PainWeek®

Prime Time or Too Soon?
Pharmacogenomics in Pain Management

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Disclosure

- Abigail Brooks
  - Nothing to disclose
- Courtney Kominek
  - Honoraria: Quest Diagnostics

- The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of any agency of the United States government, including the Department of Veterans Affairs, as well as employers, employee affiliates and/or pharmaceutical companies mentioned or specific drugs discussed.

Learning Objectives

- Review the role of pharmacogenetic testing in pain management
- Discuss relevant pharmacogenetic variants that impact pain management medications
- Provide recommendations for medication optimization based on pharmacogenetic results

Factors Affecting Drug Response

- Genetics
- Age
- Liver function
- Diet
- Concomitant therapy
- Body size
- Alcohol use
- Kidney function

Cavallari LF, Pratt VM. Building evidence for clinical use of pharmacogenomics and reimbursement testing. Adv Mole Pathol. 2018(1):125-134.

Pharmacogenomics

- Study of genetic differences and how they impact medication response
- Outcomes of variation
  - Lack of response
  - Serious adverse reactions
- Pharmacokinetic
  - HLA
  - CYP
- Pharmacodynamic
  - COMT
  - OPRM-1

Nerenz RD, Tsongalis GJ. Pharmacogenetics of opioid use and implications in pain management. JALM;2018:622-632.
Weinshilboum R, Wang L. Pharmacogenomics: precision medicine and drug response. Mayo Clin Proc. 2017;92(11):1711-1722.
Roden DM, McLeod HL, Relling MV et al. Pharmacogenomics. Lancet 2019;394:521-532.

Testing

- Preemptive vs reactive testing
- Single gene vs. panel
- Samples: buccal swab, saliva, blood
- Phenoconversion

Keeling NJ, Rosenthal MM, Strum DW, Patel A, Haidar CE, Hoffman JM. Genet Med. 2019;21(5):1224-1232.
Genetic Testing Registry. Bethesda, MD: National Center for Biotechnology Information, U.S National Library of Medicine. Accessed 2021 June 15.
Thaker DL, Savieo J, Hacha H. Bringing pharmacogenetics to prescribers. Adv Molec Pathol. 2020;3:117-129.
Nicholson WT, Formea CM, Matey ET, Wright JA, Giri J, Moyre AM. May Clin Proceedings. 2021;96(1):218-230.

Testing

- Not routine
- Laboratory vs. direct to consumer
- Lack of guidance on who to test
  - Polypharmacy
  - High-risk patients
  - Avoid significant adverse effects
  - History of multiple unexplained adverse effects
  - Medications with specific dosing recommendations
- Reasons to test
  - Minimize adverse effect
  - Help with prescribing or deprescribing

Keeling NJ, Rosenthal MM, Strum DW, Patel A, Haidar CE, Hoffman JM. Genet Med. 2019;21(5):1224-1232.
Genetic Testing Registry. Bethesda, MD: National Center for Biotechnology Information, U.S National Library of Medicine. Accessed 2021 June 15.
Thaker DL, Savieo J, Hacha H. Bringing pharmacogenetics to prescribers. Adv Molec Pathol. 2020;3:117-129.
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Evidence in Opioid Prescribing with CYP2D6

- 375 patients > 18 years of age with chronic pain receiving an opioid
- Buccal swab for CYP2D6 testing vs placebo swab
- Pharmacists provided recommendations based on phenotype
  - Poor metabolizers (PM)
  - Ultrarapid metabolizer (UM)
  - Intermediate metabolizer (IM) (if not controlled)
- Results
  - IM/PM on tramadol or codeine at baseline in CYP2D6 group had significantly more patients achieving 30% reduction in pain compared to normal care

    (CYP2D6 group 7/29 24% vs normal care group 0/16 p=0.04)

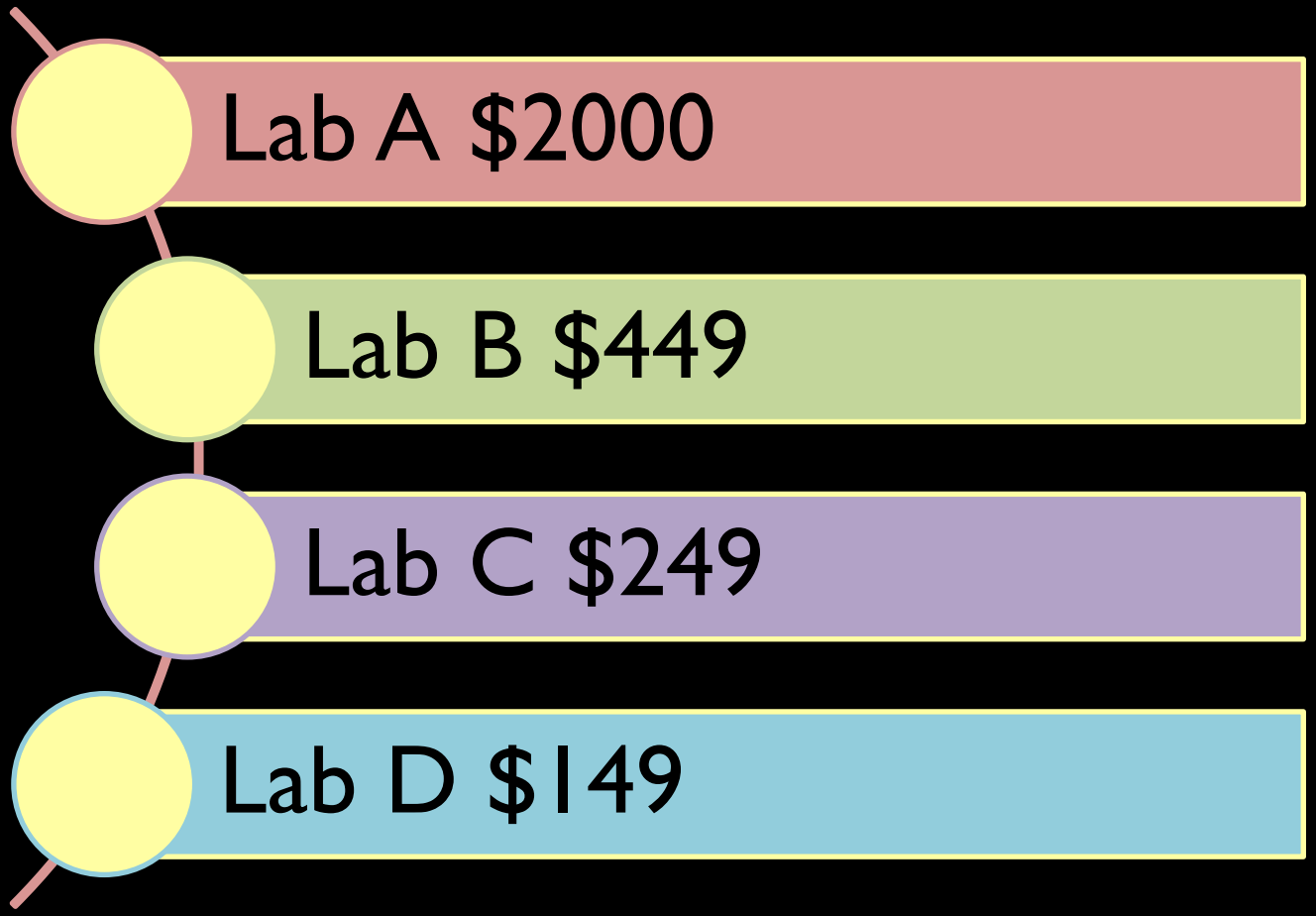
Smith DM, Weitzel KW, Elsey AR, et al. CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. Genet Med. 2019;21(8):1842-1850.

Ethical and Legal Considerations

- Genetic Information Nondiscrimination Act (GINA) of 2008
  - Prevents discrimination for health insurance and employment
  - Does not apply to life, disability, or long-term care insurance

Silva M, Jackson J, Mitroka J. Ethical issues in pharmacogenomics. Pharmacy Times. 2015;81(3). Accessed 16 June 2021.

Cost



Medicare Coverage

- Single gene, multi-gene, combination tests
- "Medications being considered for use (or already in use) that are medically necessary, appropriate, and approved for use in patient's condition and are known to have gene-drug interaction through FDA or CPIC guidelines"
- Documentation required
  - Diagnosis appropriate for medications
  - Initial personalized decision on patient-specific factors
  - Provider must document medication and indication for the test being performed

Local Coverage Determination (LCD): MoIDX: Pharmacogenomics Testing (L28394). Medicare Coverage Database. Centers for Medicare and Medicaid Services. Accessed 17 June 2021

Barriers

- Logistics of testing
- Reporting results
- Evidence for treatment algorithms
- Lack of provider knowledge
- Lack of clear recommendations
- Lack of decision support
- Cost and reimbursement

Shuldiner AR, Relling MV, Hicks JK et al. The Pharmacogenomics Research Network Translational Pharmacogenetics program: Overcoming Challenges of Real-World Implementation. Clin Pharmacol Ther. 2013;94(2):207-210.

Cytochrome P450

- Heme containing
- Found in GI tract and liver
- Phase 1 drug metabolism
- 90% of drugs metabolized by 6 enzymes
- Polymorphic
- Impact of drug interactions

Nussbaum RL, McInnes RR, Willard HF. Application of genomics to Medicine and Personalized Health Care. In: Thompson & Thompson Genetics in Medicine. 8th ed. Philadelphia, PA: Elsevier: 369-382.

Catechol-O-methyltransferase (COMT)

- Metabolism of dopamine, norepinephrine, epinephrine
- Impacts pain sensitivity and response to medications
- Most common variant 472G>A, rs4680 reduces enzyme activity 3-4 times
- Differing outcomes on COMT variants and opioids
- No guidelines on COMT and opioids

Nerenz RD, Tsongalis GJ. Pharmacogenetics of opioid use and implications in pain management. JALM;2018:622-632.
Ofoegbu A, Ettienne EB. Pharmacogenomics and morphine. J Clin Pharmacol. 2021.

OPRM-1

- Gene for mu-opioid receptor
- Primary site of action of opioids
- Most frequent polymorphism is OPRM1 118 A>G (rs1799971)
- Mixed results in studies
- Opioid responder: 118A/A
- Decreased opioid response: 118A/G
- Poor opioid response: 118G/G
- No guideline recommendations for OPRM-1 and opioids

Ofoegbu A, Ettienne EB. Pharmacogenomics and morphine. J Clin Pharmacol. 2021.

Human Leukocyte Antigen (HLA)

Part of human major histocompatibility complex (MHC)

Helps recognize self vs. non-self

Antigen presents via cell surface proteins

Usually intracellular and identified as "self"

Non-self leads to immune response

Cutaneous reactions

- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Maculopapular exanthema (MPE)

Phillips EJ. Sukasem C, Whirl-Carrillo M et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxarbazepin: 2017 Update. Clinc Pharmacol Ther. 2018;103(4):574-

Role of Pharmacist in Pharmacogenomics

Haidar CE, Petry N, Oxencis C, Douglas JS, Hoffman JM. ASHP statement on the pharmacist's role in clinical pharmacogenomics.2021. Available at: https://www.ashp.org/-/media/assets/policy-guidelines/docs/statements/pharmacists-role-clinical-pharmacogenomics.ashx?la=en&hash=2BCB55015D009686C2511A7DDF78303719AE2AC9. Accessed 29 June 2021.

Case #1

Case #1

- JP is a 55 yo female with diabetes and diabetic peripheral neuropathy
- Prescribed gabapentin 600 mg PO TID
- Pain is 8/10 and requesting additional pain relief
- You're considering adding an antidepressant
- Previous trial of paroxetine for depression (in remission) with significant side effects

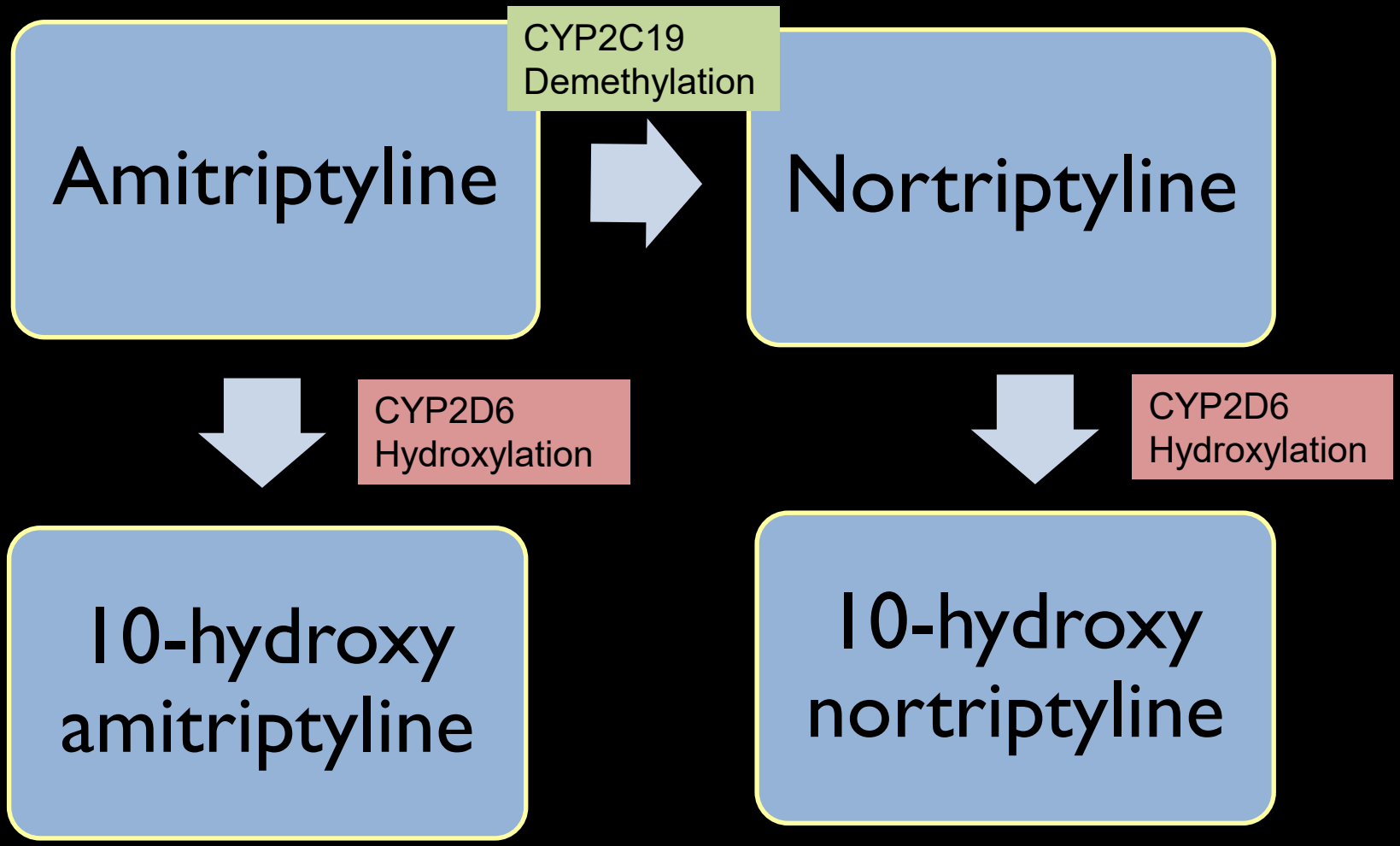
Case #1

- Discuss pharmacogenetic testing
- Patient consents
- Results from pharmacogenomic testing shows

CYP2C19
rapid
metabolizer

CYP2D6
poor
metabolizer

Tricyclic Antidepressants (TCA)



Clinical Pharmacogenetic Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*. 2017;102(1):37-44.

Gene-based Dosing for Neuropathic Pain

Low doses

- No dose adjustments for poor or intermediate CYP2D6 or CYP2C19 metabolizers

Higher doses

- Use tables in the following slides

Clinical Pharmacogenetic Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*. 2017;102(1):37-44.

Gene-based Dosing for Neuropathic Pain

CYP2D6 ultrarapid metabolizers

- Increased risk of treatment failure

Combined CYP2D6 and CYP2C19 phenotypes

- Sparse data
- Caution with combo poor or ultrarapid phenotypes

Clinical Pharmacogenetic Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*. 2017;102(1):37-44.

*Dosing recommendations apply to use of higher initial doses used for management of depression

CYP2D6, *CYP2C19* and TCA

Phenotype	Implication	Therapeutic recommendation*	Strength of recommendation
CYP2D6 Intermediate Metabolizer (1-13% of patients)	Reduced metabolism to less active metabolites Higher plasma concentrations of active drug increase likelihood of adverse drug event (ADE)	Consider 25% reduction in starting dose Use therapeutic drug monitoring to guide adjustments	Moderate
CYP2D6 Poor Metabolizer (1-10% of patients)	Greatly reduced metabolism Higher concentrations increase likelihood of ADE	Avoid due to potential for ADE Consider alternative not metabolized through CYP2D6 If use TCA, reduce dose 50% and use therapeutic drug monitoring	Strong

Clinical Pharmacogenetic Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*. 2017;102(1):37-44.

*Dosing recommendations apply to use of higher initial doses used for management of depression

CYP2D6, CYP2C19 and TCA

Phenotype	Implication	Therapeutic recommendation*
CYP2C19 Ultrarapid Metabolizer CYP2C19 Rapid Metabolizer (2-30% of patients)	Increased metabolism of tertiary amines May affect response or side effects	Avoid tertiary amines due to possibility for suboptimal response Consider alternative TCA Nortriptyline and desipramine without CYP219 involvement If using tertiary, use therapeutic drug monitoring to guide
CYP2C19 Normal Metabolizer (35-50% of patients)	Normal metabolism of tertiary amines	Initiate with standard doses

Clinical Pharmacogenetic Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*. 2017;102(1):37-44.

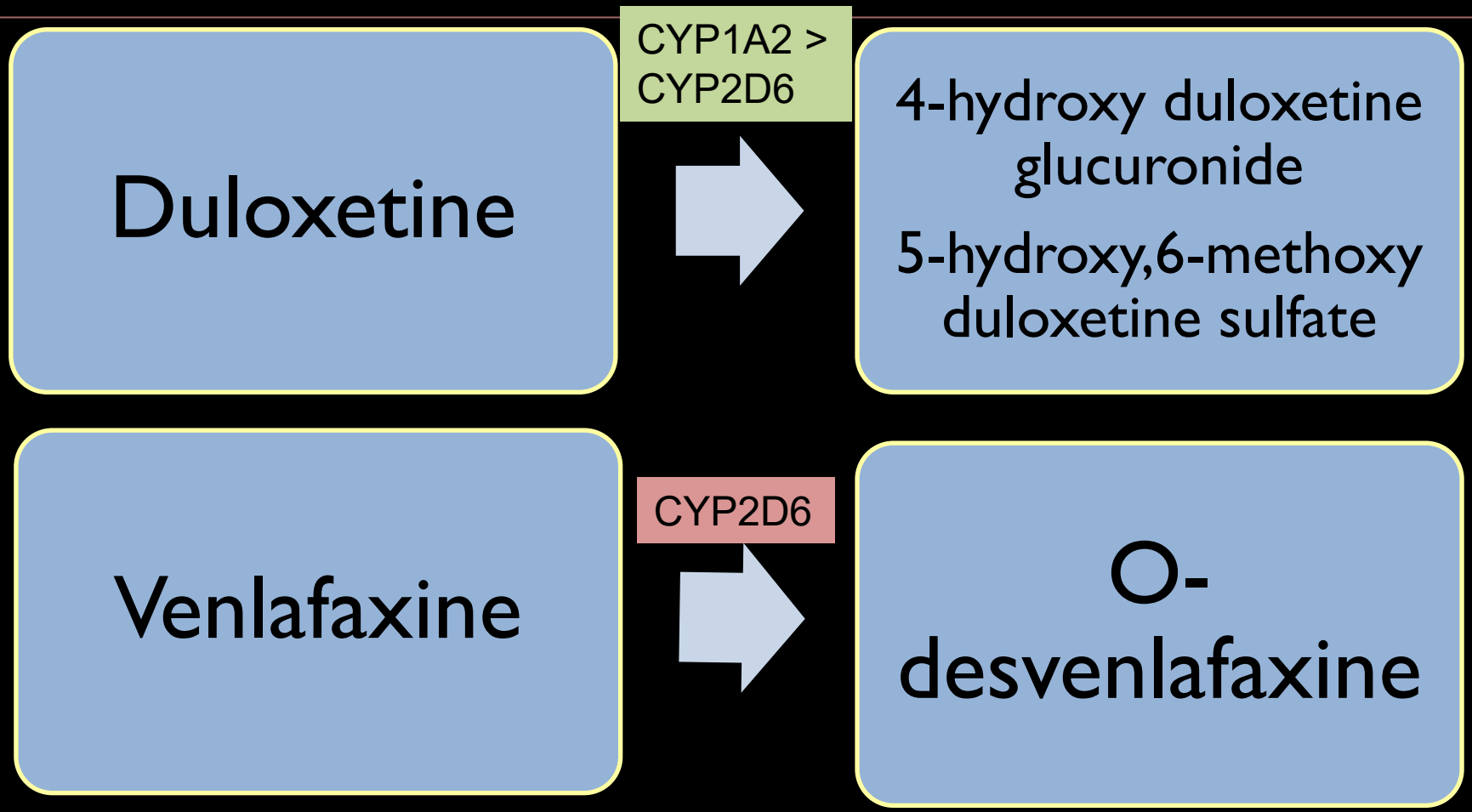
CYP2D6, CYP2C19 and TCA

*Dosing recommendations apply to use of higher initial doses used for management of depression

Phenotype	CYP2D6 Ultrarapid Metabolizer	CYP2D6 Normal Metabolizer	CYP2D6 Intermediate Metabolizer	CYP2D6 Poor Metabolizer*
CYP2C19 Ultrarapid Metabolizer	Avoid amitriptyline	Consider alternative not metabolized by CYP2C19	Consider alternative not metabolized by CYP2C19	Avoid amitriptyline
CYP2C19 Normal Metabolizer	Avoid amitriptyline. If used, need higher dose	Initiate at standard dose	Consider 25% reduction in starting dose	Avoid amitriptyline. If amitriptyline used, consider 50% reduction
CYP2C19 Intermediate Metabolizer	Avoid amitriptyline	Initiate at standard dose	Consider 25% reduction in starting dose	Avoid amitriptyline. If amitriptyline used, consider 50% reduction
CYP2C19 Poor Metabolizer	Avoid amitriptyline	Avoid amitriptyline. If amitriptyline used, 50% dose reduction	Avoid amitriptyline	Avoid amitriptyline

Clinical Pharmacogenetic Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*. 2017;102(1):37-44.

Serotonin Norepinephrine Reuptake Inhibitors (SNRI)



Cymbalta package insert. Indianapolis, IN: Eli Lilly and Company; 2020 May.
Effexor package insert. Philadelphia, PA: Wyeth Pharmaceuticals Inc; 2008 Feb.
National Center for Biotechnology Information. PubChem Compound Summary for CID 60835, Duloxetine. https://pubchem.ncbi.nlm.nih.gov/compound/Duloxetine. Accessed June 11, 2021.

SNRIs

Duloxetine

- Not a gene-drug interaction
- No dose adjustments suggested

Venlafaxine

- Increased venlafaxine:O-desmethylvenlafaxine ratios
- Increase potential for ADE
- Reduce chance of efficacy
- Choose an alternate
- If used
  - Reduce dose
  - Monitor for efficacy and tolerability
  - Check plasma concentration

Royal Dutch Association for the Advancement of Pharmacy. Dutch Pharmacogenetic Working Group Guidelines. November 2018. Available at: https://www.knmp.nl/downloads/pharmacogenetic-recommendations-november-2018.pdf (accessed 2021 June 11).
Royal Dutch Association for the Advancement of Pharmacy. Dutch Pharmacogenetic Working Group Guidelines. https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf August 2019 . Available at: (accessed 2021 June 11).

Case #1

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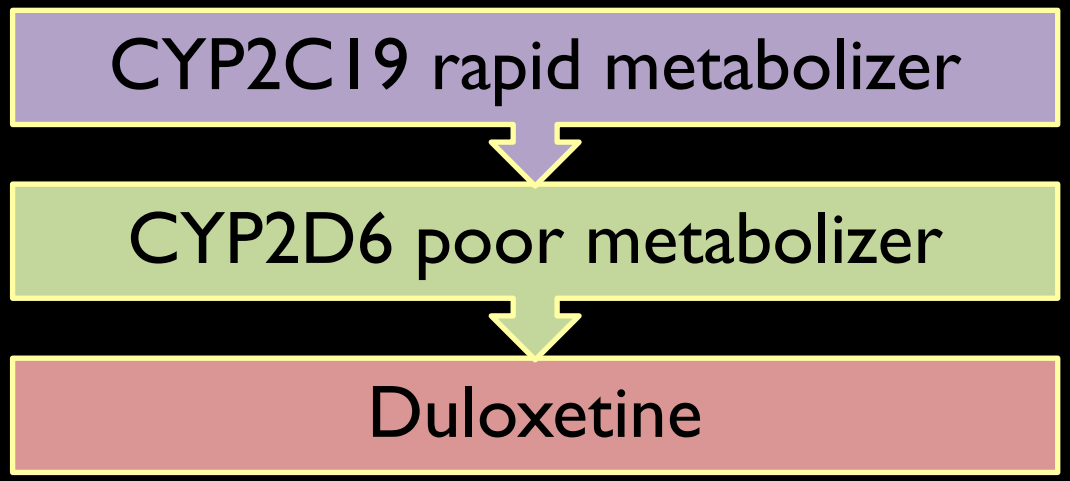


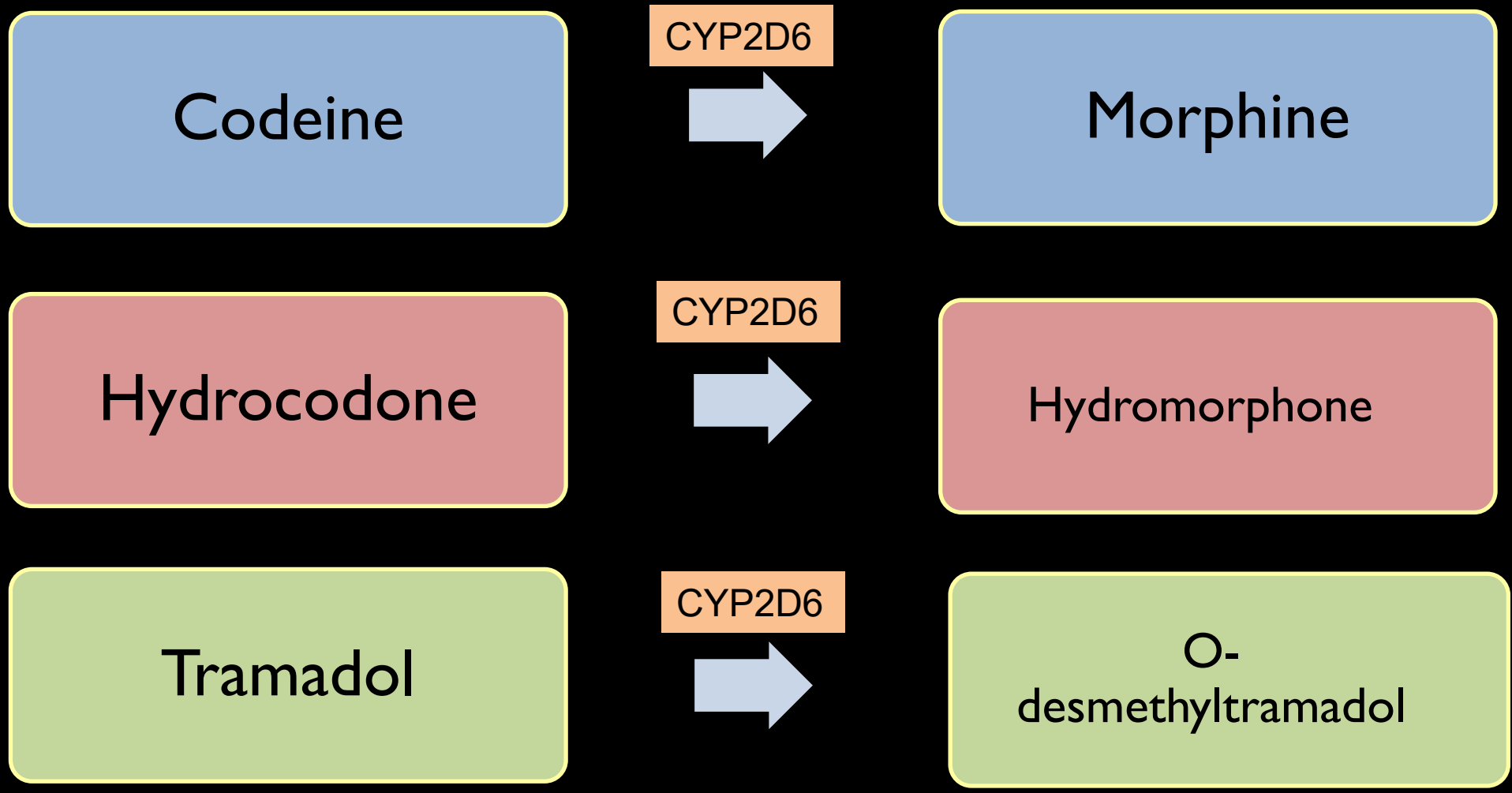
Case #2

Case #2

- BT is a 62 yo male presenting to clinic with right hip pain after recent fall
- Imaging shows right hip fracture which requires surgery
- Recent pharmacogenomic testing shows

CYP2D6 rapid metabolizer

Opioid Metabolism



Obeng AO, Hamadeh I, Smith, M. Review of opioid pharmacogenetics and considerations for pain management. Pharmacother. 2017;37(9):1105-1121.

CYP2D6 – Codeine

Phenotype	Recommendations	Strength
CYP2D6 ultrarapid metabolizer	Avoid codeine. Consider non-tramadol opioid	Strong
CYP2D6 normal metabolizer	Use codeine label recommendations	Strong
CYP2D6 intermediate metabolizer	Use codeine label recommended age-specific or weight-specific dosing. If no response, consider a non-tramadol opioid	Moderate
CYP2D6 poor metabolizer	Avoid codeine. Consider non-tramadol opioid	Strong

Crews KR, Monte AM, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. Clin Pharmacol Ther. 2021.

CYP2D6 – Hydrocodone

Phenotype	Dose adjustments	Strength of recommendation
CYP2D6 ultrarapid metabolizer	No recommendation Minimal evidence of adverse effects or impact on analgesia	No recommendation
CYP2D6 normal metabolizer	Standard dosing	Strong
CYP2D6 intermediate metabolizer	Standard dosing	Optional
CYP2D6 poor metabolizer	Standard dosing If no response and opioid appropriate, use non-codeine and non-tramadol opioid	Optional

Crews KR, Monte AM, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. Clin Pharmacol Ther. 2021.

CYP2D6 – Tramadol

Phenotype	Recommendations	Strength of Recommendation
CYP2D6 Ultrarapid metabolizer	Avoid tramadol	Strong
CYP2D6 Normal metabolizer	Standard dosing	Strong
CYP2D6 Intermediate metabolizer	Standard dosing If no response, consider non-codeine opioid	Optional
CYP2D6 poor metabolizer	Avoid tramadol	Strong

Crews KR, Monte AM, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. Clin Pharmacol Ther. 2021.

No recommendations

COMT

Methadone

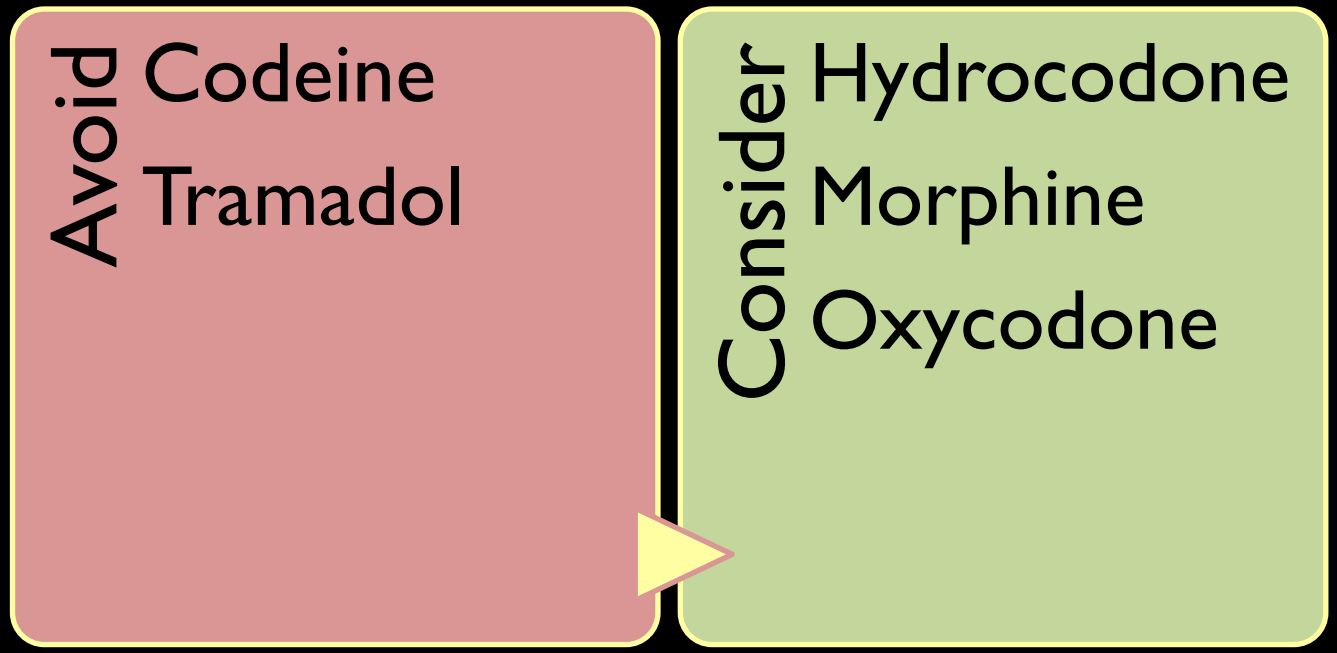
OPRM

Oxycodone

Crews KR, Monte AM, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. Clin Pharmacol Ther. 2021.
Royal Dutch Association for the Advancement of Pharmacy. Dutch Pharmacogenetic Working Group Guidelines. November 2018. Available at: https://www.knmp.nl/downloads/pharmacogenetic-recommendations-november-2018.pdf (accessed 2021 June 11).

Case #2

- BT is a 62 yo male presenting to clinic with right hip pain after recent fall
- Imaging shows right hip fracture which requires surgery
- Recent pharmacogenomic testing shows – CYP2D6 rapid metabolizer



Case #3

Case #3

- CT is a 61 yo Asia male with facial pain diagnosed with trigeminal neuralgia
- Plan to initiate carbamazepine or oxcarbazepine
- Decide to order pharmacogenetic testing
- Pharmacogenetic testing shows

HLA-B*15:02	HLA-A*31:01
negative	positive

Ethnic and Geographical Distribution

*HLA-B**15:02 Frequency

- East Asian 6.9%
  - Lower in Japanese < 1% and Korean < 2.5%
- South/Central Asian 4.6%
  - Higher in Vietnamese, Cambodian, Thai, Malaysian, Indian
- Oceanian 5.4%
- Rare in Africans, African Americans, Middle Easterners, Caucasians, and Hispanics/South Americans < 1%

*HLA-A**31.01 Frequency

- Japanese 8%
- Hispanic/South Americans 6%
- South Koreans 5%
- Caucasians 3%
- South/Central Asians 2%

Phillips EJ. Sukasem C, Whirl-Carrillo M et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxarbazepin: 2017 Update. Clinc Pharmacol Ther. 2018;103(4):574-

HLA-A*31.01 and HLA-B*15.02 and Carbamazepine (CBZ)

Genotype	Implication	Therapeutic Recommendation
HLA-B*15.02 negative and HLA-A*31:01 negative	Normal risk	Use standard dosing
HLA-B*1502 negative and HLA-A*31.01 positive	Greater risk of SJS/TEN, DRESS, and MPE	CBZ naïve, consider alternative medications and avoid CBZ If use CBZ, increase monitoring and discontinue ASAP if ADE CBZ experienced for 3 months, low risk
HLA-B*15.02 positive and any HLA-A*31.01	Greater risk of SJS/TEN	CBZ naïve, avoid CBZ experienced for 3 months, low risk

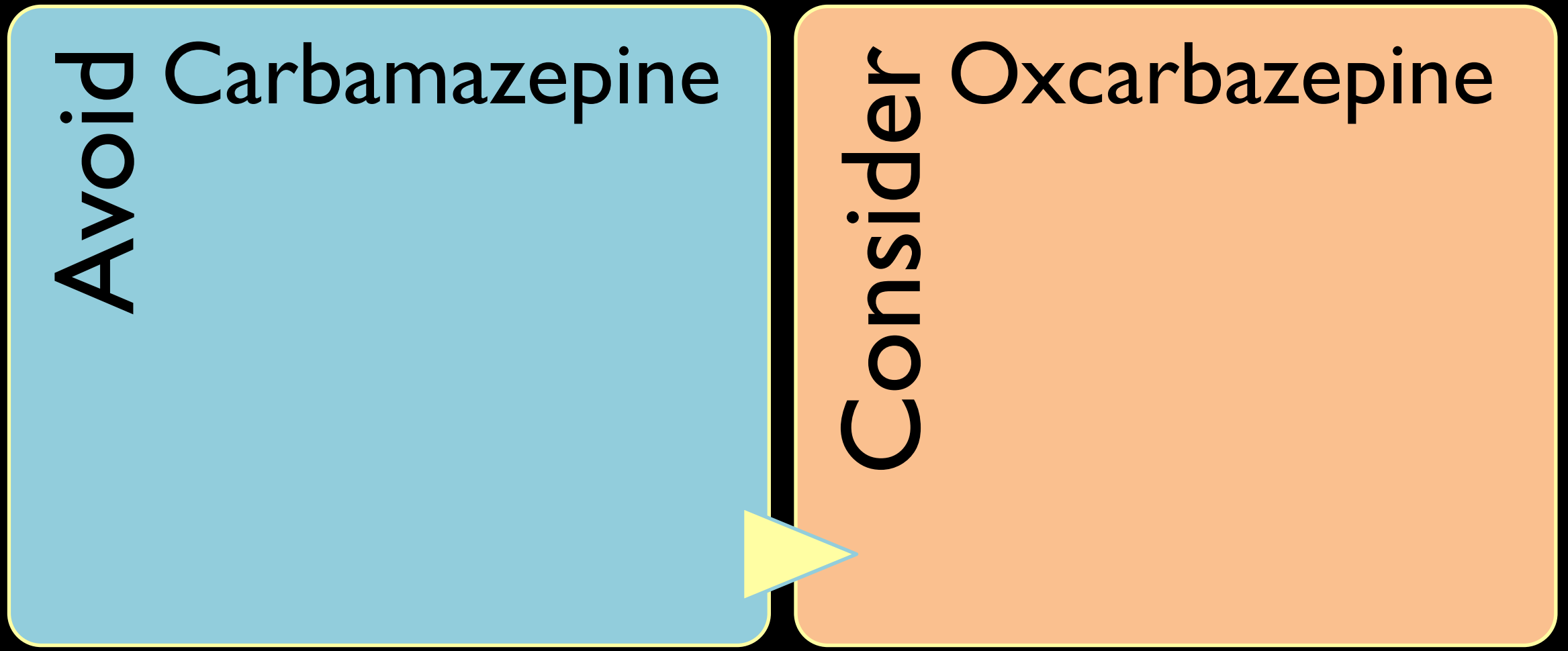
Phillips EJ. Sukasem C, Whirl-Carrillo M et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxarbazepin: 2017 Update. Clinc Pharmacol Ther. 2018;103(4):574-

HLA-B*15.02 and Oxcarbazepine (OXCBZ)

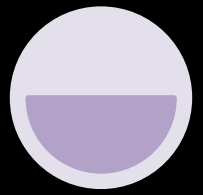
Genotype	Implication	Therapeutic recommendation
HLA-B*15.02 negative	Normal risk	Use standard dosing
HLA-B*15.02 positive	Greater risk of SJS/TEN	If OXCBZ naïve, avoid. If OXCBZ experienced for 3 months, low risk

Phillips EJ. Sukasem C, Whirl-Carrillo M et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxarbazepine: 2017 Update. Clinc Pharmacol Ther. 2018;103(4):574-581.

Case #3



Prime Time or Too Soon?



Prime Time

CYP2D6

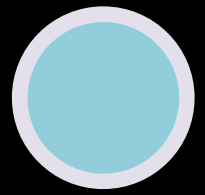
- Codeine
- Tramadol
- SSRIs
- TCAs

CYP2C19

- TCAs

HLA

- Carbamazepine
- Oxcarbazepine



Too Soon

Who to test

When to test

OPRM + opioids

COMT + opioids

Learning Assessment Question #1

- Guidelines recommend pharmacogenetic testing in pain management in which of the following situation

A. No guideline recommendations on who and when to test
B. Patient with at least 5 adverse drug reactions
C. Patients taking more than 5 medications
D. All patients before being prescribed tramadol or codeine

Learning Assessment Question #2

- DK is a 47 yo male with recent humerus fracture. Patient a known CYP2D6 poor metabolizer. What opioid do you recommend for management of his acute pain?
  A. Codeine
  B. Tramadol
  C. Morphine
  D. Fentanyl patch

Learning Assessment Question #3

- 55 year-old patient with trigeminal neuralgia. The patient is HLA-B*15:02 positive and HLA-A*31:01 positive. What options are safest to prescribe?

A. Oxcarbazepine
B. Carbamazepine or Oxcarbazepine
C. Carbamazepine
D. Gabapentin