Therapeutic Reviews

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Variability in Response to Drugs

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There is great inter-individual variability in the way people respond to a drug (Box A). Some of this variability is predictable in the presence of clinical factors known to impact upon the pharmacokinetics and/or pharmacodynamics of a drug. For example, an age-related decrease in overall metabolic capacity of the liver, because of reductions in liver mass, liver enzyme activity and hepatic blood flow, results in the elderly being at a significantly higher risk of toxicity from drugs metabolized in the liver. Similarly, an age-related decline in renal function can reduce the excretion of active drugs and metabolites, e.g., morphine-6-glucuronide and morphine-3-glucuronide, increasing the risk of toxicity from morphine.

Genetic variations also contribute towards differences in drug response. Clinically, these are less predictable, although some may be detected with specific testing. They are particularly important for drugs metabolized by cytochrome P450 (CYP450) with the rate of metabolism either reduced or increased. Examples of how these manifest include:

- reduced or no response because of
  - ➢ the failure to convert a pro-drug to its active form
  - ➢ increased metabolism of an active drug to an inactive metabolite
- increased toxicity because of
  - ➢ more rapid conversion to the active form or to a metabolite which is more active than the parent drug
  - ➢ failure to metabolize an active drug to inactive metabolite(s).

Other genetic variations, such as genes coding for receptors or drug transporters also can influence overall response, e.g., the μ-opioid receptor or P-glycoprotein transporter and the response to opioids. Induction or inhibition of CYP450 activity also can result from a drug–drug or drug–food interaction causing similar manifestations to those resulting from genetic variation. Each of these factors is considered in more detail below.

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Box A. Common factors affecting response to drugs

Adherence
Whether drug regimen adhered to or not

Genetic variation/polymorphism
Sequence variation including single nucleotide polymorphisms, gene deletions, gene duplications resulting in altered protein function, e.g., receptors, enzymes, drug transporters

Pharmacokinetics
Absorption
Distribution
Metabolism
Drug–drug and drug–food interactions
Excretion

Pharmacodynamics
Receptor–drug interaction and effect
Drug–drug and drug–food interactions
Decreased/increased receptor affinity due to concurrent disease state

Physiological factors
Gender
Age
Ethnicity
Hormonal changes
Circadian and seasonal factors

Environmental factors
Diet
Environmental toxins
Alcohol and recreational drugs
Smoking

Potential specific associations/concomitant disease
Diabetes mellitus
GI microbiology
Hypoalbuminemia
Liver failure
Malabsorption
Malnutrition
Obesity
Renal failure

Variability in response to opioids

Many factors contribute to the inter-individual variation in response to opioids.[1–4]

μ-Opioid receptor

This is the key receptor mediating opioid analgesia.[5] Genetic variation in the μ-opioid receptor gene has been associated with variation in opioid response in acute post-operative pain,[6–8] chronic non-cancer pain,[9,10] and cancer pain.[11,12] However, meta-analysis of opioid pain studies showed no overall association with pain and only weak associations with morphine dose or undesirable effects.[13]

P-glycoprotein

The membrane-bound drug transporter P-glycoprotein influences drug absorption and drug excretion.[14,15] It limits the uptake of compounds from the GI tract, regulates the transfer of various drugs across the blood–brain barrier,[16] and influences drug excretion by the liver and kidneys. It is encoded by the ATP-binding cassette subfamily B member 1 (ABCB1) gene.

P-glycoprotein modulation of opioid CNS concentrations varies substantially between opioids, with morphine, fentanyl, and methadone being among those most affected.[17,18] In animals, removal of P-glycoprotein activity ("knockout" mice) or inhibition by cyclosporine enhances absorption and increases CNS concentrations of fentanyl and morphine, resulting in prolonged analgesia.[19] Thus, inhibitors of P-glycoprotein (e.g., clarithromycin, cyclosporine, erythromycin, itraconazole, ketoconazole [not UK], quinidine [not UK], verapamil) could increase CNS effects of opioids.

Variation in ABCB1 has been associated with increased pain relief with morphine in cancer pain[11] and decreased opioid requirements in mixed chronic pain.[10] Studies have shown conflicting results in relation to opioid-induced nausea and vomiting and other undesirable effects.[20–22]

Catechol-O-methyltransferase

Catechol-O-methyltransferase (COMT) is an enzyme that has a significant impact on the metabolism of several important neurotransmitters: dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline). The COMT gene is polymorphic, and <25% of Caucasians have low activity variants.

One common variant in which the amino acid valine is substituted for methionine results in a 3–4 times decrease in COMT activity. It has been associated with increased pain sensitivity and higher μ-opioid system activation in experimental pain,[23,24] and increased morphine dose requirements in cancer patients.[25] Other variants of the COMT gene are associated with increased undesirable opioid effects, e.g., nausea and vomiting.[20,26,27]

Hepatic metabolism

Opioid metabolism takes place primarily in the liver. Opioids are metabolized via two main pathways, cytochrome P450 (CYP450) and UDP-glycosyltransferase (UGT; Table 1). Two phases of metabolism are generally described: phase 1 metabolism (modification reactions) and phase 2 metabolism (conjugation reactions).

Table 1
Major opioid enzyme pathways

	Pathway[a]			
Drug	CYP2D6	CYP3A4/5	CYP2B6	UGT
Alfentanil		++		
Buprenorphine		++		+
Codeine	++			+
Dihydrocodeine	+			+
Fentanyl		++		
Hydrocodone	+			
Hydromorphone				++
Methadone		++	+	
Morphine				++
Oxycodone	+	++		
Oxymorphone		+		+
Sufentanil		++		
Tapentadol				++
Tramadol	++	++		

[a]++ for CYP pathways may result in clinically important drug–drug interactions (see Appendix).

The most important phase 1 reaction is oxidation, catalyzed by CYP450. The most important phase 2 reaction is glucuronidation, catalyzed by UGT. Glucuronidation produces molecules that are highly hydrophilic and thus easily excreted by the kidneys.[28] Drug–drug interactions can occur as a result of changes in CYP450 or UGT activity, although the latter is less well documented.[29]

Genetic polymorphism in cytochrome P450 (CYP450)

About 75% of all drugs are metabolized partly or completely by cytochrome P450 (Box B). Thus, variation in activity of the cytochrome P450 system can have a major impact on drug action.

Box B. Cytochrome P450 (CYP450)[30,31]

CYP450 is a super-family of numerous enzymic proteins responsible for the oxidative metabolism of many drugs and some endogenous substances (e.g., fatty acids, eicosanoids, steroids, bile acids).
The root symbol used in naming the individual enzymes is CYP, followed by:
- a number designating the enzyme family (18 in humans)
- a capital letter designating the subfamily (44 in humans)
- a number designating the individual enzyme.

CYP450 enzymes exist in virtually all tissues, but their highest concentration is in the liver.
The enzymes concerned with drug metabolism are mostly CYP1–CYP3; these account for about 70% of the total CYP450 content of the liver.
The most important enzyme is CYP3A4, followed by CYP2D6 and CYP2C9
The presence of CYP3A4 in the wall of the GI tract is important; it probably acts in conjunction with P-glycoprotein, and together determine the extent of the intestinal absorption and metabolism of CYP3A4 substrates.

Some 20–25% of drugs are affected by genetic variants of drug-metabolizing enzymes.[32] The bulk of the population will manifest a normal distribution in terms of the rate of drug metabolism, with activity ranging from well below-average to well above-average, but generally lumped together as extensive metabolizers (EM).[33] In addition, there are discrete genetic populations of individuals who fall beyond the ends of the spectrum. These are designated poor (PM) and ultra-rapid metabolizers (URM). More recently, intermediate metabolizers have been identified for some enzymes (Table 2).[30]

Table 2
Metabolizer status[34]

Category	Description	Possible impact
Poor (PM) *or* slow	Lacks functional enzyme (deletion of gene or non-functional variant)	Increased toxicity due to slower drug metabolism (e.g., phenytoin, flecainide) *or* Therapeutic failure due to poor metabolism of a pro-drug to its active form (e.g., codeine) or a parent drug to an active metabolite (e.g., tramadol, tamoxifen)
Intermediate	Has two decreased-function enzymes or one decreased, one non-functional	Comparable to slow metabolizer but less marked
Extensive (EM) *or* rapid	Has at least one fully-functional enzyme	This is the norm
Ultra-rapid (URM)	Increased enzyme activity (duplication of gene or other mutation); relatively rare	Therapeutic failure due to faster drug metabolism *or* Increased toxicity due to faster conversion of parent drug to more active metabolite (e.g., tramadol) *or* pro-drug to active form (e.g., codeine)

As a general rule, an URM may need a higher dose to obtain a therapeutic effect, and a PM a lower dose to prevent increased undesirable effects (Table 3).[32] Exceptions are 'pro-drugs' where metabolites are mostly responsible for the effect of the drug (see below). The effects of such genetic variations can be further modified by the co-administration of the relevant CYP450 inhibitor or inducer.

Of particular note is codeine, for which most of its analgesic effect results from partial conversion to morphine by O-demethylation catalyzed by CYP2D6.[38,39] Compared with the general population (EM), a PM produces little or no morphine from codeine, and obtains little or no pain relief. On the other hand, undesirable effects are comparable in both categories.[40,41] At the other extreme, URM produce more morphine; this can lead to life-threatening opioid toxicity, which, rarely, has been fatal in children (following adenoidectomy/tonsillectomy; altered respiratory drive due to obstructive sleep apnea was a probable contributing factor).[42–46]

Table 3
Genetic polymorphism and PM/URM status[a] [28,30,35–37]

Pathway	A selection of affected drugs	Population affected
CYP2C9	NSAIDs	Caucasians 35%
	Phenytoin	Asian/African <1%
	Sulfonylureas (glipizide, tolbutamide)	
	Warfarin	
CYP2C19	Antidepressants (imipramine, sertraline)	Asians 10–35%
	Clopidogrel[b]	Africans 15%
	Diazepam	Caucasians 2–5%
	PPIs	
CYP2D6	β-Blockers (metoprolol)[c]	Africans 0–34%
(debrisoquine hydroxylase)	Codeine[b]	Caucasians 5–10%
	Flecainide	Asians ≤1%
	Oxycodone	
	SSRIs (some, e.g., paroxetine)	
	Tamoxifen[b]	
	TCAs (imipramine, nortriptyline)[d]	
	Tramadol[b]	

[a]There is roughly a similar number of URM as PM.
[b]Enzyme conversion produces the main active or a more active metabolite.
[c]70% Dose reduction recommended in PM; note also that co-administration with paroxetine (2D6 inhibitor) increases plasma concentrations four times.
[d]TCAs most likely to need a lower dose.

Genetic variation involving CYP2D6 is also important in relation to tramadol, for which the (+) O-desmethyltramadol metabolite is responsible for the opioid analgesic effect. A PM produces little or none and thus obtains little or no analgesic benefit;[47] conversely, an URM produces higher levels with a potential to cause opioid toxicity.[48]

Polymorphism in CYP3A4/5 may be of less clinical significance when considering opioid response.[49] Nonetheless, CYP3A4 activity varies up to 10 times and could be partly responsible for different dose requirements.[50] Opioids potentially affected are fentanyl (and related drugs, alfentanil, sufentanil), methadone, oxycodone and, to a lesser extent, buprenorphine.

Although genetic variation can result in serious consequences, pharmacogenetic testing is not routine, partly because it is not cost-effective, e.g., the impact of testing in relation to warfarin dosing.[51,52] Thus, generally, close clinical monitoring is recommended for drugs with a major metabolic enzyme pathway affected by genetic polymorphism (see Table 3 and Appendix). However, in some settings, e.g., oncology, testing has been used to determine if an individual is likely to respond to a specific drug, e.g., cetuximab (colorectal cancer), trastuzumab (breast cancer), and dasatinib (acute lymphoblastic leukemia).

CYP450 drug–drug interactions

Pharmacokinetic drug–drug interactions mediated through increased or decreased activity of CYP450 enzymes are common, but the resultant clinical impact is difficult to predict.[30,53–55] Some drugs (inducers) increase the activity of specific CYP450 enzymes and others (inhibitors) decrease enzyme activity (see Table 7).

When CYP450 inhibitors or inducers are co-administered with drugs that are already affected by genetic polymorphisms, they will either augment or mitigate the clinical effects of the genetic variation.

Induction

Onset and offset of enzyme induction is gradual, possibly 2–3 weeks, because:

- onset depends on drug-induced synthesis of new enzyme
- offset depends on elimination of the enzyme-inducing drug and the decay of the increased enzyme stores.

Induction of the rate of drug biotransformation generally leads to a decrease in the parent drug plasma concentration, and thus a *decreased effect*. However, if the substrate drug is an inactive pro-drug, or metabolism produces a more active metabolite, induction will result in an *increased effect* and possible toxicity.

The impact of enzyme induction depends on the relative importance of the induced pathway to the substrate's metabolism, whether active metabolites are present, and on the concentration (dose) of the inducer. Sequential dose adjustments, either up or down, may be necessary to maintain the desired clinical effect of the affected drug.[30] Converse dose adjustments may be required if the inducer is discontinued, e.g., methadone toxicity has occurred following discontinuation of carbamazepine, an inducer.[56]

Some anti-epileptics (e.g., carbamazepine, phenobarbital, phenytoin) and some other drugs (e.g., rifampin, St. John's wort) induce members of the CYP3A subfamily (Table 4). Rifampin is the most potent clinically used inducer of cytochrome CYP3A. Some estrogens are metabolized by CYP3A4/5, and induction by rifampin (or another enzyme inducer) can cause oral contraceptive failure.

Chronic alcohol consumption can induce CYP450 enzymes, mostly CYP2E1 and possibly CYP3A. However, in cirrhosis, overall enzyme activity is reduced.

Table 4
Examples of drug interactions based on enzyme induction of CYP3A4/5

Substrate	Inducers	Outcome
Carbamazepine	Phenytoin	Metabolism ↑, effect ↓
Methadone	Carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort	Metabolism ↑, effect ↓ (possible recurrence of pain ± withdrawal symptoms)[57]
Midazolam	Carbamazepine, phenytoin	Metabolism ↑, effect ↓[58]
Phenytoin	Rifampin	Metabolism ↑, half-life halved, effect ↓[59]
Protease inhibitors (for HIV)	St. John's wort	Metabolism ↑, treatment failure[60–62]

Inhibition

Inhibition of drug biotransformation begins *within a few hours* of the administration of the inhibitor drug. For most drugs, inhibition leads to an increase in the plasma concentration and effect of the substrate drug, and increased risk of toxicity. However, the converse is true with *pro-drugs*, e.g., clopidogrel, where the plasma concentration of the active metabolite is reduced, increasing the risk of therapeutic failure. Table 5 gives examples of altered drug effects resulting from enzyme inhibition.

Table 5
Examples of drug interactions based on enzyme inhibition

Substrate	Inhibitors	Outcome
Codeine	Quinidine (not UK) (CYP2D6)	Biotransformation to morphine ↓, analgesic effect ↓[63]
Clopidogrel	PPIs (CYP2C19)	Biotransformation to active metabolite ↓, antithrombotic effect ↓[64–67]
Diazepam	Cimetidine (multiple CYP)	Metabolism ↓, effect ↑[68]
Lovastatin (not UK), simvastatin	Clarithromycin, erythromycin (CYP3A4/5)	Metabolism ↓, risk of undesirable effects ↑ (e.g. raised CK plasma concentration, muscle pain, rhabdomyolysis)
Theophylline	Ciprofloxacin (CYP1A2)	Metabolism ↓ (18–113%), effect ↑[69]
TCAs	SSRIs (multiple CYP)	Metabolism ↓ (plasma concentrations ↑ 50–350%), effect ↑[70–72]
Warfarin	Fluvoxamine (multiple CYP)	Metabolism ↓ (plasma concentration ↑ 65%), effect ↑[73]

The mechanism of enzymatic inhibition is either reversible or irreversible. In reversible inhibition, the inhibitor drug (e.g., azole antifungals) binds to the P450 enzyme and prevents the metabolism of the substrate drug.[74,75] The extent of inhibition of one drug by another depends on their relative affinities for the P450 enzyme, and the respective doses. In irreversible inhibition, the enzyme is destroyed or inactivated by the inhibitor drug or its metabolites (e.g., clarithromycin, erythromycin).

CYP450 drug–drug interactions in palliative care

It can be challenging to determine the likelihood of a clinically relevant drug–drug interaction in practice. Many patients receiving palliative care are elderly and have several chronic conditions, resulting in the use of numerous drugs, typically 7–8 (range 1–20).[76,77] This polypharmacy increases the likelihood of drug interactions involving CYP450, with possibly 10–20% of patients receiving a combination likely to produce a clinically relevant CYP-mediated interaction (Table 6).[76,77] For a longer list of commonly used drugs that are moderate-to-potent enzyme inhibitors or inducers, also see Appendix.

Table 6
Common drug combinations likely to produce clinically important CYP-mediated interactions in palliative care patients[76,77]

Drug combination	Likely outcome of the interaction[a]
Benzodiazepines[b] + CYP3A4 inhibitor e.g., diazepam + itraconazole	Diazepam ↑
Benzodiazepines[b] + CYP3A4 inducer e.g., midazolam + carbamazepine	Midazolam ↓
Corticosteroids + CYP3A4 inhibitor e.g., dexamethasone + clarithromycin	Dexamethasone ↑
Corticosteroids + CYP3A4 inducer e.g., dexamethasone + phenytoin	Dexamethasone ↓
Diazepam + omeprazole[c]	Diazepam ↑
Opioids[b] + CYP3A4 inhibitor e.g., oxycodone + fluconazole	Oxycodone ↑
Opioids[b] + CYP3A4 inducer e.g., fentanyl + carbamazepine	Fentanyl ↓

[a] ↑ = drug effect increased; ↓ = effect decreased.
[b] Which are full or part substrates of CYP3A4 (see Appendix).
[c] Inhibitor of CYP2C19 (see Appendix).

In one series, about 50% of the interactions involved corticosteroids, and 25% analgesics.[76] In a second series, the most frequently used inducers or inhibitors of CYP450 (and/or P-glycoprotein, or UGT) were dexamethasone, esomeprazole, omeprazole, fluconazole, ciprofloxacin, carbamazepine, carvedilol and verapamil (also see Appendix).[77] Interactions may be missed, e.g., recurrence of pain may be interpreted as disease progression rather than altered analgesic metabolism. The US FDA has a comprehensive list of drug interactions and their significance.[78]

Serotonin toxicity is generally a pharmacodynamic interaction resulting from the combination of two or more serotonergic drugs. However, in some circumstances, a pharmacokinetic interaction may contribute to an increase in serotonergic transmission, e.g., fluoxetine (a CYP2D6 and CYP2C19 inhibitor) and amitriptyline.

The addition of a CYP450 inhibitor to a drug known to prolong the QT interval may result in increased plasma levels, QT prolongation and risk of *torsade de pointes*, e.g., itraconazole (a CYP3A4 inhibitor) and methadone.

CYP450 drug–food interactions

An important interaction associated with CYP450 inhibition is a food–drug interaction involving grapefruit juice and CYP3A substrates administered PO, including some benzodiazepines (diazepam, midazolam, triazolam [not UK]), some statins (atorvastatin, lovastatin [not UK], simvastatin), buspirone, cyclosporine, felodipine, nifedipine, and saquinavir.[30,79–82]

Grapefruit juice contains several bioflavonoids (naringenin, naringin, kaempferol and quercetin) and furanocoumarins (bergamottin), which non-competitively inhibit oxidation reactions mediated by CYP3A enzymes in the wall of the GI tract.[81,83,84] The effect is unpredictable because the quantity of these components in grapefruit products varies considerably.[85,86]

The effect is maximal when grapefruit juice is ingested 30–60min before the drug. A single 250mL glass of grapefruit juice can inhibit CYP3A for 24–48h and regular intake continually suppresses GI CYP3A.[30,81] Thus, patients taking drugs metabolized by CYP3A are warned to avoid grapefruit juice, particularly if the drug has a narrow therapeutic index, e.g., cyclosporine. Pomelo, Seville orange and lime juices may also inhibit CYP3A;[87,88] apple juice has not been implicated.

Besides inhibiting CYP3A, naringin (and thus grapefruit juice) inhibits organic anion-transporting polypeptide 1A2 (OATP1A2), a carrier protein in the wall of the GI tract that is responsible for the uptake of several drugs. Orange juice (through its major flavonoid, hesperidin) has a similar effect[89] and possibly apple juice.[90] Drugs that may have their absorption reduced by this inhibition include some β-blockers (atenolol, celiprolol (not USA), cyclosporine, etoposide, fexofenadine, itraconazole, and quinolone antibacterials (ciprofloxacin, levofloxacin).[89,90]

Case reports of serious adverse events related to grapefruit-drug interactions include:

- amiodarone → torsade de pointes
- atorvastatin and simvastatin → rhabdomyolysis.

Other drugs that may be affected by grapefruit include novel oral anticoagulants (apixaban, rivaroxaban), calcium channel blockers (amlodipine, felodipine, verapamil), CNS drugs (quetiapine, buspirone), cytotoxics (nilotinib, lapatinib), and immunosuppressants (cyclosporine, tacrolimus, sirolimus).[91] Interactions are generally drug-specific, not a class effect, and the PI should be referred to for more information.

There is also concern that ingestion of cranberry juice may also modify drug action, mediated through flavonoids that specifically inhibit CYP2C9. Warfarin is an example of a drug that might be affected by this interaction and, indeed, early reports linked cranberry juice with adverse events associated with warfarin.[92–95] However, recent reports suggest that this interaction is unlikely to occur with the amounts of cranberry juice recommended for prophylaxis against UTIs.[96–99]

Nonetheless, an interaction with warfarin cannot be ruled out, particularly when large volumes of cranberry juice are drunk regularly, or when cranberry products other than juice are taken.[96,97,100] Thus, the INR should be monitored more closely in patients on warfarin if they consume large amounts of cranberry juice or take other cranberry supplements for prophylaxis against UTIs.[96]

Quantifying the effects of CYP450 inhibition and induction

Quantification of the effects of CYP450 inhibitors and inducers is still evolving. The more important enzymes for drug metabolism have generally accepted "probe" substrates and potent inhibitors and inducers (Table 7), and these are used to determine reliable results, e.g., for new drugs in development. Increasingly, data are becoming available that predict the clinical importance of drug–drug interactions. However, there is still much to be determined and, in palliative care where polypharmacy is the norm, in addition to understanding the pharmacokinetics of any drug used, a general awareness of potential interactions is important (see Appendix).

Table 7
Examples of in vivo probe substrates and potent inhibitors and inducers used for evaluation (all PO)[78]

Enzyme	Substrate	Inhibitor	Inducers
CYP1A2	Caffeine Theophylline	Fluvoxamine	Tobacco smoking
CYP2B6	Efavirenz		
CYP2C8	Repaglinide	Gemfibrozil	Rifampin
CYP2C9	Tolbutamide Warfarin	Amiodarone Fluconazole	Rifampin
CYP2C19	Esomeprazole Lansoprazole Omeprazole Pantoprazole	Fluvoxamine Omeprazole	Rifampin
CYP2D6	Dextromethorphan	Fluoxetine Paroxetine Quinidine (not UK)	None known
CYP3A4	Midazolam	Clarithromycin Itraconazole Ketoconazole Ritonavir	Carbamazepine Rifampin

Abbreviations

ATP	Adenosine triphosphate
CNS	Central nervous system
EM	Extensive (rapid) metabolizer
FDA	Food and Drug Administration
GI	Gastrointestinal
HIV	Human immunodeficiency virus
INR	International normalized ratio
NSAID	Nonsteroidal anti-inflammatory drug
PI	Package insert
PM	Poor (slow) metabolizer
PO	Per os, by mouth
PPI	Proton-pump inhibitor
SSRI	Selective serotinin re-uptake inhibitor
TCA	Tricyclic antidepressant
UDP	Uridine diphosphate
UGT	UDP-glycosyltransferase
URM	Ultra-rapid metabolizer
UTI	Urinary tract infection

References

1. Droney J, Riley J, Ross JR. Evolving knowledge of opioid genetics in cancer pain. Clin Oncol (R Coll Radiol) 2011;23:418–428.

2. Branford R, Droney J, Ross JR. Opioid genetics: the key to personalized pain control? Clin Genet 2012;82:301–310.

3. Ross JR, Riley J, Quigley C, Welsh KI. Clinical pharmacology and pharmacotherapy of opioid switching in cancer patients. Oncologist 2006;11:765–773.

4. Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. Clin Pharmacol Ther 2007;81:429–444.

5. Matthes H, Maldonado R, Simonin F, et al. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. Nature 1996;383:819–823.

6. Chou WY, Yang LC, Lu HF, et al. Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. Acta Anaesthesiol Scand 2006;50:787–792.

7. Chou WY, Wang CH, Liu PH, et al. Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. Anesthesiology 2006;105:334–337.

8. Sia AT, Lim Y, Lim EC, et al. A118G single nucleotide polymorphism of human mu-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. Anesthesiology 2008;109:520–526.

9. Janicki PK, Schuler G, Francis D, et al. A genetic association study of the functional A118G polymorphism of the human mu-opioid receptor gene in patients with acute and chronic pain. Anesth Analg 2006;103:1011–1017.

10. Lotsch J, von Hentig N, Freynhagen R, et al. Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. Pharmacogenet Genomics 2009;19:429–436.

11. Campa D, Gioia A, Tomei A, Poli P, Barale R. Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. Clin Pharmacol Ther 2008;83:559–566.

12. Klepstad P, Rakvåg TT, Kaasa S, et al. The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004;48:1232–1239.

13. Walter C, Lotsch J. Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment. Pain 2009;146:270–275.

14. Schinkel AH. The physiological function of drug-transporting P-glycoproteins. Semin Cancer Biol 1997;8:161–170.

15. Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. Clin Pharmacol Ther 2004;75:13–33.

16. Ross JR, Quigley C. Pharmacogenetics and opioids. In: Davis MP, Glare PA, Hardy J, Quigley C, eds. Opioids in cancer pain, 2nd ed. Oxford: Oxford University Press, 2009:287–299.

17. Dagenais C, Graff CL, Pollack GM. Variable modulation of opioid brain uptake by P-glycoprotein in mice. Biochem Pharmacol 2004;67:269–276.

18. Barratt DT, Coller JK, Hallinan R, et al. ABCB1 haplotype and OPRM1 118A > G genotype interaction in methadone maintenance treatment pharmacogenetics. Pharmgenomics Pers Med 2012;5:53–62.

19. Thompson SJ, Koszdin K, Bernards CM. Opiate-induced analgesia is increased and prolonged in mice lacking P-glycoprotein. Anesthesiology 2000;92:1392–1399.

20. Ross JR, Riley J, Taegetmeyer AB, et al. Genetic variation and response to morphine in cancer patients: catechol-O-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. Cancer 2008;112:1390–1403.

21. Zwisler ST, Enggaard TP, Noehr-Jensen L, et al. The antinociceptive effect and adverse drug reactions of oxycodone in human experimental pain in relation to genetic variations in the OPRM1 and ABCB1 genes. Fundam Clin Pharmacol 2010;24:517–524.

22. Coulbault L, Beaussier M, Verstuyft C, et al. Environmental and genetic factors associated with morphine response in the postoperative period. Clin Pharmacol Ther 2006;79:316–324.

23. Kim H, Lee H, Rowan J, Brahim J, Dionne RA. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. Mol Pain 2006;2:24.

24. Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158-met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 2003;299:1240–1243.

25. Rakvag TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain 2005;116:73–78.

26. Laugsand EA, Fladvad T, Skorpen F, et al. Clinical and genetic factors associated with nausea and vomiting in cancer patients receiving opioids. Eur J Cancer 2011;47:1682–1691.

27. Kolesnikov Y, Gabovits B, Levin A, Voiko E, Veske A. Combined catechol-O-methyltransferase and mu-opioid receptor gene polymorphisms affect morphine postoperative analgesia and central side effects. Anesth Analg 2011;112:448–453.

28. Smith HS. Opioid metabolism. Mayo Clin Proc 2009;84:613–624.

29. Baxter K, Preston CL. Stockley's drug interactions. London: Pharmaceutical Press, 2013. Available at: www.medicinescomplete.com. Accessed July 2014.

30. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 2005;352:2211–2221.

31. Ingelman-Sundberg M, Daly AK, Nebert DW, eds. Human Cytochrome P450 (CYP). Allele Nomenclature Committee, 2005. Available at: www.CYPalleles.ki.se. Accessed October 14, 2014.

32. Stamer UM, Zhang L, Stüber F. Personalized therapy in pain management: where do we stand? Pharmacogenomics 2010;11:843–864.

33. Meyer U. Genotype or phenotype: the definition of a pharmacogenetic polymorphism. Pharmacogenetics 1991;1:66–67.

34. Sajantila A, Palo JU, Ojanperä I, Davis C, Budowle B. Pharmacogenetics in medico-legal context. Forensic Sci Int 2010;203:44–52.

35. Poulsen L, Arendt-Nielsen L, Brøsen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. Clin Pharmacol Ther 1996;60:636–644.

36. Riddick D. Drug biotransformation. In: Kalant H, Roschlau W, eds. Principles of medical pharmacology, 6th ed. New York: Oxford University Press, 1997:38–54.

37. Williams DG, Patel A, Howard RF. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. Br J Anaesth 2002;89: 839–845.

38. Persson K, Hammarlund-Udenaes M, Mortimer O, Rane A. The postoperative pharmacokinetics of codeine. Eur J Clin Pharmacol 1992;42:663–666.

39. Findlay JWA, Jones EC, Butz RF, Welch RM. Plasma codeine and morphine concentrations after therapeutic oral doses of codeine-containing analgesics. Clin Pharmacol Ther 1978;24:60–68.

40. Eckhardt K, Li S, Ammon S, et al. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. Pain 1998;76:27–33.

41. Susce MT, Murray-Carmichael E, de Leon J. Response to hydrocodone, codeine and oxycodone in a CYP2D6 poor metabolizer. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1356–1358.

42. Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004;351:2827–2831.

43. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006;368: 704.

44. Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007;7:257–265.

45. Racoosin JA, Roberson DW, Pacanowski MA, Nielsen DR. New evidence about an old drug - risk with codeine after adenotonsillectomy. N Engl J Med 2013;368:2155–2157.

46. MHRA. Codeine: restricted use as an analgesic in children and adolescents after European safety review. Drug Safety Update 2013;6:S1. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON287006. Accessed October 14, 2014.

47. Stamer UM, Musshoff F, Kobilay M, et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007; 82:41–47.

48. Stamer UM, Stüber F, Muders T, Musshoff F. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. Anesth Analg 2008;107: 926–929.

49. Pirmohamed M, Park BK. Cytochrome P450 enzyme polymorphisms and adverse drug reactions. Toxicology 2003;192:23–32.

50. Haddad A, Davis M, Lagman R. The pharmacological importance of cytochrome CYP3A4 in the palliation of symptoms: review and recommendations for avoiding adverse drug interactions. Support Care Cancer 2007;15:251–257.

51. Kimmel SE, French B, Kasner SE, et al. COAG Investigators. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med 2013;369:2283–2293.

52. Pirmohamed M, Burnside G, Eriksson N, et al. EU-PACT Group. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med 2013;369:2294–2303.

53. Aeschlimann J, Tyler L. Drug interactions associated with cytochrome P-450 enzymes. J Pharmaceut Care Pain Symptom Control 1996;4:35–54.

54. Johnson MD, Newkirk G, White JR Jr. Clinically significant drug interactions. Postgrad Med 1999;105:193–222.

55. Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. Mol Diagn Ther 2013;17:165–184.

56. Benitez-Rosario MA, Salinas Martín A, Gómez-Ontañón E, Feria M. Methadone-induced respiratory depression after discontinuing carbamazepine administration. J Pain Symptom Manage 2006;32:99–100.

57. Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin-induced methadone withdrawal. N Engl J Med 1976;294:1104–1106.

58. Backman J, Olkkola KT, Ojala M, Laaksovirta H, Neuvonen PJ. Concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. Epilepsia 1996;37:253–257.

59. Kay L, Kampmann JP, Svendsen TL, et al. Influence of rifampicin and isoniazid on the kinetics of phenytoin. Br J Clin Pharmacol 1985;20:323–326.

60. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St. John's wort. Lancet 2000;355:547–548.

61. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St. John's wort (Hypericum perforatum): drug interactions and clinical outcomes. Br J Clin Pharmacol 2002;54:349–356.

62. Flexner C. Dual protease inhibitor therapy in HIV-infected patients: pharmacologic rationale and clinical benefits. Annu Rev Pharmacol Toxicol 2000;40:649–674.

63. Sindrup S, Arendt-Nielsen L, Brøsen K, et al. The effect of quinidine on the analgesic effect of codeine. Eur J Clin Pharmacol 1992;42:587–591.

64. MHRA. Interactions between the use clopidogrel and proton pump inhibitors. Safety warnings and messages for medicines. July 6, 2009. Available at: www.mhra.gov.uk/safetyinformation. Accessed October 16, 2014.

65. Society for Cardiovascular Angiography and Interventions. A national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated with clopidogrel following coronary stenting: The

Clopidrogrel Medco Outcomes Study. 2009. Available at: www.scai.org.

66. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713–718.

67. Ho M, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937–944.

68. Klotz U, Reimann I. Delayed clearance of diazepam due to cimetidine. N Engl J Med 1980;302:1012–1014.

69. Nix D, DeVito JM, Whitbread MA, Schentag JJ. Effect of multiple dose oral ciprofloxacin on the pharmacokinetics of theophylline and indocyanine green. J Antimicrob Chemother 1987;19:263–269.

70. Vandel S, Bertschy G, Bonin B, et al. Tricyclic antidepressant plasma levels after fluoxetine addition. Neuropsychobiology 1992;25:202–207.

71. Finley P. Selective serotonin reuptake inhibitors: pharmacologic profiles and potential therapeutic distinctions. Ann Pharmacother 28:1359–1369.

72. Pollock B. Recent developments in drug metabolism of relevance to psychiatrists. Harv Rev Psychiatry 1994;2:204–213.

73. Tatro D. Fluvoxamine drug interactions. Drug Newsletter 1995;14:20ff.

74. Monaham B. Torsades de Pointes occurring in association with terfenadine. JAMA 1990;264:2788–2790.

75. Honig P, Wortham DC, Zamani K, et al. Terfenadine-ketoconazole interaction. Pharmacokinetic and electrocardiographic consequences. JAMA 1993;269:1513–1518.

76. Wilcock A, Thomas J, Frisby J, et al. Potential for drug interactions involving cytochrome P450 in patients attending palliative day care centres: a multicentre audit. Br J Clin Pharmacol 2005;60:326–329.

77. Kotlinska-Lemieszek A, Paulsen O, Kaasa S, Klepstad P. Polypharmacy in patients with advanced cancer and pain: a European cross-sectional study of 2282 patients. J Pain Symptom Manage 2014. Apr 26. [Epub ahead of print].

78. Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. Available at: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm. Accessed July 7, 2014.

79. Benton R, Honig PK, Zamani K, Cantilena LR, Woosley RL. Grapefruit juice alters terfenadine pharmacokinetics, resulting in prolongation of repolarization on the electrocardiogram. Clin Pharmacol Ther 1996;59:383–388.

80. Maskalyk J. Grapefruit juice: potential drug interactions. CMAJ 2002;167:279–280.

81. Dahan A, Altman H. Food-drug interaction: grapefruit juice augments drug bioavailability-mechanism, extent and relevance. Eur J Clin Nutr 2004;58:1–9.

82. MHRA. Statins and cytochrome P450 interactions. Current Problems in Pharmacovigilance 2004;30:1–2.

83. Rouseff RL. Liquid chromatographic determination of naringin and neohesperidin as a detector of grapefruit juice in orange juice. J Assoc Off Anal Chem 1988;71:798–802.

84. Gibaldi M. Drug interactions. Part II. Ann Pharmacother 1992;26:829–834.

85. Tailor S, Gupta AK, Walker SE, Shear NH. Peripheral edema due to nifedipine-itraconazole interaction: a case report. Arch Dermatol 1996;132:350–352.

86. Fukuda K, Guo L, Ohashi N, Yoshikawa M, Yamazoe Y. Amounts and variation in grapefruit juice of the main components causing grapefruit-drug interaction. J Chromatogr B Biomed Sci Appl 2000;741:195–203.

87. Savage I. Forbidden fruit: interactions between medicines, foods and herbal products. Pharm J 2008;281:f17.

88. Baxter K. Drug interactions and fruit juices. Pharm J 2008;281:333.

89. Bailey DG, Dresser GK, Leake BF, Kim RB. Naringin is a major and selective clinical inhibitor of organic anion-transporting polypeptide 1A2 (OATP1A2) in grapefruit juice. Clin Pharmacol Ther 2007;81:495–502.

90. Sampson M. New reasons to avoid grapefruit and other juices when taking certain drugs. Report from the 236th National Meeting of the American Chemical Society. Philadelphia, August 19, 2008. Available at: www.eurekalert.org/pub_releases/2008-08/acs-nrt072308.php.

91. Bailey DG, Dresser G, Arnold JM. Grapefruit-medication interactions: forbidden fruit or avoidable consequences? CMAJ 2013;185:309–316.

92. Grant P. Warfarin and cranberry juice: an interaction? J Heart Valve Dis 2004;13:25–26.

93. Committee on Safety of Medicines. Interaction between warfarin and cranberry juice: new advice. Current Problems in Pharmacovigilance 2004;30:10.

94. MHRA. Possible interaction between warfarin and cranberry juice. Current Problems in Pharmacovigilance 2003;29:8.

95. Suvarna R, Pirmohamed M, Henderson L. Possible interaction between warfarin and cranberry juice. BMJ 2003;327:1454.

96. O'Mara N. Does a cranberry juice-warfarin interaction really exist? Detail document. Pharmacist's Letter/Prescriber's Letter 2007;23:1–3.

97. Aston JL, Lodolce AE, Shapiro NL. Interaction between warfarin and cranberry juice. Pharmacotherapy 2005;26:1314–1319.

98. Lilja JJ, Backman JT, Neuvonen PJ. Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam–probes of CYP2C9, CYP1A2, and CYP3A4. Clin Pharmacol Ther 2007;81:833–839.

99. Li Z, Seeram NP, Carpenter CL, et al. Cranberry does not affect prothrombin time in male subjects on warfarin. J Am Diet Assoc 2006;106:2057–2061.

100. Welch J, Forster K. Probable elevation in international normalized ratio from cranberry juice. J Pharm Technol 2007;23:104–107.

Appendix

Examples of enzyme or transporter protein substrates, inhibitors and inducers which may result in clinically significant drug interactions[a29,77,78]

Enzyme or transporter protein	Substrates	Moderate or potent inhibitors	Moderate or potent inducers
CYP1A2	Amitriptyline Clomipramine Duloxetine Flecainide Imipramine Melatonin Mirtazapine Olanzapine Propranolol Ramelteon (not UK) Theophylline Tizanidine Trimipramine	Cimetidine[b] Ciprofloxacin Fluvoxamine	Phenytoin Rifampin Tobacco smoking
CYP2B6	Methadone		Rifampin
CYP2C8	Loperamide Pioglitazone Repaglinide Rosiglitazone (not UK)		Rifampin
CYP2C9[c]	Celecoxib Chlorpropamide (not UK) Diclofenac Flurbiprofen Fluvastatin Gliclazide (not USA) Glimepiride Glipizide Glyburide Ibuprofen Irbesartan Losartan Nateglinide Phenytoin Tolbutamide Torsemide Warfarin	Amiodarone Fluconazole	Carbamazepine Rifampin
CYP2C19[c]	Amitriptyline Citalopram Clomipramine Clopidogrel Diazepam Fluoxetine Imipramine Lansoprazole Omeprazole Pantoprazole Phenytoin Sertraline	Esomeprazole Fluconazole Fluoxetine Fluvoxamine Omeprazole Ticlopidine Voriconazole	Rifampin
CYP2D6[c]	Amitriptyline Carvedilol Codeine Desipramine (not UK) Dextromethorphan Dihydrocodeine (not USA) Duloxetine Flecainide Fluoxetine Hydrocodone (not UK) Imipramine	Cimetidine[b] Duloxetine Fluoxetine Paroxetine	

(*Continued*)

Continued

Enzyme or transporter protein	Substrates	Moderate or potent inhibitors	Moderate or potent inducers
	Metoprolol		
	Mirtazapine		
	Nebivolol		
	Nortriptyline		
	Ondansetron		
	Oxycodone		
	Paracetamol		
	Paroxetine		
	Pindolol		
	Propranolol		
	Risperidone		
	Sertraline		
	Tamoxifen		
	Timolol		
	Tolterodine		
	Tramadol		
	Trazodone		
	Trimipramine		
	Venlafaxine		
CYP3A4/5[d,e]	Acetaminophen	Cimetidine[b]	Carbamazepine
	Alfentanil	Ciprofloxacin	Modafinil
	Alprazolam	Clarithromycin	Phenobarbital (and other barbiturates)
	Amiodarone	Diltiazem	Phenytoin
	Aprepitant	Erythromycin	Rifampin
	Atorvastatin	Fluconazole	St. John's wort
	Budesonide (PO)	Grapefruit juice	
	Buprenorphine	Itraconazole	
	Carbamazepine	Verapamil	
	Clarithromycin	Voriconazole	
	Clonazepam		
	Clorazepate		
	Codeine		
	Dexamethasone		
	Diazepam		
	Diltiazem		
	Domperidone (not USA)		
	Erythromycin		
	Estradiol		
	Ezopiclone (not UK)		
	Felodipine		
	Fentanyl		
	Haloperidol		
	Imipramine		
	Itraconazole		
	Ketamine		
	Loperamide		
	Losartan		
	Lovastatin (not UK)		
	Methadone		
	Methylprednisolone		
	Midazolam		
	Mirtazapine		
	Nifedipine		
	Omeprazole		
	Oxybutynin		
	Oxycodone		
	Phenytoin		
	Quetiapine		
	Risperidone		
	Sertraline		
	Simvastatin		
	Tamoxifen		
	Tolterodine		
	Tolvaptan		
	Toremifene		
	Tramadol		
	Trazodone		
	Venlafaxine		

(*Continued*)

Continued

Enzyme or transporter protein	Substrates	Moderate or potent inhibitors	Moderate or potent inducers
	Verapamil Voriconazole Warfarin Zolpidem Zopiclone (not USA)		
P-glycoprotein[e]	Digoxin Loperamide	Amiodarone Carvedilol Clarithromycin Diltiazem Erythromycin Felodipine Itraconazole Verapamil	Carbamazepine Dexamethasone Phenytoin Rifampin St. John's wort

[a]*Not* an exhaustive list; limited to drugs most likely to be encountered in palliative care and *excludes* anticancer, HIV and immunosuppressive drugs (seek specific information).
[b]Cimetidine is classified as a weak inhibitor of multiple CYP enzymes.
[c]Enzyme can also be subject to genetic polymorphism, see Table 3.
[d]CYP3A enzyme is also expressed in the GI mucosa resulting in substantial first-pass metabolism of some drugs during absorption.
[e]There is a large overlap between the substrates, inhibitors and inducers of P-glycoprotein and CYP3A.