



Drug Interactions in Cancer Patients Requiring Concomitant Chemotherapy and Analgesics

As more cancer drugs are prescribed in outpatient settings, there is a greater need to ensure that patients are monitored for potential adverse events related to their dual chemotherapy and analgesic regimens.

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The development of oral antineoplastic agents has revolutionized the treatment of cancer. They offer carefully selected patients the option of managing complex regimens at home.¹ However, because these potential regimens may be complex and patients may be receiving other non-cancer chronic medications, this new trend requires pharmacovigilance. Compared to intravenously administered chemotherapy, oral agents undergo hepatic first-pass metabolism and are more likely to have drug interactions. Particularly with regard to chronic pain management, there are many interactions among some

oral antineoplastics and various pain medications.

This article will focus on the one-third of the cancer patient population that is actively receiving cytotoxic chemotherapy on an outpatient basis who require ongoing analgesic therapy to control their pain.

What Are DDIs?

Drug–drug interactions (DDIs) are manifestations that occur when one drug either increases or decreases the efficacy of another drug due to pharmacological and/or pharmacokinetic interactions that arise.² While the exact incidence of DDIs are unknown in cancer patients, it has

been estimated that about one-third of cancer outpatients are at risk of developing a DDI.³ Approximately 20% to 30% of all adverse events (AEs) are caused by interactions between drugs.⁴ Drug interactions can be divided into different categories: pharmaceutical, pharmacokinetic (PK), and pharmacodynamic (Table 1, page 53).⁵

The most common PK interactions in oncology are those that affect drug metabolizing enzymes: the cytochrome P450 (CYP450) enzymes, the efflux pump p-glycoprotein (P-gp), and protein-binding displacement (generally albumin or α -glycoprotein).⁶ A review of the literature found no publications examining the drug interactions between patients requiring cytotoxic chemotherapy and concurrent pain medications. Since cancer patients also may have multiple comorbid manifestations, it is important to know if and how the chemotherapy regimen can affect some of their non-neoplastic analgesic remedies. In this commentary, we thoroughly evaluate instances where chemotherapeutic agents utilized in the presence of pain medications can potentiate effects and induce toxicities or render medications less effective.

Chemotherapy and Drug Metabolism

Because the list of all chemotherapy agents is too extensive to publish here, we have highlighted the agents most commonly associated with potential DDIs with analgesic agents and their drug metabolism enzymes (Table 2, page 53).

Tyrosine Kinase Inhibitors

The tyrosine kinase inhibitors (TKIs) (imatinib [Gleevec], dasatinib [Sprycel], nilotinib [Tasigna], bosutinib [Bosulif], and ponatinib [Iclusig]) used in the treatment of chronic myelogenous leukemia (CML)⁷ are a class of medications involved in multiple drug interactions.

These agents are metabolized extensively by the hepatic CYP450 enzymes. Imatinib is a substrate of CYP3A4 and CYP3A5. It is also a weak inhibitor of CYP2D6 and CYP2C9. Dasatinib, bosutinib, and ponatinib are substrates of CYP3A4 and the solubility of these drugs are pH-dependent. Ponatinib must be reduced to 30 mg daily when used concurrently with significant CYP3A4 inhibitors. Nilotinib is a CYP3A4 substrate as well as a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UDP glucuronosyltransferase 1A1 (UGT1A1).

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator used in breast cancer treatment. It is metabolized extensively by CYP3A4, CYP3A5, CYP2C9, and CYP2D6. It is also an inhibitor of P-gp. The main metabolite found in plasma is N-desmethyl tamoxifen, a metabolite with similar activity as the parent drug formed by CYP3A4/5. Additional metabolites catalyzed by CYP2D6 are 4-hydroxytamoxifen and endoxifen, the latter of which is an active metabolite that may eventually be marketed as a new drug.⁸ Compared to tamoxifen, endoxifen and 4-hydroxytamoxifen have a 100-fold greater affinity for the estrogen receptor and 30 to 100-fold potency in suppressing any estrogen-dependent cell proliferation.⁹

Epidermal Growth Factor Receptor Inhibitors

Among the epidermal growth factor receptor (EGFR) inhibitors, erlotinib (Tarceva) and gefitinib (Iressa) represent high risk for common CYP450 interactions. Although we acknowledge that gefitinib has been removed from the US market, it still represents a significant potential for drug interactions because of its availability in Europe. Erlotinib is a major CYP3A4 substrate and undergoes extensive hepatic

metabolism by this isoenzyme. It is also metabolized to a lesser extent by CYP1A2 and the extra-hepatic isoform CYP1A1. Gefitinib is predominantly metabolized by CYP3A4 to multiple metabolites, with only O-desmethyl gefitinib having exposure comparable to gefitinib.

Lapatinib (Tykerb) is a TKI that inhibits two EGFR inhibitors: ERB1 and ERB2 (HER2). It is both a substrate and an inhibitor of CYP3A4.

Vascular Endothelial Growth Factor Receptor Inhibitor

Pazopanib (Votrient) is an oral multikinase angiogenesis inhibitor. It inhibits vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)- α and - β , fibroblast growth factor receptor (FGFR)-1 and -3, cytokine receptor (kit), interleukin-2 receptor inducible T-cell kinase (itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms).¹⁰ Pazopanib is a substrate of P-gp and is indicated for renal cell carcinoma and soft-tissue sarcoma.

BRAF Inhibitor

A single in vivo study showed that vemurafenib (Zelboraf), a BRAF inhibitor used in the management of malignant melanoma, is a moderate inhibitor of CYP1A2, a weak inhibitor of CYP2D6, and an inducer of CYP3A4.¹⁰ In vitro studies suggested that vemurafenib is both a substrate and inhibitor of CYP3A4 and P-gp, the result of which will elevate serum levels in the absence of a more potent 3A4 inducer.¹¹

Pain Therapy and Drug Metabolism

Opioids

Most medications used to treat cancer pain undergo extensive metabolism

by the CYP450 system. The opioids that are least affected by CYP450 metabolism are morphine, hydromorphone, oxycodone, and tapentadol (Nucynta). Morphine is a prototypical opioid analgesic substrate of UGT1A1 and depends on P-gp for gastric absorption and transport across the blood brain barrier.¹² Fentanyl, on the other hand, is a weak substrate of CYP2D6, CYP3A4, and P-gp.¹³⁻¹⁵ Medications that inhibit or induce these enzymes may significantly increase or decrease drug exposure, respectively.¹³

The following opioids undergo metabolism by the CYP450 system. Tramadol is extensively metabolized by CYP3A4 and CYP2D6 and is also a substrate of CYP2B6.^{16,17} Tramadol's μ -opioid receptor (encoded by gene OPRM1) is affected by the parent drug and O-desmethyltramadol (metabolite M1). The M1 metabolite has superior analgesia compared to the parent compound and it is likely enhanced by the inhibited reuptake of norepinephrine. First-pass metabolism, therefore, is necessary for opioid analgesic effect. Further metabolism of the M1 metabolite occurs via N-demethylation to N-desmethyltramadol (M2), which is metabolized by CYP2B6 and CYP3A4. Three more metabolites (M3-M5) are then glucuronidated to inactive forms. Obviously, this is quite complex and creates a large potential for drug interactions with CYP450 substrates.

About 70% to 80% of an administered dose of codeine undergoes glucuronidation to codeine-6-glucuronide (C6G), and by O-demethylation to morphine (5%-10%) and N-demethylation to norcodeine (\approx 10%).¹⁸ Codeine also requires metabolism to methyl morphine by 2D6 in order to provide analgesic activity.¹⁸ Inhibition of 2D6 isoenzymes by, for example, certain antidepressants or nilotinib may, therefore, block this conversion rendering codeine an ineffective analgesic.¹⁹

Oxycodone is extensively metabolized via N-demethylation to noroxycodone, which partially depends on CYP3A4 and CYP3A5, with eventual O-demethylation to oxycodone by CYP2D6.²⁰

Methadone is unique due to the number of drug-metabolizing enzymes (DMEs) that affect its metabolism and transport. It is a substrate of CYP3A4 (primarily), CYP2B6, and CYP2C19.²¹⁻²³ Methadone is also affected, to a lesser extent, by CYP2C9 and CYP2D6. It also undergoes extensive first-pass metabolism in the gastrointestinal tract as a substrate of P-gp; thus, the transport of methadone across the intestinal wall (and through the blood brain barrier) may be increased in the presence of P-gp inhibitors.²³

Tapentadol undergoes metabolism mostly by glucuronidation via UGT (70%)²⁴ and to a minor extent by CYP2C9, CYP2C19 (13%), and CYP2D6 (2%).²⁵ It is thought not to be affected by CYP450 enzyme interactions.

Antidepressants

Duloxetine (Cymbalta) undergoes extensive hepatic oxidation to inactive metabolites. It is metabolized by CYP2D6 and CYP1A2 with moderate potential for drug interactions involving CYP2D6. Duloxetine is both a substrate and an inhibitor of CYP2D6.²⁶ Venlafaxine is a CYP2D6 substrate and undergoes metabolism by CYP3A4 (minor).²⁷ The tricyclic antidepressants (TCAs) are inactivated largely by CYP450 enzymes, specifically by demethylation of tertiary TCAs to their secondary amine metabolites, followed by hydroxylation then subsequent glucuronidation to metabolites excreted in urine.²⁸ TCAs also share similar properties to the Class IA antiarrhythmics and, therefore, may potentially enhance a patient's risk of developing arrhythmias when

administered concurrently with cardiotoxic chemotherapy agents such as the anthracyclines.

Milnacipran (Savella)—and the atypical antidepressants mirtazapine, trazodone, and nefazodone—are effective in the management of pain due to their inhibition of norepinephrine reuptake. Among these, only milnacipran has an indication for the management of pain.²⁹ Milnacipran undergoes minimal CYP450 metabolism, and as such would not be involved in drug interactions involving hepatic DMEs.²⁹ In an open-label crossover trial, 15 mg and 30 mg of mirtazapine were effective in improving multiple symptoms in cancer patients with advanced disease, including pain as well as depression.³⁰ In vitro studies indicated that mirtazapine is a substrate of CYP2D6, CYP1A2, and CYP3A4. According to the manufacturer, clinically significant pharmacokinetic interactions are not likely with medications that are metabolized by hepatic enzymes.³¹ Although the clinical significance has not been established, nefazodone inhibits CYP3A4.³² Trazodone was found to be just as efficacious as amitriptyline among cancer patients with different neuropathic pain disorders.³³ Trazodone is a substrate of CYP2D6 and CYP3A4.

Although there is obvious extensive involvement of the above medications overall with P450 isoenzymes, the extent to which the activity affects therapeutic outcomes are very much dependent on alternative metabolic pathways and polymorphism. In fact, pharmacogenomics is gaining popularity in clinical monitoring in order to predict whether serum levels will be elevated or diminished for individual patients.³⁴ Polymorphisms of different DMEs and drug transporters affect drug response and toxicity in the susceptible individual. Regarding DMEs, they can be divided into four

Table 1. Types of Drug Interactions

Type	Description
Pharmaceutical	Pharmaceutical drug interactions occur when drugs interact secondary to their physical properties or structure of the drug.
Pharmacokinetic	Pharmacokinetic drug interactions occur when concurrent use of two or more drugs affects the absorption, distribution, metabolism, and/or elimination of at least one drug.
Pharmacodynamic	Pharmacodynamic drug interactions involve either an additive, synergistic, or antagonistic interaction that may favor or harm the patient.

Table 2. Metabolizers of Common Chemotherapeutic Agents

Antineoplastics (Brand)	Cytochrome P450 Isoenzymes							P-glycoprotein	UDP
	1A1	1A2	2C8	2C9	2D6	3A4	3A5	P-gp	UGT1A1
Tyrosine Kinase Inhibitors									
Bosutinib (Bosulif)	-	-	-	-	-	SUB	-	-	-
Dasatinib (Sprycel)	-	-	-	-	-	SUB	-	-	-
Imatinib (Gleevec)	-	-	-	INH (weak)	INH (weak)	SUB	SUB	-	-
Nilotinib (Tasigna)	-	-	INH	INH	INH	SUB	-	-	INH
Ponatinib (Iclusig)	-	-	-	-	-	SUB	-	-	-
Selective Estrogen Receptor Modulator									
Tamoxifen (Nolvadex, Soltamox, generic)	-	-	-	SUB	SUB	SUB	SUB	INH	-
Epidermal Growth Factor Receptor Inhibitors									
Erlotinib (Tarceva)	SUB (minor)	SUB (minor)	-	-	-	SUB	-	-	-
Gefitinib (Iressa)^a	-	-	-	-	-	SUB	-	-	-
Lapatinib (Tykerb)^b	-	-	-	-	-	SUB INH	-	-	-
Others									
Pazopanib (Votrient)	-	-	-	-	-	-	-	SUB	-
Vemurafenib (Zelboraf)	-	INH (moderate)	-	-	INH (weak)	IND INH SUB	-	INH SUB	-

^aAgent not available in United States, but used extensively in Europe

^bBoth a tyrosine kinase inhibitor and epidermal growth factor receptor inhibitor

IND, inducer; INH, inhibitor; SUB, substrate; UGT1A1, UDP glucuronosyltransferase 1A1

phenotypes: ultrarapid metabolizers (UM), extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM).³⁵ As we can infer, CYP2D6 plays an enormous role in the activation or inaction of several opioids used in pain management.³⁶ Patients who are classified as UM will have an increase in metabolism, whereas EM patients would be characteristic of the normal population; IM patients would have a reduction in enzymatic activity and PM patients may not exert any activity at all. For example, when patients are administered the prodrug codeine, it requires biotransformation via demethylation from CYP2D6 to its active metabolite, morphine. In PM-classified patients, they would not experience effective analgesia whereas in UM-classified patients, they would experience faster metabolism and may be at a greater risk of morphine-induced toxicities.³⁶

DDIs: Analgesics and Chemotherapy

As noted earlier, medications used to treat mild to moderate cancer pain often include non-opioid analgesics, opioids, antidepressants, and/or anti-convulsants. The following is a practical review of the most common DDIs occurring between analgesic and chemotherapeutic agents (Table 3).

Acetaminophen

Acetaminophen may be utilized in treating mild cancer pain. In children, the primary metabolism of acetaminophen is through sulfation. However, in adults, acetaminophen undergoes glucuronidation to be removed from the serum. Therefore, acetaminophen should be avoided with hepatotoxic antineoplastics. The TKI imatinib, for example, may affect the metabolism of acetaminophen as seen in a phase II trial where a patient died secondary to hepatic failure within 12 days

of receiving 600 mg per day of the agent.³⁷ In this case, the patient was also receiving concurrent acetaminophen 3,000 to 3,500 mg per day for about 1 month. Six days after initiating imatinib therapy, the patient developed upper quadrant pain, jaundice, hyperbilirubinemia, and elevated serum transaminases. Imatinib therapy was discontinued on day 7, and subsequent tests for a potential infection were negative; however, the patient's condition returned.³⁷ The potential mechanism of this toxicity is presumably a result of imatinib-induced inhibition of O-glucuronidation.³⁸

In addition, it is advisable for patients to limit their acetaminophen intake, including any prescription that may include acetaminophen. An *in vitro* study using human hepatic chromosomes concluded that dasatinib, imatinib, and sunitinib (Sutent) were potent inhibitors of acetaminophen glucuronidation.³⁹ Another *in vitro* study found that dasatinib metabolism results in the formation of a highly reactive metabolite that bears similarity to an intermediate formed from acetaminophen metabolism.⁴⁰ Formation of the reactive intermediate may result in excessive hepatocellular damage especially when administered concurrently with another hepatotoxic agent. The National Comprehensive Cancer Network practice guidelines for CML include a warning about the potential interaction between acetaminophen–imatinib and recommend a maximum dose of 1,300 mg per day in patients receiving imatinib.⁴¹ These recommendations were not extended to sunitinib or dasatinib.⁴¹

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used in the treatment of mild to moderate cancer pain.⁴² However, NSAIDs are known to cause significant thrombocytopenia

and increase a patient's chance of bleeding. NSAID-associated bleeding can vary depending on their selectivity of cyclooxygenase (COX) inhibition. Among them, etodolac, celecoxib (Celebrex), and meloxicam are normally preferred in patients at an increased risk of bleeding due to the drugs' preferential inhibition of COX-2 over COX-1.⁴³ Concurrent use with antineoplastic agents must be monitored closely for signs and symptoms of bleeding.

In addition, NSAIDs can induce renal hypoperfusion secondary to inhibition of renal COX activity and prostaglandin synthesis.⁴⁴ As a result, NSAID therapy can also decrease renal clearance of methotrexate especially at high doses, which can lead to prolonged exposure to the cytotoxic anti-metabolite.⁴⁵ This is because methotrexate is primarily excreted into urine in an unchanged form and the kidneys handle methotrexate elimination via glomerular filtration, tubular secretion, and reabsorption. Methotrexate excretion is thought to be a major site of interaction with other drugs.⁴⁶ While the exact mechanism is unknown, it has been postulated that NSAID-induced inhibition of prostaglandin synthesis may lower the renal perfusion rate and inhibit methotrexate clearance as well as inhibit methotrexate efflux transporters MRP2 and MRP4 in the kidneys.⁴⁷ Information about this interaction is limited and conflicting. A retrospective review noted four studies totaling 36 subjects with methotrexate toxicity in patients receiving concurrent administration of ketoprofen.⁴⁸ Three of the patients died.

Administration of naproxen in 9 patients decreased total clearance of methotrexate by 22%, but did not have a significant effect on renal clearance of methotrexate.⁴⁹ Conflicting results have also been reported with the use of ketoprofen, piroxicam, or flurbiprofen;

Table 3. DDIs Between Antineoplastic Agents and Cancer Pain Agents

Agent (Brand)	Interacting Agents	Interaction	Mechanism of Interaction	Clinical Management
Non-opioids				
Acetaminophen (Tylenol, generic)	Imatinib	Imatinib increases serum levels of acetaminophen	Unknown	Monitor liver function tests
NSAIDs				
NSAIDs^a	All antineoplastic drugs; methotrexate	Both NSAIDs and anti-neoplastic agents can cause thrombocytopenia. NSAIDs can increase serum methotrexate levels	Additive effects; NSAIDs decrease renal clearance of methotrexate	Consider alternative pain therapy. Do not administer NSAIDs before, during, or after intermediate- to high-dose methotrexate
Celecoxib (Celebrex)	Cisplatin	Both can potentiate nephrotoxicity	Additive nephrotoxic side effects	Use with caution
	Imatinib, sorafenib	Imatinib and sorafenib will increase serum celecoxib levels	Imatinib and sorafenib both inhibit CYP2C9; celecoxib is a CYP2C9 substrate	Effect is more pronounced in patients who are poor CYP2C9 metabolizers. Use lowest effective dose of celecoxib in these patients
	Methotrexate	Celecoxib as an NSAID and can potentially increase serum methotrexate levels	Celecoxib could potentially reduce renal methotrexate excretion	Celecoxib 200 mg bid did not affect pharmacokinetics of low-dose methotrexate. Use with caution
	Pemetrexed	Celecoxib may increase systemic pemetrexed exposure	Celecoxib may inhibit renal clearance of pemetrexed	Use with caution
Diclofenac (Voltaren, generic)	Imatinib, dasatinib	Increased serum levels of dasatinib, imatinib	Diclofenac inhibits P-gp	Monitor
	Sorafenib	Increased levels of diclofenac	Sorafenib inhibits CYP2C9	
Ibuprofen (Advil, Motrin, generic)	Dasatinib	Increased serum ibuprofen concentration	Dasatinib inhibits CYP2C8	Monitor
	Imatinib		Imatinib inhibits CYP2C9	
	Nilotinib		Nilotinib inhibits CYP2C8 and CYP2C9	
Meloxicam (Mobic, generic); nabumetone (generic)	Cisplatin	Increased levels of cisplatin	Inhibition of prostaglandins	Unknown
Piroxicam (Feldene, generic)	Cisplatin, sorafenib	Increased levels of cisplatin; increased serum concentration of piroxicam	Inhibition of prostaglandins; sorafenib inhibits CYP2C9	Monitor

Table 3. DDIs Between Antineoplastic Agents and Cancer Pain Agents (continued)

Agent (Brand)	Interacting Agents	Interaction	Mechanism of Interaction	Clinical Management
Opioids				
Fentanyl/TIRF (Abstral, Actiq, Duragesic, Fentora, Lazanda, Onsolis)	Imatinib	Imatinib and nilotinib may increase bioavailability of fentanyl and/or decrease clearance of fentanyl	Imatinib inhibits CYP3A4	Monitor patients for fentanyl toxicity: oversedation, respiratory depression, and hypotension
	Nilotinib		Nilotinib inhibits CYP3A4 and P-gp	
Hydrocodone/Acetaminophen (Vicodin, generic)	Imatinib	Imatinib may decrease analgesic benefit of hydrocodone	Imatinib inhibits CYP2D6	Adjust dose of hydrocodone/acetaminophen; monitor patients for enhanced sedation, respiratory depression
Methadone (Dolophine, generic)	Crizotinib, lapatinib	QTc prolongation	Crizotinib and lapatinib inhibit CYP3A4 and P-gp	Use with caution
	Imatinib	Increases serum methadone levels	Imatinib inhibits CYP3A4	Use with caution
	Nilotinib	Increases serum methadone levels	Nilotinib inhibits CYP2D6, CYP3A4, and P-gp	Avoid
	Pazopanib	Increases serum methadone levels	Pazopanib inhibits CYP3A4 and CYP2D6 (weak)	Use with caution
	Vemurafenib	Increases serum methadone levels	Vemurafenib inhibits CYP3A4	Use with caution
	Doxorubicin, epirubicin, daunorubicin, idarubicin	Acute cardiac toxicity/cumulative dose-dependent toxicity	Additive cardiotoxicity	Use with caution
	Arsenic trioxide, dasatinib, eribulin, sunitinib, toremifene, vandetanib	All these medications increase risk of QTc prolongation	Additive effect on prolonging QTc interval	Use methadone cautiously
Morphine (Avinza, Kadian, MS Contin, others, generic)	Nilotinib	Nilotinib may increase morphine concentrations	Nilotinib inhibits UGT1A1 and P-gp	Monitor closely for morphine-induced toxicity
Oxycodone (OxyContin, generic)	Aldesleukin, dasatinib, tamoxifen	All will increase oxycodone concentrations	Aldesleukin, dasatinib, and tamoxifen inhibit CYP3A4	Monitor closely for oxycodone-induced toxicity
	Imatinib, nilotinib		Imatinib and nilotinib inhibit CYP3A4 and CYP2D6	

Table 3. DDIs Between Antineoplastic Agents and Cancer Pain Agents (continued)

Agent (Brand)	Interacting Agents	Interaction	Mechanism of Interaction	Clinical Management
Tramadol (Ryzolt, Ultram, generic)	Gefitinib	All will increase tramadol concentrations	Gefitinib inhibits CYP2D6	Monitor patient for tramadol-related toxicities including serotonin syndrome or seizure
	Dasatinib		Dasatinib inhibits CYP3A4	
	Imatinib, nilotinib		Imatinib and nilotinib inhibit CYP2D6 and CYP3A4	
Antidepressants				
Serotonin Norepinephrine Reuptake Inhibitors				
Duloxetine (Cymbalta)	Tamoxifen	Duloxetine will inhibit conversion of tamoxifen to endoxifen	Duloxetine inhibits CYP2D6	Avoid if possible. Venlafaxine can be used in place of duloxetine
	Vemurafenib	Vemurafenib increases serum levels of duloxetine	Vemurafenib inhibits CYP1A2	Monitor for symptoms of serotonin syndrome
Venlafaxine^b (Effexor, generic)	Gefitinib, nilotinib	Both will increase serum concentration of venlafaxine	Both inhibit CYP2D6	Increasing venlafaxine levels will predispose patients to toxicity. Monitor for QTc prolongation
	Imatinib	Increases levels of venlafaxine	Imatinib inhibits CYP2D6 and CYP3A4	
	Arsenic trioxide, crizotinib, daunorubicin, doxorubicin, epirubicin, idarubicin, eribulin, lapatinib, dasatinib, nilotinib, pazopanib, sorafenib, sunitinib, toremifene, vandetanib, vemurafenib	Synergistic effects of QTc prolongation	All affect QTc prolongation	
Atypical Antidepressants				
Nefazodone^b (Serzone, generic)	Docetaxel, vinblastine, vincristine, vinorelbine	Nefazodone may effect metabolism of these agents	Nefazodone inhibits CYP3A4	Use with caution
	Gefitinib	Increase gefitinib concentrations	Gefitinib is a substrate of CYP3A4	Use with caution

Table 3. DDIs Between Antineoplastic Agents and Cancer Pain Agents (continued)

Agent (Brand)	Interacting Agents	Interaction	Mechanism of Interaction	Clinical Management
Trazodone^b (Desyrel, generic)	Arsenic trioxide, crizotinib, dasatinib, epirubicin, lapatinib, pazopanib, sorafenib, sunitinib, toremifene, vandetanib, vemurafenib	Synergistic effects of QTc prolongation	Prolong QT/QTc interval, torsades de pointes	Avoid concurrent use with other drugs that have potential to increase QTc interval
	Nilotinib	Risk of QT prolongation; impairs metabolism of trazodone	Nilotinib inhibits CYP2D6 and CYP3A4	Avoid concurrent use
Tricyclic Antidepressants^b				
Amitriptyline (Generic)	Arsenic trioxide, crizotinib, daunorubicin, doxorubicin, epirubicin, idarubicin, eribulin, lapatinib, dasatinib, nilotinib, pazopanib, sorafenib, sunitinib, toremifene, vandetanib, vemurafenib	Synergistic effects on QTc prolongation	All affect QTc prolongation	Use cautiously and monitor closely
Clomipramine (Anafranil, generic)				
Desipramine (Norpramin, generic)				
Doxepin (Silenor, generic)				
Imipramine (Tofranil, generic)				
Nortriptyline (Pamelor, generic)				
Select Anticonvulsants				
Carbamazepine (Tegretol)	Undetermined	Potential to lower serum levels of any CYP3A4 substrates	Potent CYP3A4 induction	Consider oxycarbazepine or other second-generation anticonvulsant
Gabapentin (Neurontin, Gralise, generic)	N/A	N/A	N/A	N/A
Pregabalin (Lyrica)	N/A	N/A	N/A	N/A
Other				
Baclofen^b (Gablofen, generic)	N/A	N/A	N/A	N/A

^aApplies to all NSAIDs

^bNot FDA approved for pain

CYP, cytochrome P; DDIs, drug–drug interactions; NSAIDs, non-steroidal anti-inflammatory drugs; P-gp, p-glycoprotein; TIRF, transmucosal immediate-release fentanyl; UGT1A1, UDP glucuronosyltransferase 1A1

naproxen, and indomethacin. NSAIDs should not be administered prior to, concurrently, or after intermediate or high doses of methotrexate.⁵⁰ Patients who are exposed to the concurrent therapy may also be at an increased risk of gastrointestinal bleeding, especially in patients who develop methotrexate-induced thrombocytopenia.

Pemetrexed (Alimta) is an antifolate used in the treatment of patients with mesothelioma. Renal clearance of pemetrexed is reduced by 20% in patients with normal renal function who are also taking ibuprofen 400 mg four times per day.⁵¹ It is recommended that patients with creatinine clearance between 45 and 79 mL per minute should avoid taking NSAIDs with short half-lives for 2 days prior, during, and 2 days after pemetrexed administration.⁵¹ In the absence of any substantial data, NSAIDs with half-lives exceeding 9 hours should be avoided by patients 5 days prior, during, and 2 days after pemetrexed administration. We selected 9 hours here because, based on basic pharmacokinetic theory, in the absence of other drug interactions and external variables, these drugs should be eliminated within 2 days. If used concurrently, patients are at increased risk of developing myelosuppression, renal injury, and gastrointestinal side effects.

Meloxicam, piroxicam, and nabumetone interact with cisplatin⁵² due to inhibition of prostaglandins. Sorafenib (Nexavar)⁵³ is a competitive inhibitor of CYP2C9, which may increase serum concentration levels of piroxicam and diclofenac. Among the TKIs, all three will increase ibuprofen and diclofenac exposure. Imatinib acts on ibuprofen by inhibiting CYP2C9, dasatinib exerts its effects by inhibiting CYP2C8, and nilotinib increases ibuprofen exposure by inhibiting CYP2C8 and CYP2C9. Diclofenac inhibits P-gp; thus, it can increase exposure to imatinib and dasatinib.

Celecoxib interacts with a number of antineoplastic agents. Just like the non-selective NSAIDs, celecoxib also interacts with CYP2C9 inhibitors imatinib, methotrexate, cisplatin, pemetrexed, and sorafenib for the same reasons explained above.⁵⁴

Opioids

Fentanyl transdermal is approved for persistent moderate to severe chronic pain in patients who require continuous around-the-clock dosing and are tolerant to opioids such that they are currently receiving at least 60 mg of oral morphine or its equivalent daily. Other fentanyl products include the transmucosal immediate-release fentanyl (TIRF) formulations, all of which require the highest level of risk evaluation mitigation strategies (REMS) by the FDA. TIRFs are FDA approved for breakthrough cancer pain in opioid-tolerant patients who concurrently require at least 60 mg of oral morphine or its equivalent daily. Imatinib is a known CYP3A4 inhibitor and nilotinib inhibits both CYP3A4 and P-gp.¹⁹ Therefore, concomitant use of any fentanyl product with either nilotinib or imatinib may predispose the patient to increased sedation and other effects from fentanyl, although confirming therapeutic *in vivo* data are lacking.¹⁴

Morphine, the most common opioid used in the treatment of cancer pain, is a substrate of UGT1A1.⁵⁵ Morphine undergoes phase II transformation via hepatic transformation to morphine 3-glucuronide and morphine-6-glucuronide, which contribute to morphine's analgesic activity.¹² In addition, morphine is also a substrate of P-gp and as such its absorption could be significantly affected by medications that inhibit this efflux pump.⁵⁶ Nilotinib, a potent inhibitor of the efflux transporter P-gp ABCB1 as well as a competitive inhibitor of UGT1A1, poses

a potential problem when given concurrently with morphine.

Hydrocodone is also an opioid used to treat cancer pain. The concurrent administration of any dosage form of hydrocodone with imatinib may potentially increase a patient's chance of developing opioid toxicity. In addition to inhibiting CYP3A4, imatinib also inhibits CYP2D6 and since hydrocodone, in part, depends on CYP2D6 for conversion to its active form, the patient may have diminished analgesic benefit.³⁸

Potential drug interactions can arise when patients receive oxycodone with aldesleukin (Proleukin), dasatinib, or tamoxifen, which are CYP3A4 inhibitors. Oxycodone serum concentrations are increased by imatinib and nilotinib. Both increase oxycodone exposure by inhibition of CYP3A4 and CYP2D6.³⁸

Methadone has a unique set of properties that make it useful in the management of cancer pain. However, it has been associated with an increased risk for QTc prolongation and torsades de pointes, especially at higher doses (>200 mg/day but averaging 400 mg/day).^{38,57-60} Methadone should be used cautiously in patients receiving treatment with any of these chemotherapeutic agents: arsenic trioxide (Trisenox),⁶¹⁻⁶³ dasatinib,⁶⁴ eribulin (Halaven),⁶⁵ sunitinib,⁶⁶ toremifene (Fareston),⁶⁷ and vandetanib.⁶⁸ Crizotinib (Xalkori)⁶⁹ and lapatinib⁷⁰ can potentially increase the risk for QTc prolongation and also inhibit both CYP3A4 and P-gp; thus, they may interact with concurrent use of methadone. Furthermore, caution should be exercised when administering methadone with any of the chemotherapeutic agents in the anthracycline class due to an inherent risk for cardiotoxicity. Patients may experience acute cardiotoxicity during administration with daunorubicin or doxorubicin;

accumulate, dose-dependent cardiomyopathy may also occur.⁷¹ Imatinib is a potent inhibitor of CYP3A4 and can increase serum methadone levels and increase the risk of QTc prolongation. Among chemotherapeutic agents that carry the triple threat, nilotinib poses a major problem with concomitant use of methadone because it inhibits CYP2D6, CYP3A4, and P-gp. Pazopanib may cause a similar toxicity secondary to its weak inhibition of CYP3A4 and CYP2D6. Vemurafenib also may increase methadone levels due to inhibition of the enzymes that act on methadone (CYP3A4).

Gefitinib is a CYP2D6 inhibitor⁷² and tramadol is primarily metabolized by CYP2D6 and CYP3A4. Therefore, the concurrent use of these two drugs could reduce metabolism of tramadol, with the end result being tramadol toxicity such as serotonin syndrome or seizure. This interaction may actually cause reduced tramadol efficacy because the analgesic activity significantly depends on the O-desmethyltramadol metabolite.¹⁶ Formation of this metabolite is dependent on CYP2D6. In short, inhibiting CYP2D6 and CYP3A4 reduces tramadol clearance and may increase tramadol-related toxicities. The TKIs also reduce tramadol bioactivation while increasing its exposure. They perform these actions by imatinib inhibition of CYP3A4 and CYP2D6, while dasatinib performs these actions through inhibition of CYP3A4, and nilotinib inhibits CYP3A4 and CYP2D6.

Tapentadol is another pain medication with structural similarity and mechanism to tramadol. Tapentadol is metabolized mainly by glucuronidation and the glucuronide metabolites are excreted in the urine. Some of the tapentadol, however, is metabolized by CYP2C9 and CYP2C19 to N-desmethyl tapentadol (13%) and by CYP2D6 to hydroxyl tapentadol

(2%). These products undergo conjugation via glucuronidation prior to urinary excretion. None of the metabolites contribute to tapentadol's analgesic activity. Since the majority of tapentadol undergoes conjugation, potential drug interactions between tapentadol and inhibitors or inducers of CYP2C9, CYP2C19, and CYP2D6 are not considered to be clinically significant.²⁵

Adjuvant Analgesics

Among the adjuvant analgesics used to treat cancer pain, especially neuropathic cancer pain, drug interactions have been found to occur with concurrent use of duloxetine, venlafaxine, and TCAs.

As a moderate inhibitor of CYP2D6, duloxetine could potentially interact with tamoxifen. Tamoxifen is converted to endoxifen and other active metabolites by CYP2D6 and CYP3A4. A CYP2D6 inhibitor can reduce plasma levels of endoxifen. In a trial of 1,298 patients with breast cancer, the rate of breast cancer recurrence was compared in patients on tamoxifen with or without a CYP2D6 inhibitor. Patients receiving tamoxifen in combination with a CYP2D6 inhibitor were found to have a significantly higher rate of breast cancer recurrence at 2 years (13.9% vs 7.5%, $P < 0.001$).⁷³ Co-administration of duloxetine and potent inhibitors of CYP1A2 is discouraged because duloxetine is partially metabolized by CYP1A2. Vemurafenib is a CYP1A2 inhibitor and concurrent use with duloxetine can increase patient exposure to duloxetine and increase likelihood of serotonergic activity. A study involving the use of a potent CYP1A2 inhibitor concurrent with duloxetine revealed a significant increase in duloxetine activity.⁷⁴

Venlafaxine is a serotonin norepinephrine reuptake inhibitor indicated for depression, generalized anxiety disorder, panic disorder, and social anxiety

disorder.²⁷ It also is used off label for the management of neuropathic pain. There are data supporting the use of venlafaxine as an adjuvant analgesic for neuropathic cancer pain. However, in clinical trials for various indications, QTc prolongation was documented with a mean increase in QTc of 1.5 to 4.7 msec for extended release venlafaxine versus a decrease of 0.7 to 1.9 msec for placebo.²⁷ Several chemotherapeutic agents such as arsenic trioxide, crizotinib, daunorubicin, doxorubicin, epirubicin, idarubicin, eribulin, lapatinib, dasatinib, nilotinib, pazopanib, sorafenib, sunitinib, toremifene, vandetanib (Caprelsa), and vemurafenib also increase risk of QTc prolongation. As a result, concomitant use of these chemotherapeutic agents with venlafaxine could potentiate the risk of developing torsades de pointes. Venlafaxine is a CYP2D6 substrate and—to a lesser extent—a minor substrate of CYP3A4, and may interact with gefitinib and nilotinib, both of which are CYP2D6 inhibitors. Co-administration of these two medications could increase concentrations of venlafaxine. Imatinib increases venlafaxine levels through inhibition of CYP3A4 and CYP2D6.

Thus far, there has not been a systematic screening of TCA interactions with CYP450 in cancer patients. Doxepin, imipramine, and amitriptyline are more potent inhibitors of CYP2C19 compared to desipramine or nortriptyline. Potential interactions could occur with amitriptyline and imipramine that are moderate inhibitors of CYP1A2. All the TCAs are weak inhibitors of CYP2D6. Among the TCAs, only imipramine has been shown to minimally inhibit CYP3A4.²⁸ TCAs share pharmacological properties similar to the Class IA antiarrhythmic agents and have potential to increase the QTc interval and similar drug interactions with chemotherapeutic agents that interact with venlafaxine.

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Atypical Antidepressants

As an inhibitor of CYP3A4, nefazodone may affect the metabolism of docetaxel and the vinca alkaloids (vinblastine, vincristine, and vinorelbine).^{32,75} It is recommended that nefazodone be administered cautiously with concurrent use of these antineoplastic agents. Another antineoplastic agent of concern is gefitinib, which is a substrate to CYP3A4. Concomitant use of gefitinib and nefazodone will decrease the metabolism of gefitinib and increase gefitinib concentrations, which may increase the likelihood of clinically significant side effects.⁷² Therefore, caution should be exercised when administering nefazodone with gefitinib.¹³ Although trazodone is unlikely to be involved in drug interactions featuring hepatic cytochrome P450 enzymes, it may prolong the QT/QTc interval at therapeutic doses.⁷⁶ In addition, there are post-marketing reports of torsades de pointes. As a result, the manufacturer recommends avoiding concurrent use of trazodone with other drugs that have potential to increase the QTc interval. Among the antineoplastic agents, these include arsenic, crizotinib, dasatinib, eribulin, lapatinib, pazopanib, sorafenib, sunitinib, toremifene, vandetanib, and vemurafenib. Nilotinib has a possible risk for QT prolongation and in addition, could impair the metabolism via inhibition of CYP2D6 and CYP3A4, thereby increasing the risk of torsades de pointes.

Anticonvulsants

The most common first generation anticonvulsants include phenytoin, barbiturates such as phenobarbital, primidone, ethosuximide, carbamazepine, and valproic acid. Phenytoin, phenobarbital, and primidone have clearly lost favor for the treatment of neuropathic pain in large part because of complex pharmacokinetics, significant toxicity profiles, and their potent

CYP3A4 induction and auto-induction properties. Carbamazepine remains a commonly used cost-efficient analgesic for neuropathic pain, but is also well known to be a potent CYP3A4 inducer with a specific indication for trigeminal neuralgia. Although data are lacking, clinicians should always be cognizant of potential enzyme interactions between carbamazepine and chemotherapeutic agents listed in Table 2. Most particularly, carbamazepine could significantly reduce serum levels of all drugs listed in Table 2 beneath column 3A4 that are listed as “SUB.” The second-generation anticonvulsants such as gabapentin and pregabalin do not have the same risk, as their involvement with CYP450 is not clinically significant or is nonexistent.

Summary

Drug interactions among chemotherapy agents and pain medications used in the management of cancer pain are a common phenomenon. It is a frequent manifestation that can induce preventable AEs in patients who are exposed to them. When reviewing the data herein, one has to wonder to what extent patients are affected by these interactions that for the most part are understated in the literature and package inserts and, therefore, go unnoticed. Moreover, if a chemotherapeutic agent lowers serum levels of certain drugs, for example an opioid, the discontinuation of the chemotherapy could potentially cause the opposite, and the elevation of the opioid and death. There is an urgent need to address these potential drug interactions in a systematic way and to provide this information to prescribers and pharmacists for inclusion into prescribing and dispensing databases. Providers must appropriately adhere to precautions set forth by manufacturers unless otherwise proven in subsequent pharmacokinetic studies. Since more cancer drugs are currently prescribed in the outpatient setting

and are in the form of oral therapy, there is even greater need to ensure that patients are monitored for potential AEs. ■

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Dr. Fudin is on the speakers' bureau for Janssen Pharmaceuticals, Inc, and Purdue Pharma. He is a consultant to Practical Pain Management in the development of the online Opioid Calculator. Dr. Sasu-Tenkoramaa has no financial information to disclose.



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Tapering Patients Off High-dose Opioids

I just wanted to pass on that I love PPM's opioid calculator! But I am wondering, is there a calculator available for opioid tapering as well? I am not looking at transitioning from one opioid to another, but for a total taper off high-dose opioids. Are there any guidelines that can be followed regarding tapers?

—Lorraine Granau, PharmD
Tempe, Arizona

Dear Dr. Granau,

Your inquiry about opioid tapering is a practical one. No, there isn't a calculation for tapering, but there is an old standard that comes out of methadone maintenance for opioid addicts. The taper was to average about 5% to 10% of the daily methadone dosage each

week. In this manner, the addict would be methadone free after about 3 to 4 months. As this old standard was practiced, practitioners found they could start the taper as high as 20% in the first couple of weeks, but the end part of the taper might be as little as 1% to 3%. Interestingly, the addict will sometimes taper down to as little as 1 mg to 5 mg per day, but can't go to zero.

The pain patient who is maintained on opioids can use the same schedule of 5% to 10% per week only if the patient has cured or totally eliminated their pain. In a controlled setting, it can be done much faster and in a matter of days. The key is whether the patient's pain has resolved. This actually happens sometimes because opioid maintenance can act as a "pharmacologic

splint" and allows the patient to participate in an exercise, nutrition, motivation, or regeneration program that proves to be curative.

If the patient still has pain and wants to taper, reducing the dosage to zero is probably not realistic, as the pain will re-emerge in a major way at some point during the taper. In other words, if you taper the opioid dosage in a patient who still has pain, be prepared to maintain the patient at a lower opioid dosage or with a different opioid. There are many myths and even fraudulent claims involving tapering or "detoxifying" from opioids in a pain patient. The main one is that detoxification or withdrawal will "cure" one's pain. The sales pitch is that opioids are causing the pain. Great rhetoric, but it's not true. Pain patients start

opioids to relieve their pain, and they would obviously stop them in the first week of treatment if they produced more pain. Pain clinics around the country have loads of pain patients who were lulled into the false belief that a "rapid detoxification" would cure their pain. Put simply, carefully taper a patient with pain and be prepared to continue opioid treatment if the patient's pain re-emerges.

—Forest Tennant, MD, DrPH

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