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Trainee Council

PEARLS OF LABORATORY MEDICINE

Pharmacogenomics in Pain Management

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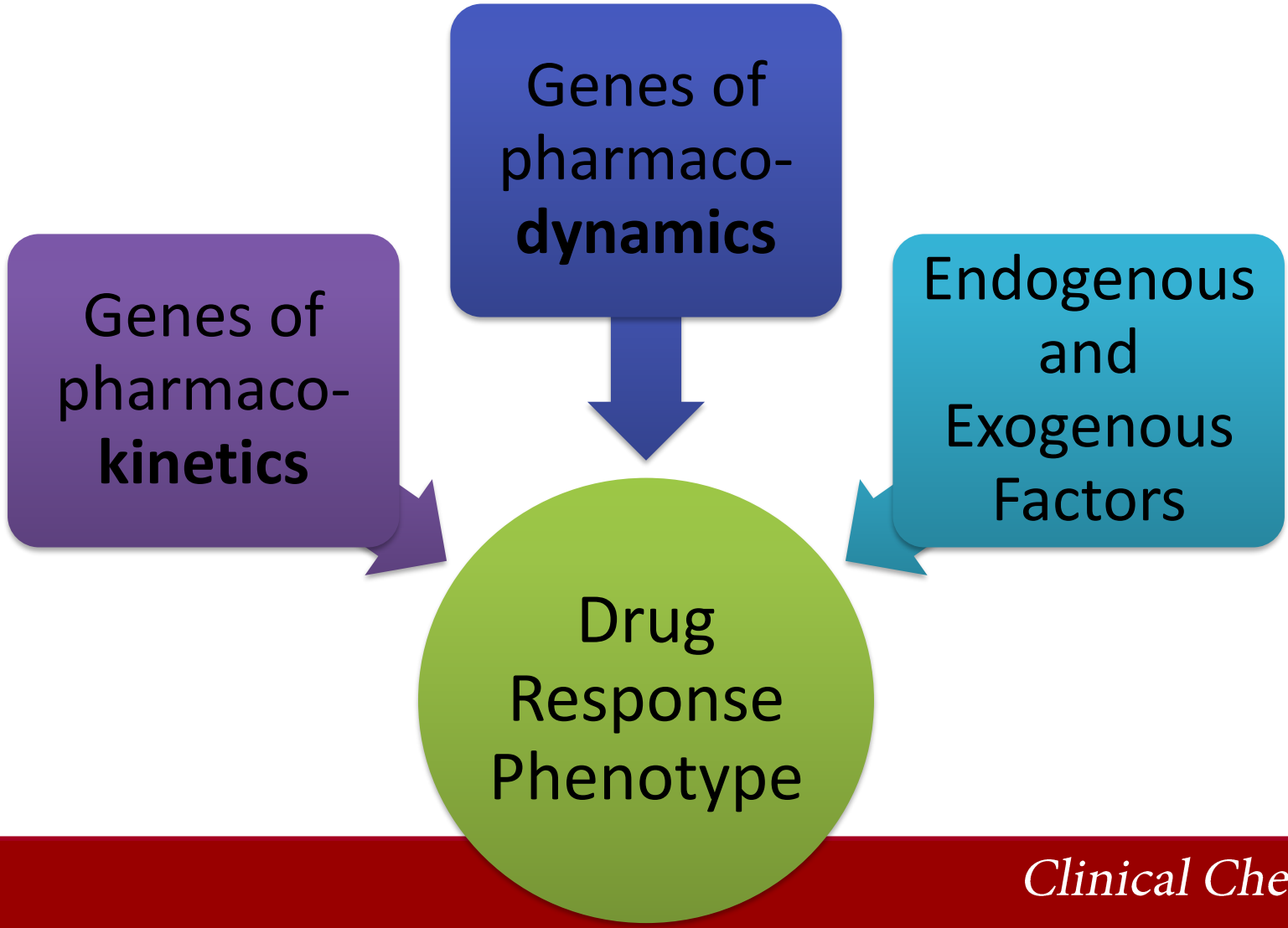
Pharmacogenomics of Drug Response

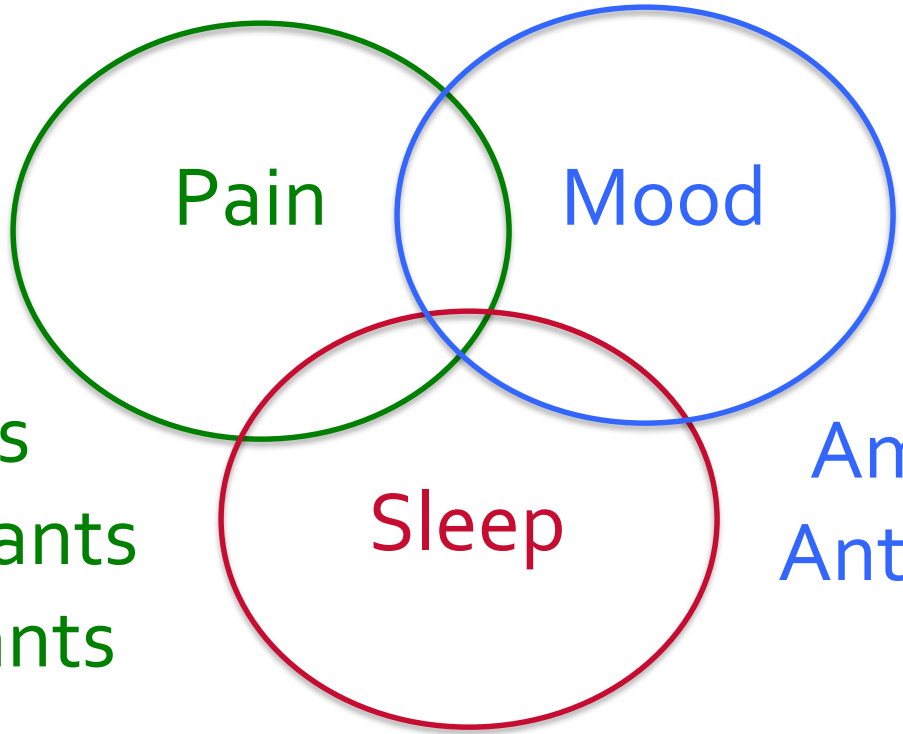


Examples Pharmacogenomic Targets

- Pharmacokinetics genes
  - Drug metabolizing enzymes
    - *CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5*
    - *TPMT, NAT1/2, DPYD, G6PD, UGT1A1, UGT2B7*

- Pharmacodynamics genes
  - Receptors, ion channels, enzymes
    - *VKORC1, IL28B, OPRM1, COMT, KRAS, EGFR, ABL1, ALK, BCR, KIT, DRD2, SCN9A, HLA-B, LDLR, ESR1/2*

Drugs Used for Management of Pain



Opioids
NSAIDs
Cannabinoids
Muscle relaxants
Anticonvulsants
Others

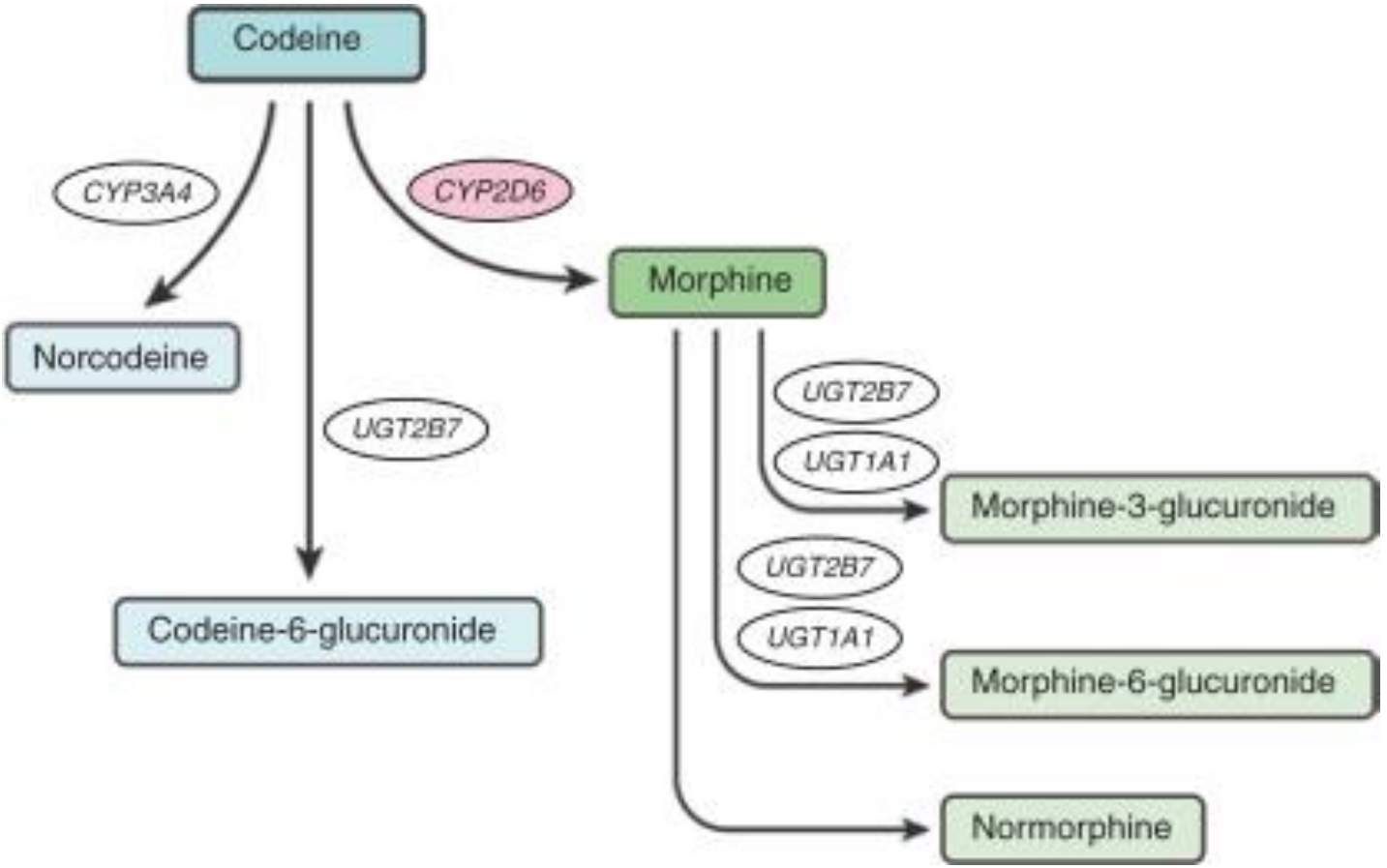
Anxiolytics
Amphetamines
Antidepressants

Benzodiazepines

Opioids

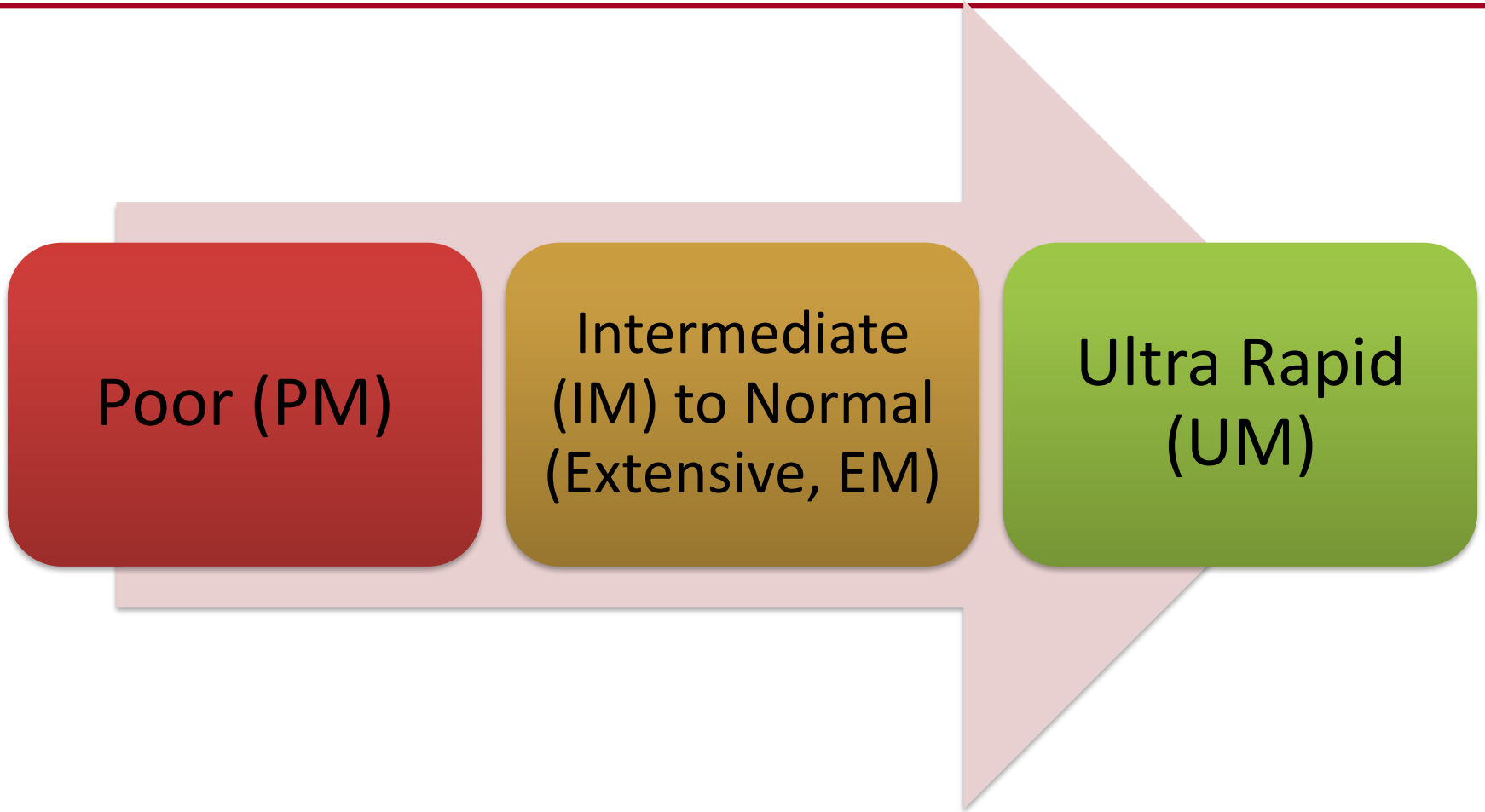
Drug	Times more potent than codeine	Pro drug?	Plasma Half-life (hrs)
Tramadol	1	Y	4-8
Hydrocodone	6	Y	3-9
Morphine	10	N	1-7
Oxycodone	20	Y	3-6
Oxymorphone	70	N	8-10
Buprenorphine	400	N	26-42
Fentanyl	1000	N	3-12
Carfentanyl	100,000	N	7-8

Simplified Codeine Metabolism



This pathway diagram was downloaded from http://www.pharmgkb.org with permission given by PharmGKB and Stanford University (accessed August 29th, 2013)

CYP2D6 Phenotypes



Can be affected by genotype and non-genetic factors

CPIC guidance: CYP2D6 PM

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.	**STRONG**

Crews KR, Gaedigk A, Dunnenberger HM, et al. CPIC guidelines for codeine therapy in the context of cytochrome P450 2D6 (*CYP2D6*) genotype. Clin Pharmacol Ther. 2012;91:321-6.

CPIC guidance: CYP2D6 UM

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.	**STRONG**

Crews KR, Gaedigk A, Dunnenberger HM, et al. CPIC guidelines for codeine therapy in the context of cytochrome P450 2D6 (*CYP2D6*) genotype. Clin Pharmacol Ther. 2012;91:321-6.

Example CYP2D6-Related Drugs

Substrates activated by CYP2D6	Substrates inactivated by CYP2D6	Strong inhibitors	Moderate-Weak inhibitors
Codeine	Fluoxetine	Fluoxetine	Diphenhydramine
Tramadol	Paroxetine	Paroxetine	Duloxetine
Tamoxifen	Amphetamine	Quinidine	Oral contraceptives
Risperidone	Atomoxetine	Bupropion	Methadone

Examples of CYPs and Analgesics

Analgesic	CYP2D6	CYP2C19	CYP2B6	CYP3A4
Buprenorphine				*inactivated*
Codeine	**ACTIVATED**			
Fentanyl				*inactivated*
Hydromorphone				
Methadone	inhibitor	*inactivated – minor route*	*inactivated*	*inactivated*
Morphine	*inactivated – minor route*			
Oxycodone	**ACTIVATED**			*inactivated*
Tramadol	**ACTIVATED**		*inactivated – minor route*	*inactivated*

Lexicomp Drug Information Handbook, 22nd Ed, 2013

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Conclusions

- Pharmacogenomic testing can add to the information used to guide drug and dose selection, and personalize pharmacotherapy
- Pre-therapeutic *CYP2D6* genotype testing may identify patients at risk for therapeutic failure or adverse effects when administered codeine, and potentially other *CYP2D6* substrates

References

Review articles:

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Websites:

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- http://www.cypalleles.ki.se
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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

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