum pain management,[16] just like any other pain management, from abandoning primary opioid-based pain management to reviving primary non-opioid-based pain management, the concerns regarding CYP2D6-metabolism-dependent opioids use (codeine, hydrocodone and oxycodone) are still highlighted in the current ACOG Committee Opinion dated May 18, 2018.[19]

The current study has few limitations. As it was missed out at the time of designing the study, the data was not collected, analyzed and thus separated between the patients who underwent vaginal deliveries vs. the patients who underwent cesarean sections which might have highlighted the differences (if any) in their pain medications' requirements. In this female-patient-only population based retrospective study, the only demographic that was collected during the project was patients' age as shown in Table 1. Although other demographics like height, weight, body mass index and race/ethnicity would have enhanced data analysis, they were not collected during this retrospective study due to logistics with the author being the lone researcher collecting and analyzing the

multi-thousand patient charts' data. Antiemetics' usage data was collected as an indirect evidence of side-effects of CYP2D6-metabolism-dependent opioids assuming a potential risk for increased antiemetics' requirements in undiagnosed ultra-rapid metabolizers. However, while antiemetics' usage data as a reflection of variability in side-effects of oral opioids (codeine, hydrocodone and oxycodone) became integral and thus inseparable to the overall data analysis as incorporated in Table 2, the comparative analysis which could have enhanced the significance of antiemetics' usage's incorporation into this retrospective analysis could not be performed because as compared to 1,714 patients receiving CYP2D6-metabolism-dependent opioids orally (codeine, hydrocodone and/or oxycodone), only one patient received CYP2D6-metabolism-independent opioids orally (morphine and/or hydromorphone). Although it would have been better to explore the incidence of respiratory depression and over-sedation secondary to undiagnosed ultra-rapid metabolizers among these patients, objectively capturing data about respiratory depression and over-sedation retrospectively was extremely difficult for this study. Even though it was not feasible for this retrospective study to collect neonatal outcomes data with (a) neonates' medical records being separate from their mothers' medical records and (b) post-discharge hospital-revisit data not being explored at all during this study, inclusion of such neonatal outcomes data like potentially increased toxicity among the neonates being breastfed in hospital and/or at home by undiagnosed ultra-rapid metabolizers would have enhanced the effect of breast-feeding data. However, the breast-feeding mothers' prevalence data itself highlighted at least the enormity of neonatal population being exposed to the risks when they are being breast-fed by mothers who are consuming prescribed CYP2D6-metabolism-dependent opioids.

Conclusion

The CYP2D6-metabolism-dependent opioids use as analgesics among postpartum patients was very commonly prevalent during 2013-2014 at the author's institute. Future studies are required to ascertain if the clinical scenario was historically similar in other institutes in the U.S. around the similar time periods and whether things had changed in accordance to FDA/ACOG recommendations after 2017 or will change after ACOG committee opinion dated May 18, 2018.

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