Applying Patient-Centered Care in Pain Management
Target Audience: Pharmacists
ACPE#: 0202-0000-18-069-L04-P
Activity Type: Knowledge-Based
Disclosures

Elvin T. Price and Nicholas E Hagemeier disclose no relevant, real or apparent personal or professional financial relationships with proprietary entities that produce health care goods and services presented.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Describe the concept of patient-centered care from the pharmacist’s perspective.
2. Summarize the science of patient-centered communication in pain management.
3. Describe pharmacogenetic tests that are available to guide the use of opioids in pain management.
4. Discuss research opportunities related to patient-centered care and genetic testing in pain management.
5. Describe strategies used by pharmacists to implement genetic testing in clinical pharmacy practice.
Assessment Question #1

Patient-centeredness in health systems is often evaluated based on:
A. Patient satisfaction scores
B. Patient out of pocket expenses
C. Readmission rates
D. Physician self-report
Assessment Question #2

Research indicates all of the following domains explain the extent to which pharmacist provided care is patient-centered except:

A. Pharmacists’ attitudes
B. Pharmacists’ self-perceived communication competence
C. Pharmacists’ subjective norm beliefs
D. Years in practice
A chief event of life is the day in which we have encountered a mind that startled us

- Ralph Waldo Emerson
Pharmacists’ Patient Care Process
Pharmacists use a patient-centered approach in collaboration with other providers on the healthcare team to optimize patient health and medication outcomes.

Using principles of evidence-based practice, pharmacists:

**Collect**
The pharmacist assures the collection of the necessary subjective and objective information about the patient in order to understand the relevant medical/medication history and clinical status of the patient.

**Assess**
The pharmacist assesses the information collected and analyzes the clinical effects of the patient’s therapy in the context of the patient’s overall health goals in order to identify and prioritize problems and achieve optimal care.

**Plan**
The pharmacist develops an individualized patient-centered care plan, in collaboration with other health care professionals and the patient or caregiver that is evidence-based and cost-effective.

**Implement**
The pharmacist implements the care plan in collaboration with other health care professionals and the patient or caregiver.

**Follow-up: Monitor and Evaluate**
The pharmacist monitors and evaluates the effectiveness of the care plan and modifies the plan in collaboration with other health care professionals and the patient or caregiver as needed.

Providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.

-IOM, 2001
Patient-Centered Care – Key Tenets

- Requires relationship and rapport
- Clinical care plus emotional, mental, spiritual, social, and financial care
- Shared decision-making...particularly “big deal” decisions
  - “Decisions about major surgery, medications that must be taken for the rest of one's life, and screening and diagnostic tests that can trigger cascades of serious and stressful interventions”
- Pain management – as well as potential downstream consequences - are a “big deal”

Pain Management

- The prevention, diagnosis, and treatment of **pain**
- Multiple modalities with context-specific evidence
- Pain can be a symptom of a disease or a disease itself
- Affects more Americans than diabetes, heart disease and cancer combined
- Pharmacists intimately involved across multiple settings

Morphine Milligram Equivalents Prescribed Per Capita (2015)

Health care providers in different states prescribe at different levels.

Number of painkiller prescriptions per 100 people

**Lowest**

- AZ 82
- NE 79
- WA 77
- ND 75
- TX 74
- IA 73
- CO 71
- WY 70
- VT 67
- IA 65
- AK 65
- SD 66
- HI 52
- CA 57

**Average**

- SC 102
- NC 97
- OH 100
- NV 94
- MO 95
- DE 91
- KS 94
- PA 88
- OR 89
- SC 86
- UT 86
- ME 85
- ID 86
- ME 109

**Highest**

- MS 120
- AL 143
- WA 138
- TN 143
- OK 128
- KY 128

**State Abbreviation**

- GA 91

**Number of painkiller prescriptions per 100 people**

SOURCE: IMS, National Prescription Audit (NPA™), 2012.
How we got here...

The relentless marketing of pain pills. Crews from one small Mexican town selling heroin like pizza. The collision has led to America's greatest drug scourge.

The True Tale of America's Opiate Epidemic
Buchanan et al. 2017 Exponential Growth of the USA Overdose Epidemic.
http://www.biorxiv.org/content/biorxiv/early/2017/05/09/134403.full.pdf

Graph: USA Deaths/Year Due to Accidental Poisoning, 1979-2015
- Data fit to log-linear model
- Good fit for 37 years
- Average increase per year = 9%
- Yearly increases for last 25 years
- Doubling time = 8 years

Equation: Cases = 10^((3.2871 + (0.0372 * (Y - 1979)))
- R^2 = 0.99
GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

IMPROVING PRACTICE THROUGH RECOMMENDATIONS

CDC’s Guideline for Prescribing Opioids for Chronic Pain is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose. The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.
Patient-Centered Pain Management

- Primary duty is health improvement, not reduction in pain intensity

  \[
  \text{Pain intensity} \quad \rightarrow \quad \text{Physical, social, emotional functioning}
  \]

- “It is surely a good thing to reduce pain, but it is neither the only good thing nor the most important thing, even if patients desire it.”

- “Optimizing capacity for personally meaningful action”

PCPM Measurement

- Providers
  - Communication behaviors
    - Davis Observation Codes
    - SOS-PCC – biopsychosocial perspective; patient-as-person; sharing power and responsibility; and therapeutic alliance
  - OPTION Scale – shared decision making

PCPM Measurement

- Patients
  - Self-report
  - PCO Questionnaire – pain, fatigue, distress, interference

- Systems
  - Patient report (often satisfaction)

PCPM in Community Pharmacies
Our Science: Communication Behaviors

Patient

Prescriber  Pharmacist
“The truth is that many people set rules to keep from making decisions”
- Mike Krzyzewski
“I think personally I would just rather go with the flow than confront issues like [drug abuse]; it’s definitely harder to confront.” Pharmacist

“I just tell them I don’t have them [prescribed medications].” Pharmacist

“You like to think what we’re trying to do is help these people fix their problems and some people, I mean, to be quite honest, it’s just not pleasant to deal with. I mean, I just discharge you and I’m done. That’s awful to say but it’s true.” Physician
“They’re [physicians] not talkin’ to their patients enough . . . [and] I don’t think that people talk to their doctors like they should. Tellin’ ‘em what they feel or anything ‘bout drugs or anything.” Patient

“I've called with questions about my [buprenorphine] prescription, whatever trying to find a place [pharmacy] and I have been talked to just with utter disrespect. There’s been those few [pharmacists] that are really nice and have treated me like I was any other patient with any other medicine . . . but it’s so much . . . that you know at times there was this barrier like we we’re “those people” coming into the door.” Patient
Quantitative Follow-Up

- Objectives
  - Evaluate community pharmacists’ engagement in primary, secondary, and tertiary prescription drug abuse prevention behaviors
  - Evaluate the extent to which theory of planned behavior and communication domains explain pharmacists’ behaviors
  - Census of TN community pharmacists and TN physicians with specialties of family medicine, internal medicine, neurology, pain medicine (N=4264)
Methods

- Theory of Planned Behavior, Communication Apprehension, Self-Perceived Communication Competence, Willingness to Communicate
- General and situational communication/dispensing behaviors evaluated
- 4 paper-based waves from September – November 2017
- Bowl of Hygiea emblem business card holder and fidget spinner as incentive (separate study)
- Response rate = 17.1%
Preliminary Pharmacist Findings (N=441)

- 44% chain, 38% independent, 17% supermarket/mass merchandise
- 43% PIC, 42% staff, 13% owners
- 52% female
- 87% white
- Mean age = 47.1 ± 13.6 years
- Years in practice = 20.8 ± 14.0 years
Trait-level Communication with Patients

- Of 10 patients presenting with a new prescription...
  - Talk to 7.8 ± 2.4 of them
  - Would like to talk to 8.9 ± 2.1 of them
  - Spend 88.3 ± 73.2 seconds talking to those with whom they talk, beyond saying hello
Trait-Level Domain Results

- 91% no difference in comfort across gender
Setting Characteristics

- Conversations involving opioids occur in setting that is:
  - Private (15.5%)
  - Semi-private (62.1%)
  - Not private at all (22.4%)

- 73% perceive setting to have a counseling area that would be considered HIPAA compliant
Trait-level Communication with CS Prescribers

- Of 10 CS prescribers telephoned to establish professional relationship, would get to speak directly with $1.7 \pm 2.0$.
- Of 10 new CS prescribers, respondents would attempt to talk to $4.5 \pm 5.5$ directly to establish a professional relationship.
Scenario 1

A new patient presents to your community pharmacy with a prescription for a 7-day supply of a schedule II controlled substance from a new physician in your area. The daily morphine milligram equivalence is 60mg. This is the only controlled substance medication the patient takes. You check the Controlled Substance Monitoring Database and note no concerns. You note no other red flags with this patient or prescriber.
Preliminary Findings – Scenario 1

- Administer Risk Assessment (15.6% ever use)
- Communicate risks
- Dispense
Preliminary Domain Results – Communicating Risk

1 7

Apprehension

Norms

Attitude

PBC

SPCC
Scenario 2

A patient established at the community pharmacy where you practice has been on prescription opioids for 6 months. The patient is taking 120 morphine milligram equivalents (MMEs) daily. Over the last three months, the patient has been consistently requesting early fills on the prescription opioid. The patient started taking a benzodiazepine for generalized anxiety disorder last month. The benzodiazepine is prescribed by the same prescriber as the prescription opioid, a prescriber with whom you are familiar. You check the Controlled Substance Monitoring Database and note no prescriptions filled at other pharmacies. The patient is requesting the prescription opioid be filled today, which is 28 days since his last 30-day prescription was dispensed.
Preliminary Findings – Scenario 2

Dispense

Discuss naloxone co-dispensing

- Screen for Misuse
- Communicate with prescriber
- Communicate risks

• 66% have dispensed naloxone
Preliminary Domain Results – Discussing Naloxone Co-Dispensing
Perceptions of Quality...

- 37.6 ± 29.1% of pain management clinic prescribers in respondents’ area perceived to be engaged in evidence-based pain management

- 30.0 ± 29.0% of buprenorphine prescribers in respondents’ area perceived to be engaged in evidence-based medication-assisted treatment
Integrating Evidence-Based Solutions in Pharmacy Practices
Evaluate default behaviors...and change them if needed
Screen for risk and abuse
Train staff
Query your PDMP

But don’t let it make decisions for you
Integrate the Science of Safety

Standardize
- Checklists
- Default conversations

Create Independent Checks
- Staff engagement
- System hard stops

Learn from Defects
- Getting duped
- Patient feedback
Take-Aways...

- Patient-centered care is tough to assess, and tougher to assess in tough to assess disease states like pain management.
- Our default communication behaviors are often self- or policy-centered.
- Communication science can help us be effective and efficient.
- Trait ≠ situational communication.
The single biggest problem in communication is the illusion that it has taken place.

- George Bernard Shaw

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The NIH Reports That Pain Is The Most Common Reason For Seeking Medical Care

Pain in the U.S.

25.3 million American adults suffer from daily pain

23.4 million American adults report a lot of pain
Prescription Drugs Used For Pain Control Are Among The Top 200 Prescribed

Selected Prescription Medications Used For Pain Control

Selected Drugs From The Top 200 Most Prescribed Drugs

Balancing Effective Pain Control And Adverse Outcomes

Opioids for chronic nonecancer pain: A position paper of the American Academy of Neurology
Gary M. Franklin
Neurology 2014;83:1277-1284
Genetic Variability Influences Responsiveness To Pharmacotherapy
Patients with same diagnosis

- Predicted increased toxicity risk: Decrease dose or use different drug
- Predicted good response to tested drug
- Predicted poor or nonresponse: Use different drug
Pharmacogenomics: Genetic Variability Influences Responsiveness to Pharmacotherapy

- Targets
- Transporters
- Metabolizing Enzymes

- Pharmacodynamics
- Pharmacokinetics

Variability in Efficacy/Toxicity
Interactive Quiz:

How Many Drugs Used For Analgesia Have Validated Pharmacogenomics (PGx) Biomarkers Listed Within The Package Insert?

Pharmacogenomics: Genetic Variability Influences Responsiveness to Pharmacotherapy

Figure 1  The response to opioids is multifactorial with contributions to different degrees between people from (a) common nongenetic pharmacological factors (right hand side); (b) pain/addiction phenotype factors (left hand side); and (c) pharmacogenomic factors potentially involving metabolism (CYP2D6, CYP2B6), brain penetration (β-glycoprotein- minor role), and target site (mu receptor) (upper right hand side). The latter represents the most comprehensively studied genes.
The Pharmacologic Response To Opioids: The Mu Opioid Receptor (OPRM1/MOR)
The Pharmacologic Response To Opioids: The Mu Opioid Receptor (OPRM1/MOR)

X: Genetic Variants In the MOR Influence Opiate Response
Polymorphisms in drug metabolizing enzymes can result in increased or decreased metabolism of drugs. The Pie charts below characterize the percentage of commonly used drugs that are metabolized by the respective enzymes.

DOI: 10.1126/science.286.5439.487
The Pharmacologic Response To Opioids: CYP₄₅₀s Drug Metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP2D6</th>
<th>CYP3A4/5</th>
<th>CYP2B6</th>
<th>UGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Tapentadol</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*++ for CYP pathways may result in clinically important drug−drug interactions (see Appendix).*
The Pharmacologic Response To Opioids: CYP2D6 Variation And Drug Metabolism

Table 2 Common CYP2D6 alleles and their in vivo enzyme activity

<table>
<thead>
<tr>
<th>CYP2D6 alleles</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1A</td>
<td>Wild type</td>
</tr>
<tr>
<td>*1xN, *2xN, 35x2</td>
<td>Increased activity</td>
</tr>
</tbody>
</table>

CYP cytochrome P450

* Based on Karolinska Institutet’s The Human Cytochrome P450 (CYP) Allele Nomenclature Database; for a complete list, see http://www.cypalleles.ki.se

Drugs (2013) 73:533–543
DOI 10.1007/s40265-013-0036-0
The Pharmacologic Response To Hydrocodone: CYP2D6 and CYP3A4

Figure 1
Metabolic pathway showing the O-demethylation and N-demethylation of hydrocodone to hydromorphone and norhydrocodone, respectively. The structure of codeine is also depicted.

Br J Clin Pharmacol | 57:3 | 287–297 | 287
The Pharmacologic Response To Oxycodone: CYP2D6 and CYP3A4

Fig. 1 Oxycodone structure and metabolism. The main metabolic pathway of oxycodone is the formation of the pharmacologically inactive noroxycodone by CYP3A4.
The Pharmacologic Response To Codeine: CYP2D6 and CYP3A4

Figure 1 Codeine metabolism pathway in an individual with cytochrome P450 2D6 (CYP2D6) extensive metabolism. Asterisks (*) denote active metabolites.
Direct To Consumer (DTC) Genomics & PGx

- Direct to consumer genomics companies are becoming increasingly popular and the prices are becoming increasingly affordable.
- Patients are willing to pay out of pocket for genomics testing in hopes of achieving better therapeutic outcomes.
- Pharmacists are the most prepared healthcare professionals to help patients understand predictors of pharmacotherapeutic outcomes.
Available PGx Resources

- FDA Center for Drug Evaluation and Research: Genomics Group

- NIH Funded Pharmacogenomics Research Network (PGRN) Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines
Explore Current FDA Pharmacogenomic Recommendations via the Link Below

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm
The Genomics and Targeted Therapy Group (Located within the FDA’s Office of Clinical Pharmacology)

Pharmacogenomics: Overview of the Genomics and Targeted Therapy Group

Pharmacogenomics, an important part of precision medicine, is the study of how a person's genetic makeup can affect their response to a drug. Health care providers can use pharmacogenomic information to help decide the most appropriate treatment for each individual. Some examples include choosing a drug that is more likely to work, avoiding drugs that might have side effects, adjusting the dose of a drug, or determining if closer monitoring is needed. In addition, pharmacogenomics now plays an important role in the drug development process, opening new opportunities in drug discovery.

Learn More About Pharmacogenomics at CDER
- Table of Pharmacogenomic Biomarkers in Drug Labeling
- Other FDA Resources Related to Pharmacogenomics

The Genomics and Targeted Therapy Group is located within FDA's Office of Clinical Pharmacology and works to apply pharmacogenomics and other biomarkers in drug development and clinical practice. FDA scientists work in multiple ways to ensure that pharmacogenomic strategies are applied appropriately in all phases of drug development. Core functions include regulatory review, research, policy development, and education and outreach.
The Genomics and Targeted Therapy Group
(Located within the FDA’s Office of Clinical Pharmacology)
NIH Funded Pharmacogenomics Research Network (PGRN) Clinical Pharmacogenetics Implementation Consortium (CPIC)
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KR Crews¹, A Gaedigk²,³, HM Dunnenberger¹, JS Leeder²,³, TE Klein⁴, KE Caudle¹, CE Haidar¹, DD Shen⁵,⁶, JT Callaghan⁷,⁸, S Sadhasivam⁹,¹⁰, CA Prows¹¹,¹², ED Kharasch¹³ and TC Skaar⁷

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NIH Funded Pharmacogenomics Research Network (PGRN) Clinical Pharmacogenetics Implementation Consortium (CPIC)

### Table 1 Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (CYP2D6) genotypes

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Activity score</th>
<th>Genotypes</th>
<th>Examples of diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer (~1–2% of patients)</td>
<td>&gt; 2.0</td>
<td>An individual carrying more than two copies of functional alleles</td>
<td>*1/*1xN, *1/*2xN</td>
</tr>
<tr>
<td>Extensive metabolizer (~77–92% of patients)</td>
<td>1.0–2.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele</td>
<td>*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *1/*10</td>
</tr>
<tr>
<td>Intermediate metabolizer (~2–11% of patients)</td>
<td>0.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>An individual carrying one reduced-function and one nonfunctional allele</td>
<td>*4/*10, *5/*41</td>
</tr>
<tr>
<td>Poor metabolizer (~5–10% of patients)</td>
<td>0</td>
<td>An individual carrying no functional alleles</td>
<td>*4/*4, *4/*5, *5/*5, *4/*6</td>
</tr>
</tbody>
</table>

<sup>a</sup>The frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities. See Supplementary Data online for estimates of phenotype frequencies among different ethnic/geographic groups. <sup>b</sup>Note that some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and those with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients.12
### Table 2: Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapy</th>
<th>Considerations for alternative opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing.</td>
<td>Strong</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing.</td>
<td>Moderate</td>
<td>Monitor tramadol use for response.</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.</td>
</tr>
</tbody>
</table>

*Rating scheme is described in [Supplementary Data online](#). There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use postsurgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable.\(^a\,b\,c\) Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.
Drug Metabolism Case Reports
Drug Metabolism Case Reports
CYP2D6 and Codeine

- Codeine is a commonly used pharmacologic agent in treatment of pain.

- Commonly prescribed as Tylenol #3.

- Tylenol #3 is automatically ordered on many labor and surgery protocols at hospitals.
Drug Metabolism Case Reports
CYP2D6 and Codeine

In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/mL by gas chromatography–mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0–2.2 ng/mL. The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets for 2 weeks. Because of poor neonatal feeding, she stored milk on day 10, which was later assayed for morphine by GC-MS. A morphine concentration of 87 ng/mL was found—the typical range of milk concentrations after repeated maternal codeine is 1.9–20.5 ng/mL at doses of 60 mg every 6 h.
Drug Metabolism Case Reports
CYP2D6 and Codeine

Genotype analysis was done for cytochrome P450 2D6 (CYP2D6), the enzyme catalysing the O-demethylation of codeine to morphine. The mother was heterozygous for a CYP2D6*2A allele with CYP2D6*2×2 gene duplication, classified as an ultra-rapid metaboliser. This genotype leads to increased formation of morphine from codeine, consistent with the somnolence and constipation she experienced. The maternal grandfather, the father, and the infant had two functional CYP2D6 alleles (CYP2D6*1/*2 genotypes), classified as extensive metabolisers. The maternal grandmother was an ultra-rapid metaboliser.

<table>
<thead>
<tr>
<th>Action</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid codeine when breastfeeding; use paracetamol or non-steroidal anti-inflammatory drugs</td>
<td>Avoids potential neonatal toxicity</td>
<td>Potential uncontrolled maternal pain</td>
</tr>
<tr>
<td>Avoid high-dose codeine (240 mg daily) for more than a few days</td>
<td>Minimises potential neonatal toxicity</td>
<td>Suboptimal maternal pain control</td>
</tr>
<tr>
<td>Avoid breastfeeding when taking codeine</td>
<td>Avoids potential neonatal toxicity</td>
<td>Dose may still be too high a dose for ultra-rapid metabolisers</td>
</tr>
<tr>
<td>Inform and monitor mother and baby for signs of opioid toxicity</td>
<td>Ability to intervene early and prevent serious toxicity</td>
<td>Parental anxiety and false positive identification of toxicity</td>
</tr>
<tr>
<td>Genotype mother for CYP2D6</td>
<td>Predicts mothers at risk of producing excess of morphine</td>
<td>Expensive Not presently routine</td>
</tr>
</tbody>
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Table: Clinical strategies to manage breastfeeding while on codeine
Drug Metabolism Case Reports
CYP2D6 and Codeine

TO THE EDITOR: Obstructive sleep apnea is not rare in children with hypertrophic tonsils, and the common curative procedure is adenotonsillectomy.¹ Codeine is commonly prescribed for pain after adenotonsillectomy.² The respiratory depressant effects of opioids may influence the occurrence of respiratory complications.³ An estimated one third of cases of apnea in children are not resolved after adenotonsillectomy.⁴

We report on the case of a healthy 2-year-old boy weighing 13 kg, with a history of snoring and sleep-study-confirmed sleep apnea, who underwent elective adenotonsillectomy. The outpatient surgery was uncomplicated, and 6 hours after surgery the boy received 10 mg of meperidine and 12.5 mg of dimenhydrinate intramuscularly and was sent home with instructions for 10 to 12.5 mg of codeine and 120 mg of acetaminophen syrup to be administered orally every 4 to 6 hours as needed. On the second evening after surgery, fever and wheezing developed in the child. At 9 a.m. the next day, the child’s vital signs were absent, and resuscitation efforts failed.

Postmortem examination showed evidence of chronic tracheitis, aspiration of food particles, and bilateral consolidation in the lungs that was consistent with bronchopneumonia. Codeine (0.70 mg per liter) and morphine (32 ng per milliliter) were detected in the femoral blood by means of gas chromatography–mass spectrometry; there was no evidence of other drugs or metabolites. Cytochrome P-450 2D6 (CYP2D6) genotyping revealed functional duplication of the CYP2D6 allele, resulting in the ultrarapid-metabolizer phenotype.

In this case, the prescribed and administered dose of codeine was within the recommended range of 1 to 3 mg per kilogram of body weight per day.¹ ² Increased conversion of codeine to morphine due to ultrarapid metabolism resulted in toxic accumulation of morphine. The concentration of 32 ng per milliliter of morphine at autopsy exceeded therapeutic levels and may have contributed to respiratory depression and death. Respiratory depression has been shown in young children with serum morphine concentrations exceeding 20 ng per milliliter.³

The boy had other contributing factors that should be considered. Autopsy results indicated evidence of bronchopneumonia, further enhancing the risk of hypoxemia. As many as a third of young children with obstructive sleep apnea remain symptomatic after adenotonsillectomy,⁴ showing decreased responsiveness to increases in the partial pressure of carbon dioxide.⁵ Recurrent episodes of hypoxemia may lead to alterations in the μ-opioid receptor and increased sensitiv-
Drug Metabolism Case Reports
CYP2D6 and Codeine

U.S. News & World Report
Family Health

Taking Codeine While Breast-Feeding May Harm Infant

Nervous systems of babies of women with certain genotype more affected, study finds

Posted: August 25, 2008

By Alan Mozes
HealthDay Reporter

MONDAY, Aug. 25 (HealthDay News) -- Breast-feeding moms who take medicines containing codeine may be unwittingly risking the health of their infant, new Canadian research suggests.

The study indicates that a relatively rare genetic predisposition causes some women to metabolize codeine-laced drugs into morphine far faster than normal -- possibly harming the infant's central nervous system in the process.

In such cases, the threat of a morphine overdose appears to be reversible if the woman stops taking the medication. However, for mothers with the genetic vulnerability, the unabated ingestion of codeine and gradual build-up of morphine in a baby's system can prompt extreme sleepiness, abnormal breathing, and even death, the researchers warned.
85 Year Old CYP2D6 Poor Metabolizer Case Report

Case report
Response to hydrocodone, codeine and oxycodone in a CYP2D6 poor metabolizer

Margaret T. Susce, Elaina Murray-Carmichael, Jose de Leon *

University of Kentucky, Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA
Available online 24 April 2006
85 Year Old CYP2D6 Poor Metabolizer Case Report

- 85 Year old white female that was admitted for hip surgery.

- The patient has a long history of Codeine intolerance resulting in nausea and vomiting (listed as an allergy on her chart).

- She was genotyped after her initial hip surgery one year ago and was found to carry CYP2D6*4/*6 alleles.
85 Year Old CYP2D6 Poor Metabolizer Case Report

- The patient was discharged to a rehab facility for 17 days where she lost 20 lbs and was considered non-compliant to her rehab plans due to lack of pain tolerance.

- The patient experienced uncontrollable nausea and vomiting while being treated with Oxycodone with APAP 5/500 mg q 12H, followed by 10/1000 mg, and finally 7.5/750 mg q 6 hours.
85 Year Old CYP2D6 Poor Metabolizer Case Report

- 1 Year later this patient was scheduled for a second surgery for hip replacement due to avascular necrosis from the original pins.

- After 4 days, the patient was discharged to the same rehab facility but the family reported that the patient was genotyped a year earlier and classified as a CYP2D6 poor metabolizer

- The physicians started Hydrocodone 5/500 mg achieving better outcomes than previous attempts with opioids
The Pharmacologic Response To Hydrocodone: CYP2D6 and CYP3A4

Figure 1
Metabolic pathway showing the O-demethylation and N-demethylation of hydrocodone to hydromorphone and norhydrocodone, respectively. The structure of codeine is also depicted.
The Pharmacologic Response To Oxycodone: CYP2D6 and CYP3A4

Fig. 1 Oxycodone structure and metabolism. The main metabolic pathway of oxycodone is the formation of the pharmacologically inactive noroxycodone by CYP3A4.

DOI 10.1007/s00228-010-0893-3
Fatal Hydrocodone Overdose in a Child: Pharmacogenetics and Drug Interactions
Parvaz Madadi, Doris Hildebrandt, Inna Y. Gong, Ute I. Schwarz, Catherine Ciszkowski, Colin J. D. Ross, Johanna Sistonen, Bruce C. Carleton, Michael R. Hayden, Albert E. Lauwers and Gideon Koren
Pediatrics 2010;126;e986; originally published online September 13, 2010;
5 Year old child born with developmental delays and treated with Valproic Acid 250 mg po daily for seizures.

The patient presented to the family practice physician with symptoms of a cold.

The family physician prescribed Hydrocodone Bitartrate 1mg/ml At 5mg Po TID.
Hydrocodone Fatality: Drug Interactions/PK/PGx

- Clarithromycin was prescribed for ear infections.
- The child started the prescription and received 15 mg hydrocodone on day 1 between the hours of 3PM and 11PM.
- The next morning dose was provided prior to leaving for school.
- The patient was forced to leave school due to drowsiness and lethargy.
Hydrocodone Fatality: Drug Interactions/PK/PGx

- The patient was sent home with the uncle.

- The patient was observed snoring loudly at home and in an apparent deep sleep.

- The patient’s mother found her unresponsive on the next morning at 6:45 and dialed 911.

- The patient was stiff and unresponsive on the scene.
Hydrocodone Fatality: Drug Interactions/PK/PGx

**FIGURE 1**
Metabolic pathway of hydrocodone metabolism and overview of drug-drug interactions with concomitant medications (clarithromycin and valproic acid).

PEDIATRICS Volume 126, Number 4, October 2010
The Pharmacologic Response To Tramadol: CYP2D6 Variation Influences Outcomes

- PGRN PK Pathway

- O-Desmethyl Tramadol is the primary metabolite from CYPD6

- O-Desmethyl Tramadol has 200 times more affinity for the MOR than the parent drug and other metabolites
5 Year Old CYP2D6 Ultra-Metabolizer Case Report

A Case of Respiratory Depression in a Child With Ultrarapid CYP2D6 Metabolism After Tramadol

Gilles Orliaguet, MD, PhD, Jamil Hamza, MD, PhD, Vincent Couloigner, MD, PhD, Françoise Denoyelle, MD, PhD, Marie-Anne Loriot, MD, PhD, Franck Broly, MD, PhD, Erea Noël Garabedian, MD

We discuss a case of severe respiratory depression in a child, with ultrarapid CYP2D6 genotype and obstructive sleep apnea syndrome, after taking tramadol for pain relief related to a day-case tonsillectomy.


**DOI:** 10.1542/peds.2014-2673

Accepted for publication Dec 8, 2014
Interactive Quiz:

How Many Drugs Used For Analgesia Have Validated Pharmacogenomics (PGx) Biomarkers Listed Within The Package Insert?

Take-Aways…

- Healthcare providers should work together as teams to appropriately manage pain in patients.

- Pharmacists are equipped to educate patients and healthcare providers about the results of PGx tests which may prevent severe adverse events and drug-drug interactions that could result in suboptimal outcomes.

- Pharmacists should lobby for funding to increase the evidence base of PGx for optimizing pharmacotherapy for pain management.
For Discussion...Filling the Gaps
Assessment Question #1

The extent to which pharmacists engage in patient-centered pain management can be evaluated by:

A. Patients  
B. Pharmacists  
C. Observers  
D. Accrediting bodies  
E. All of the above
Assessment Question #2

Patient-centeredness in health systems is often evaluated based on:
A. Patient satisfaction scores
B. Patient out of pocket expenses
C. Readmission rates
D. Physician self-report
Assessment Question #3

The study of how genes influence the variability of response to drugs?

a. Pharmacodynamics
b. Pharmacokinetics
c. Pharmacometrics
d. Pharmacogenetics/genomics
e. All of the above
Assessment Question #4

This governmental agency provides/establishes resources regarding Pharmacogenetic/genomic materials in package inserts of approved pharmaceutical agents?

a. NIH (National institutes of Health)
b. FDA (U.S. Food and Drug Administration)
c. CDC (Centers for Disease Control)
d. UAMS Drug Information Center