CYP2D6-Guided Opioid Prescribing and Clinical Outcomes in Chronic Pain : Evidence from the ADOPT PGx Trial linked to Medicare and Medicaid Claims

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BACKGROUND

- Pharmacogenetic (PGx) guidelines recommend avoiding certain opioids in individuals with absent or reduced CYP2D6 activity, as genetic variation or concomitant use of CYP2D6 inhibitors can alter opioid metabolism and lead to inadequate pain control.
- While CYP2D6-guided opioid prescribing may optimize chronic pain management, the clinical impact of prolonged PGx non-concordance remains unclear.
- **Objective:** To assess associations between prolonged PGx non-concordance, pain severity, and the risk of emergency department (ED) visits or hospitalization.

METHODS

- **Design and Source: Pragmatic clinical trial data (A Depression and Opioid Pragmatic Trial in Pharmacogenetics; ADOPT PGx; NCT05966129) and Medicare/Medicaid claims data**
- **Study population:**
  - Participants enrolled in ADOPT PGx linked to Medicare and/or Medicaid claims
  - Adults with ≥3 months of chronic pain
  - Using or considering tramadol, codeine, hydrocodone, or oxycodone
- **Outcomes:**
  - **Pain severity** measured by patient-reported numeric rating scale (3-15, higher scores indicate severe pain) at months 1, 3, and 6
  - **Utilization of opioids** - Morphine Milligram Equivalents (MME)
  - **Utilization of other pain medications**
  - **Pain medication cost**
  - **Healthcare utilization**
- **Exposure:**
  - **PGx concordance**: Opioid therapy consistent with CYP2D6 phenotype recommendations.
  - **PGx non-concordance**: ≥1 day of opioid non-concordant with CYP2D6 phenotype recommendations.

PGx Concordance Framework

A. Based on CYP2D6 Genotype

CYP2D6 genotype	Activity Score	Phenotype
	>2	Ultra metabolizer (UM)
	>0.75 to 2.0	Normal metabolizer (NM)
	>0.0 to 0.75	Intermediate metabolizer (IM)
	0.0	Poor metabolizer (PM)

B. Opioid Concordance by Phenotype

Phenotype	Opioids	Concordance vs. Non-concordance
UM	Tramadol, codeine, hydrocodone, or oxycodone	Non-concordance
IM or PM	Tramadol, codeine, or hydrocodone	Non-concordance
NM	(Same opioids allowed)	Concordance

C. Phenotype conversion by CYP2D6 inhibitors

+ Antidepressants	Activity Score	Phenotype Conversion	Concordance vs. non-concordance
Strong inhibitor	X0	PM	Non-concordance
Moderate inhibitor	X0.5	IM or NM	(Non-) concordance

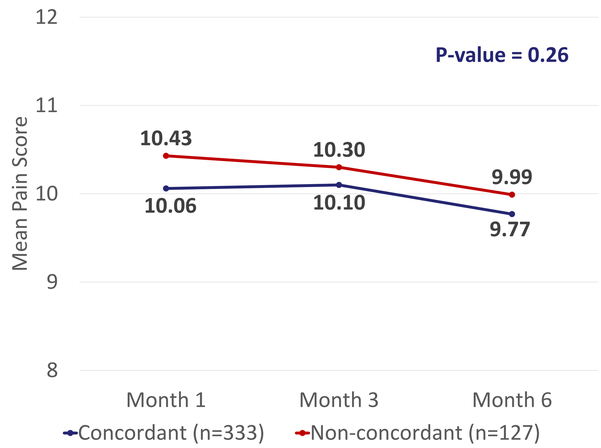
- **Statistical Analysis:** controlling for age, sex, race/ethnicity
  - Generalized estimating equations: pain scores, utilization of opioids over time
  - Poisson regression: utilization of other pain medication use
  - Tweedie analysis: pain medication costs
  - Time-varying Cox model: Healthcare utilization

Results

- Among 460 participants, 333 were PGx concordant, and 127 were non-concordant.
- **Baseline Characteristics**

	Concordant (n=333)	Non-concordant (n=127)
Age, mean (SD)	60.7 (12.5)	61.4 (10.3)
Female, n (%)	240 (72%)	98 (77%)
Hispanic, n (%)	22 (7%)	7 (6%)
Race, n (%)		
White	143 (43%)	69 (54%)
Black	152 (46%)	42 (33%)
Others	38 (11%)	16 (13%)

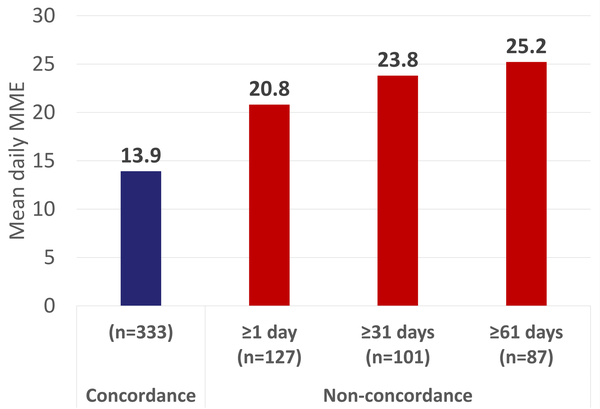
Mean Pain Scores at month 1, 3, and 6



The pain score ranges from 3 to 15, with higher scores indicating more severe pain. Adjusted by age, gender, ethnicity, and race.

- No significant association between concordant status and pain scores (p-value=0.26).

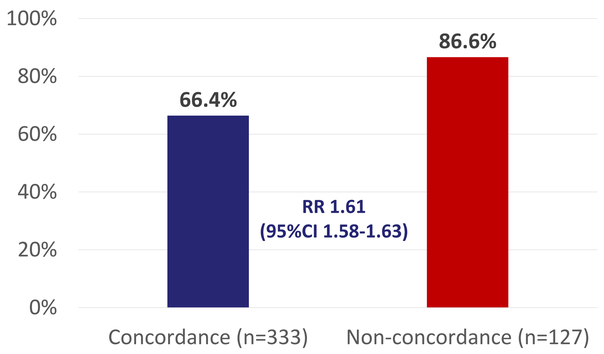
Mean Daily MME



MME conversion factors were codeine 0.15, tramadol 0.2, morphine 1, hydrocodone 1, oxycodone 1.5, and hydromorphone 5. Adjusted by age, gender, ethnicity, and race.

- Longer duration of non-concordant days was associated with the higher MME (p-<0.001).

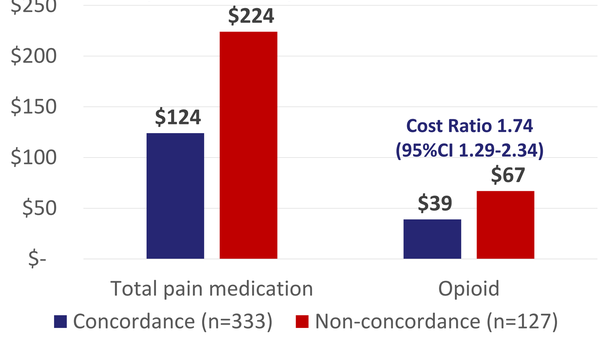
Utilization of Other Pain Medication



Included NSAID, acetaminophen, COX2-inhibitor, and Non-CYP2D6 opioids (buprenorphine, hydromorphone, morphine). Adjusted by age, gender, ethnicity, and race. RR, rate ratio; CI, confidence interval

- PGx non-concordance was associated with a 61% longer use of other pain medications.

Mean Pain Medication Cost per participant per year



Adjusted by age, gender, ethnicity, and race. CI, confidence interval

- PGx non-concordance was associated with 73% higher total pain medication costs and 74% opioid costs versus concordance.

- **Healthcare utilization:** PGx non-concordance was not significantly associated with all-cause or pain-related ED visits or hospitalization compared to concordance (all p-values>0.05).

Conclusions

- PGx non-concordant opioid use was associated with higher opioid utilization, greater concomitant pain medication use, and increased pain medication costs compared to concordant use.
- However, no significant differences were observed in pain scores or risk of pain-related healthcare utilization between PGx non-concordant and concordant groups.
- PGx-guided opioid prescribing may optimize pain management and reduce healthcare utilization.

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