Oral opioid metabolism and pharmacogenetics

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Abstract

Opioid analgesics are widely used as the standard of care for the management of moderate to severe nociceptive pain. The opioids' analgesic properties mainly emanate from stimulation of the μ-receptors, which are encoded by the OPRM1 gene. Most opioids are fat-soluble, requiring conversion to water-soluble compounds for excretion, but for some opioids, namely tramadol and codeine, hepatic metabolism is necessary for their bioactivation into more potent analgesics. Hepatic biotransformation generally occurs as Phase I and Phase II metabolism. The highly polymorphic nature of the genes, coding for Phase I and II enzymes involved in the metabolism and bioactivation of opioids, suggests potential interindividual variation in patient response in terms of efficacy and safety. Patients can be classified by their genetic ability to metabolise medication. The inherent differences in the genes that encode the CYP450 enzymes, particularly CYP3A4 and CYP2D6, can affect the metabolic capacity of an individual, leading to over- or underexposure to an opioid, making opioid pharmacokinetics and pharmacodynamics variable between individuals. Other medications that also utilise the CYP450 pathway can lead to interactions. In addition to pharmacogenomics, other factors like age, ethnicity and renal impairment also contribute to differences in opioid metabolism and variation in patient response. This article provides a review of the metabolism of commonly prescribed oral opioids, and pharmacogenetic considerations.

Keywords: opioids, opioid metabolism, pharmacogenetics, individualised pain management, cytochrome P450

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Introduction

Opioid medication is commonly prescribed for moderate or severe intensity acute and chronic pain.[1,2] This class of medicine is the cornerstone for the management of severe pain arising from malignant and non-malignant diseases and are recognised in both guidelines and evidence-based systematic reviews.[3-5] There is a great variation in patient response to standard doses of analgesic treatment, especially opioids, in terms of efficacy as well as safety.[6,7] Most opioids have a narrow therapeutic index, with respiratory depression as the major life-threatening effect, as well as a wide dosage variability because of a multitude of factors, including genetics. Opioid dosages hence need to be individualised.[8]

In April 2017 the Food and Drug Administration (FDA) issued a strong warning, contraindicating the use of codeine and tramadol in children younger than 12 years and therefore requires changes in the labeling of codeine to treat pain or cough and tramadol to treat pain.[9] Additional warnings in adolescents between 12 and 18 years of age who have significant pulmonary problems, obstructive sleep apnoea or who are obese were also included. The FDA further announced the contraindication of tramadol as pain medication after adenotonsillectomy in children under 18 years.[9] The risk of serious adverse effects, including respiratory arrest and death in breastfed children, strengthened the warning against the use of tramadol or codeine in lactating women.[9]

An increased use of prescription medications due to multiple comorbidities, increases the risk for adverse reactions and makes medication management challenging.[10] The occurrence of opioid side-effects can be enhanced by metabolic interactions within the liver, involving other medications (drug-drug interactions), as well as drug-food, drug-disease and drug-genetic interactions, or any combination thereof.[3,7] The FDA announcements illustrate the importance of the evolving recognition of the influences of genetic variation on opioid metabolism.[9,11] Furthermore, various factors such as age, gender and genetics can also affect the analgesic response.[3,7] This calls for a more individualised approach, where medication is selected for a specific patient, based on the patients' sensitivity to and metabolism of the medication, as well as his/her genetic makeup.[11,12] Individualised medicine will in turn contribute to the optimisation of patient outcomes.[3,7]

This article aims to review information regarding oral opioid metabolism and the impact of genetic polymorphisms on patients response to opioid medication.

Metabolic and hepatic pathways for metabolism of oral opioids

A basic understanding of medication metabolism is required to understand the impact of genetic polymorphisms on the variability of opioid pharmacokinetics and pharmacodynamics on analgesia. *Pharmacokinetics* (PK) studies the way in which the process of absorption, distribution, metabolism and excretion (ADME) determine the movement and fate of the molecules inside the body, while *pharmacodynamics* (PD) describes the medicines' effects on body processes at a cellular or receptor level.[13,14]

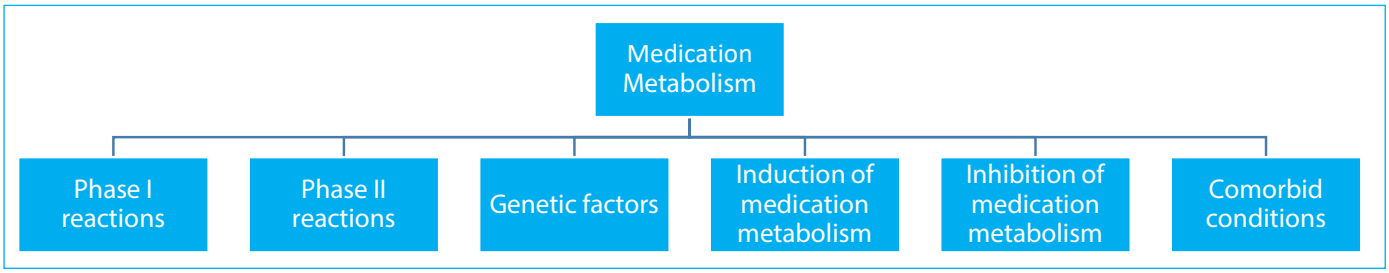

Figure I. Factors influencing metabolism of medicine[15]

Inter-individual genetic variation can influence the PK (e.g. drug transporters and drug-metabolising enzymes) and/or PD (e.g. opioid receptors and catechol-O-methyltransferase enzymes) of medicines.[13,14] Other factors with an effect on medication metabolism are listed in Figure I.

Opioid analgesics are either related to morphine in structure and action, or are synthetic derivatives with different chemical structures. In clinical practice, opioids are classified upon their degree of efficacy. A distinction is made between high-potency, low-potency or intermediate-potency opioid agents, as they act as either full agonists (with high or low affinity) or partial agonists (dualists) at the opioid receptors (mu-, delta-, kappa- or sigma receptors).[13] The opioids' main site of action is the central nervous system, where opioid peptides act as inhibitory neurotransmitters. Stimulation of the opioid receptors not only has an effect on pain, but also on mood and consciousness, breathing, blood pressure and pulse rate, as well as the gastrointestinal tract.[13] Most opioids are fat-soluble (lipophylic) enabling them to cross the blood-brain-barrier and other cellular membranes to reach their site of action. Opioids however need to be converted to water-soluble compounds for excretion, mostly in the urine.[16,17] The latter takes place in the liver and entails the biotransformation of medicine molecules into polar, water-soluble metabolites, generally occurring in two phases[13,16,17]:

- **Phase I–metabolism:** Includes oxidation, reduction and hydrolysis reactions, aimed at producing less active metabolites, rendering medicine molecules more polar and water-soluble. Hepatic metabolism for opioids is mostly via oxidative metabolism.[11,13] Possible outcomes of Phase I liver biotransformation is from a pro-drug to an active drug, for example conversion of codeine to morphine. Alternatively from an active drug to either inactive (usually excreted by the kidneys) or active metabolites (with pharmacological properties) of similar, altered or toxic activity.[13,18] Hydrocodone, as an example, undergoes oxidative metabolism via the CYP2D6 isoenzymes to form the active metabolite hydromorphone. Metabolism via the CYP3A4 isoenzymes results in the inactive metabolite, norhydrocodone.[19]

The oxidative metabolism of approximately 90% of all medications, including most opioids, is catalysed by the cytochrome P450 (CYP450) family of enzymes.[20] More than 30 CYP450 isoenzymes have been identified, but only seven (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) are clinically important. Their presence and level of actitivy vary based on a variety of factors, e.g. tobacco use, race and interactions with other medications and receptors.[21] The CYP450 enzymes are primarily located in the liver, but also in enterocytes in the epithelium of the small intestine.[22,23] These enterocytes can be a vital source of first-pass metabolism by members of the CYP3A family, as they reduce the amount of medicine that reaches the circulation to become bioavailable.[23] Except for catalysing the synthesis and degradation of endogenous steroids and lipids, the CYP450 enzymes are essential to the metabolism of many opioids.[23,24] Their reactions are primarily catalysed by CYP3A4 and CYP2D6, hence they are more prone to interactions with other commonly prescribed medications metabolised through the CYP450 system, called substrates.[3] It is important to note that several pharmaceutical opioids have active metabolites more potent than their parent compounds, whereas in the case of pro-drugs the parent compound itself is inactive. Hydromorphone, an active metabolite, for example, is 30 times more potent than the parent compound (hydrocodone). Hydromorphone is also produced commercially as an opioid on its own.[25,26]

- **Phase II-metabolism:** Includes conjugation of Phase I metabolites, other intermediates or the parent compound through the processes of glucuronidation and sulfation. These metabolites are detoxified and excreted. The majority of the opioids metabolised by Phase I also undergo Phase II metabolism.[17]

  Except for CYP450 isoenzymes, one of the most common non-CYP enzymes associated with pain medications is uridine diphosphate glucuronosyltransferase (UGT). The latter is the main metaboliser of morphine, creating either morphine-6-glucoronide (M6G) contributing to pain relief, or morphine-3-glucoronide (M3G), which is hyperalgesic (increased sensitivity to pain or enhanced intensity of pain sensation).[7,27] Opioid metabolites can thus either have analgesic properties, as the M6G metabolite has higher analgesic potency than its parent compound, or toxic effects as M3G can cause neurotoxicity.[25] The process of glucuronidation occurs in the liver and is catalysed by UGT, producing highly hydrophylic molecules for urinary excretion.[17] The enzyme UGT is also primarily responsible for metabolising oxymorphone and hydromorphone.[3] Table I provides a summary of the metabolism of oral opioids available in South Africa.

Pharmacogenomics of opioid analgesics

In recent years, there has been rapid revolving research in the field of genetics and pain, as genetic variability has been found to affect both pain susceptibility, as well as analgesic responses.[35] Genetics appear to play a larger role than previously thought in the clinical efficacy of opioid medications, which is related to high inter-individual variability in the activity level of the CYP system.[36] *Genetic polymorphisms* describes the variations in the structure of genes, which includes structural changes such as duplication, deletion and translocation.[37] A gene that has been altered by polymorphism is referred to as an *allele* of the original gene (wild-

Table I. Summary of oral opioid metabolism[3,7,8,11,20,28-34]

Oral opioid	Classification	Bioavailability	Half-life	Active/Prodrug	Metabolism	Enzymes
Codeine	Low efficacy opioid. Weak mu receptor agonist metabolised to active morphine.	Approximately 60% oral bioavailability	2.5 to 4 hours	Prodrug	Inactive codeine undergoes *O*-demethylation to its active form, morphine, and *N*-demethylation to an inactive metabolite, norcodeine. These products are glucuronidated by UGT2B7 to morphine-6-glucuronide and morphine-3-glucuronide.	CYP2D6 metabolism to active morphine and CYP3A4 metabolism to inactive norcodeine.
Dihydrocodeine	Semi-synthetic opioid with intermediate efficacy.	Approximately 20%	4 hours	Active medicine that is metabolised to dihydromorphine with more potent analgesic effects.	Phase 1 metabolism to its active metabolite, dihydromorphine, which undergoes glucuronidation by UGT2B7.	CYP2D6
Hydromorphone	Semi-synthetic high-efficacy agonist of mu opioid receptors with a weak affinity for kappa receptors.	22 to 26%	2 to 3 hours	Active medicine	Only Phase 2 metabolism, i.e. glucuroconjugation to hydromorphone-3-glucuronide.	UGT2B7 and UGT1A3
Morphine	High-efficacy natural opium alkaloid. Acts as an agonist at mu and to lesser extent at kappa opiate receptors in the CNS.	Approximately 12 to 36%	2.5 to 3 hours	Active medicine	Only Phase 2 metabolism, i.e. glucuronide conjugation.	UGT2B7 metabolism to morphine-6-glucuronide (more potent analgesic properties than morphine) and UGT1A1/3 metabolism to morphine-3-glucuronide.
Oxycodone	Semisynthetic opioid high-efficacy opioid similar in structure to codeine, but with the analgesic potency of morphine.	Up to 87%	3 hours	Active medicine. One of its metabolites, oxymorphone, is also a strong analgesic.	*N*-demethylated to noroxycodone (inactive metabolite) and *O*-demethylated to a more potent analgesic, oxymorphone. These metabolites undergo glucuroconjugation by UGT2B7 to its inactive metabolites.	CYP2D6 metabolism to oxymorphone and CYP3A4 metabolism to noroxycodone (primary metabolite).
Tilidine	A synthetic, intermediate-efficacy opioid.	6%	3.5 hours	Prodrug	*N*-demethylation by CYP3A4 to active nortilidine.	CYP3A4
Tramadol	Synthetic opioid. A non-selective, pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Inhibits neuronal re-uptake of noradrenaline and enhances serotonin release.	Oral bioavailability of 68% after a single dose, which increases to 90% at steady state.	6 to 7 hours	Prodrug	Only Phase 1 metabolism to its active metabolite, *O*-desmethyltramadol, which is an opioid receptor agonist; and to *N*-demethyltramadol.	CYP2D6 metabolism to *O*-desmethyltramadol and CYP3A4 metabolism to *N*-demethyltramadol.

type).[37,38] A *homozygous genotype* refers to two copies of the same allele, while any combination of two different alleles is called a *heterozygous genotype*. The most common altered gene form is a *single-nucleotide polymorphism* (SNP).[37] These changes in alleles may have a significant effect on pain perception and hence the use of opioids.[7]

Pharmacogenomics is the study of inherited genetic differences that result in individual responses to medications. It investigates the inter-individual genetic variability in DNA sequence of drug metabolising enzymes or disease genes, drug targets, RNA expression or protein translation of genes affecting medication responses and safety.[6,22] *Pharmacogenetics* on the other hand is the study of how allelic differences in single genes may be associated with variability in specific medication responses.[6,22]

The opioids' analgesic properties mainly emanate from stimulation of the mu (μ)-receptors, encoded by the OPRM1 gene. Activation of the μ-receptor leads to supraspinal analgesia and well-known opioid adverse effects, e.g. respiratory depression and decreased gastrointestinal motility. The OPRM1 gene is highly polymorphic, with more than 100 variants identified.[39] Given the polymorphic

Table II. Patient classification based on metaboliser type[9,30,37]

Metaboliser Type	Description	Clinical implications of genotype and phenotypic alterations in metabolism
Normal Metaboliser (NM) (previously referred to as extensive metaboliser)	Has two normal or "wild-type" alleles.	Responds as expected after medication administration, standard medication dosing schedules are designed for people with this enzyme capacity. More than 100 different alleles of CYP2D6 have been identified. For e.g. CYP2D6 NMs can be prescribed codeine at label-recommended doses.
Poor Metaboliser (PM)	Has two abnormal alleles with minimum gene activity.	A range of severity, where the most extreme cases are associated with a serious inability to clear medications and potential risk for adverse effects, due to lack of any functional CYP2D6 enzyme. For e.g. poor metabolisers of tramadol have 14-fold lower concentrations of the active metabolite O-desmethyltramadol, and may therefore have inadequate pain relief.
Intermediate Metaboliser (IM)	Can have one partially active allele or one fully defective allele.	IMs have a range of metabolic capacity less than NMs. Whereas CYP2D6 IMs were found to have lower tramadol clearance than UMs, subsequently the half-life of tramadol was approximately two times longer in IMs than UMs (3.8 vs 7.2 hours).
Rapid Metaboliser (RM)	Has at least one highly active allele.	May experience increased opioid effects with a usual dose of codeine because their rapid metabolism generates a higher concentration of morphine.
Ultra-rapid Metaboliser (UM)	Can have many copies of the normal gene, leading to activity way above the baseline level.	Rapidly clears medication, and can thereby minimise or eliminate the therapeutic response from active parent opioids. Alternatively, CYP2D6 UMs should avoid codeine, due to more rapid and complete biotransformation to morphine, hence increased risk of toxicity.

nature of genes coding for the CYP450 enzymes (regardless of whether they are Phase I or II), it can be assumed that a significant variation in drug disposition or PKs exists among individuals using opioids for analgesia.[30] Table II describes different patient metaboliser types and provides respective examples of clinical implications of genotype and phenotypic alterations in metabolism.

There is increasing interest in the role of genetics on medication targets and metabolism, especially in the field of pain management.[11,22] This is because polymorphisms can affect the PK (ADME) of the same medications on different individuals, as well as the PD brought on by the receptor binding properties of a particular medicine, including its efficacy and side-effects.[3] The inherent differences in the genes that encode the CYP450 enzymes, particularly CYP3A4 and CYP2D6, can affect the metabolic capacity of an individual leading to over- or underexposure to an opioid.[24] These are two important enzymes in opioid metabolism, as they have genetic variability, making opioid PK and PD variable between individuals.[3,16,17]

A large genetic family controls the biosynthesis of the proteins involved in the CYP450 system and as these genes are highly polymorphic, they contribute to the differences in varied individual responses to medications.[22] Genetic polymorphisms of P450 genes are one of the reasons for opioid response variation. In addition to this, the induction of drug-metabolising enzymes can also be affected by genetic variations of the receptors, intracellular and tissue concentration of the inducers, environmental elements (pollutants and diet) and physiological factors like hormones and diseases.[19]

Extensive research is done to address the use of genetic testing in clinical practice.[11,22] It is necessary to individualise pain management, as there are subsets of patients who may not experience the analgesic properties of opioids[11,22,40] and others who experience adverse effects including respiratory depression, sedation, nausea, vomiting, constipation, impaired cognition and sometimes even death.[41,42] Nevertheless, individualisation of opioid selection and dosing is not widely practised, likely due to the paucity of data regarding clinical outcomes and pharmacogenetics.[30]

Guidelines currently available are Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine and CYP2D6.[30,43] Both codeine and tramadol exert their analgesic properties via their CYP2D6 metabolites and, due to pharmacological similarities and consistency of supporting evidence, the CYP2D6 guided therapeutic recommendations for codeine can be extrapolated to tramadol in practice.[30] For example, tramadol does not have the ability to bind to the μ-receptor, but when metabolised by the CYP2D6 enzyme, its metabolite can bind weakly, to provide analgesia. Likewise, codeine cannot provide pain relief, unless metabolised by the CYP2D6 enzyme to morphine, which then binds to the μ-receptor and provides analgesia.[22,43] Where an individual has a genetic variant, which results in dysfunctional or inactive CYP2D6 enzymes, neither codeine nor tramadol is metabolised into a form that provides analgesia.[11]

While current data are intriguing and testing may offer unique information aiding in medication decision-making for the complex patient, there is still no clear evidence that genetic testing (at least for the general public) is effective.[7] Currently, the evidence is not compelling enough for widespread clinical adoption of opioid

Table III. Substrates, inducers and inhibitors of CYP26D involved in the metabolism of codeine, dihydrocodeine, oxycodone and tramadol[3,7,29,32]

Substrates*		Inhibitors		Inducers	
Drug class	**Examples**	**Drug class**	**Examples**	**Drug class**	**Examples**
Antiarrhythmic agents	Flecainide	Antiarrhythmic agents	Amiodarone	Antibiotic	Rifampicin
	Lidocaine	Antipsychotic agents	Chlorpromazine	Glucocorticoid	Dexamethasone
	Propafenone		Reduced haloperidol		
β-blockers	Carvedilol	Serotonin-norepinephrine reuptake inhibitors	Duloxetine		
	Metoprolol	Selective serotonin reuptake inhibitors	Citalopram		
	Propranolol		Escitalopram		
	Timolol		Fluoxetine		
Antipsychotic agents	Aripiprazole		Paroxetine		
	Haloperidol		Sertraline		
	Risperidone	Tricyclic	Clomipramine		
	Zuclopenthixol	Monoamine oxidase inhibitors	Moclobemide		
Serotonin-norepinephrine reuptake inhibitors	Duloxetine	Noradrenaline and dopamine reuptake inhibitors	Bupropion		
	Venlafaxine	Antihistamine	Chlorpheniramine		
Selective serotonin reuptake inhibitors	Fluoxetine	Histamine H_2-receptor antagonists	Cimetidine		
	Fluvoxamine		Ranitidine		
	Paroxetine	Nonsteroidal anti-inflammatory drugs	Celecoxib		
Tricyclics	Amitriptyline	Chemotherapy	Doxorubicin		
	Clomipramine	Antiretroviral	Ritonavir		
	Imipramine	Antifungal	Terbinafine		
Histamine H_1-receptor antagonists	Metoclopramide				
	Tamoxifen				
Antihistamine	Chlorpheniramine				
	Dextromethorphan				

* Substrates of CYP2D6 competitively inhibit binding of the opioids to the CYP2D6 enzyme and therefore deliver results similar to CYP2D6 inhibitors.

pharmacogenetics[30] and knowledge on pharmacogenomics of Phase II enzymes is not extensive.[20] As techniques for these tests are improved and made more affordable and accessible, it may become possible to develop an individualised pain management plan, which is both safe and effective, based on the patient's genetic sensitivity and responsiveness to medications.[11]

CYP450 medication interactions

The use of prescription opioids with other analgesics that also utilise the CYP450 pathway can lead to medication interactions affecting the metabolism of both substances. Many other medications can affect the metabolism of opioids and hence their clinical effects, as altered metabolism can result in an opioid or its metabolite accumulating in the body leading to toxic effects, too rapid excretion from the body or missing the location of its therapeutic target.[19] Understanding the basis of drug-drug interactions can facilitate appropriate choices in prescribing, thereby helping to avoid preventable adverse drug reactions. Tables III and IV reflect the substrates, inducers and inhibitors of CYP2D6 and CYP3A4 involved in the metabolism of some of the oral opioids.

Additional important medicine interactions applicable to all oral opioids:

Monoamine oxidase inhibitors (MAOIs) potentiate the effects of opioids and may lead to central nervous system excitation or depression with hypertensive or hypotensive crisis. Opioids should not be used concurrently with MAOIs or within 14 days after discontinuation of MAOIs treatment. The central nervous system (CNS) depressant effects of opioids are also intensified with concurrent use of other CNS depressants, e.g. alcohol, anaesthetic agents, hypnotics and sedatives, and must therefore be avoided.[3,7,32]

Other factors affecting the metabolism of opioids:

The liver is the most important site for the metabolism of opioids, thus patients with liver impairment would produce alterations in opioid metabolism. Patients with renal insufficiency again, will have a lower opioid clearance with a longer elimination half-life. The latter can be the reason why elderly patients achieve more effective pain relief, compared to young adults, when given equal

Table IV. Substrates, inducers and inhibitors of CYP3A4 involved in the metabolism of codeine, oxycodone, tilidine and tramadol[3,7,29,32]

Substrates*		Inhibitors		Inducers	
Drug class	**Examples**	**Drug class**	**Examples**	**Drug class**	**Examples**
Calcium-channel blockers	Amlodipine	Calcium-channel blockers	Amlodipine	Statins	Atorvastatin
	Diltiazem		Diltiazem		Fluvastatin
	Felodipine		Felodipine		Simvastatin
	Nifedipine		Nifedipine	Antiretroviral agents	Efavirenz
	Verapamil		Verapamil		Lopinavir
Statins	Atorvastatin	Statins	Simvastatin		Nevirapine
	Simvastatin	Antiarrhythmic agents	Amiodarone	Anticonvulsant agents	Carbamazepine
Antiarrhythmic agents	Amiodarone	Phosphodiesterase inhibitor	Tadalafil		Phenobarbital
	Digoxin	Psychiatric drugs	Bromocriptine		Phenytoin
Anticoagulant	Warfarin		Clonazepam		Valproic acid
Phosphodiesterase inhibitors	Sildenafil		Desipramine		
	Tadalafil		Fluoxetine		
Benzodiazepines	Alprazolam		Fluvoxamine		
	Clonazepam		Haloperidol		
	Flunitrazepam		Nefazodone		
	Midazolam		Nortriptyline		
	Triazolam		Sertraline		
Selective serotonin reuptake inhibitors	Citalopram	Antibiotics	Ciprofloxacin		
	Fluoxetine		Clarithromycin		
Antipsychotics	Aripiprazole		Erythromycin		
	Buspirone		Norfloxacin		
	Haloperidol		Roxithromycin		
	Risperidone		Telithromycin		
	Ziprasidone	Antifungal agents	Clotrimazole		
Dopamine receptor agonist	Bromocriptine		Fluconazole		
Serotonin and norepinephrine reuptake inhibitor	Venlafaxine		Itraconazole		
Norepinephrine reuptake inhibitor	Reboxetine		Ketoconazole		
Anticonvulsant	Carbamazepine, valproate		Voriconazole		
Cholinesterase inhibitor	Donepezil	Antiretroviral agents	Atazanavir		
Antidepressants	Mirtazapine		Efavirenz		
	Nefazodone		Indinavir		
Sleep aids	Zolpidem		Lopinavir		
	Zopiclone		Ritonavir		
Antibiotics	Azithromycin		Nevirapine		
	Clarithromycin	Chemotherapy	Imatinib		
	Erythromycin		Irinotecan		
Antifungal agents	Itraconazole		Tamoxifen		
	Ketoconazole	Hormonal therapy	Estradiol		
Antiretroviral agents	Indinavir		Levonorgestrel		
	Lopinavir		Raloxifene		
	Nevirapine	Histamine H_2-receptor antagonist	Cimetidine		
	Ritonavir	Alcohol deterrent	Disulfiram		
Chemotherapy	Cyclophosphamide	Corticosteroid	Methylprenisolone		
	Docetaxel	Monoamine oxidase inhibitor	Phenelzine		
	Doxorubicin				
	Etoposide				
	Paclitaxel				
	Tamoxifen				
	Vinblastine				
Hormonal therapy	Estradiol				
	Levonorgestrel				
	Raloxifene				
	Testosterone				

* Substrates of CYP3A4 competitively inhibit binding of the opioids to the CYP3A4 enzyme and therefore deliver results similar to CYP3A4 inhibitors.

Table V. Factors influencing opioid metabolism[19,44]

Opioid	Age	Sex	Ethnicity	Hepatic impairment	Renal impairment
Codeine	Recommended that older people should take caution	No effect	Metabolism altered in CYP2D6 allelic variants – more common in Asian and African descents	Dose adjustment recommended	Dose adjustment recommended
Hydromorphone	No effect	Women have a 25% higher C_{max} than men, but similar AUC_{0-24}	No effect	Dose adjustment recommended	Dose adjustment recommended
Morphine	Reduced clearance in older patients	No effect	Chinese patients have higher clearance of morphine	Dose adjustment recommended	Dose adjustment recommended
Oxycodone	Nominal increased concentrations in older patients	~ 25% higher concentrations in women compared to men	No effect	Dose adjustment recommended	Dose adjustment recommended
Tramadol	No studies Use extended-release capsules with caution in patients > 75 years	No significant effect	No effect	PKs significantly altered in patients with severe hepatic impairment Do not use extended-release capsules in severe hepatic impairment	PKs significantly altered only in patients with severe renal impairment Do not use extended-release capsules in severe renal impairment

doses of morphine. Age-related reduction in liver metabolism, together with a decline in renal function, might account for these observations.[25]

Apart from liver and renal function, other factors may contribute to the variability in opioid metabolism e.g. ethnic background.[25] The Chinese population clears morphine faster, attributed to increased glucuronidation to M3G and M6G, when compared to Caucasians.[19,25]

Populations stratified according to age, sex, and ethnicity, illustrate the difference in opioid metabolism among the various individual opioids (Table V).

Careful dose adjustments can address these altered metabolisms in the different population groups. Initiate both morphine and codeine at a lower dose when treating older patients and patients of Asian or African descent. Female patients receiving oxycodone should start at a lower dose relative to men. Due to genetic variability, patients with an unexplained history of poor response, although compliant, or an inability to tolerate a particular opioid, should be switched to an opioid that follows a different metabolic pathway.[19]

Conclusion

There is a spectrum of responses after administration of the same dose of an opioid to different individuals, ranging from no relief in pain to toxicity.[45] Pharmacogenetics coupled with comorbid conditions e.g. liver and renal function, as well as factors such as weight, age and concomitant medicines, can guide the actualisation of individualised pain management. An individualised approach when managing pain with opioids, will improve both treatment efficacy and safety.

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