

The Prescription

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Safety and Appropriate Use of Fentanyl Transdermal Patches

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The World Health Organization (WHO) offers guidelines and a 3-step analgesic ladder demonstrating a general, conceptual approach to management of cancer pain (Figure 1). This ladder broadly describes the order and administration of pain medications. Nonopioids (i.e. aspirin, acetaminophen, NSAIDs) should be used first, gradually increasing steps to mild, moderate, and stronger (i.e. morphine or fentanyl) opioids according to pain persistence, until the patient exhibits no pain. Adjuvant medications are used to calm fears and anxieties.¹ Arguments suggest an update is needed to the development of distinct guidelines on different categories of pain and pharmacotherapy changes of this model, but the basic premise remains useful.²

In December 2007, the U.S. Food and Drug Administration (FDA) issued an update to a public health advisory in July 2005 pertaining to the life-threatening adverse events and high fentanyl serum levels resulting from the misuse of transdermal fentanyl patches. Patients reportedly had been using the patches incorrectly, for example, changing the patches with excessive frequency (i.e. before 72 hours) or applying more than one patch at a time. Reports also included inappropriate prescribing by clinicians, including transdermal fentanyl use for mild, acute pain. Included are recommendations for healthcare professionals concerning the prescribing, management, and contraindications for transdermal fentanyl usage.³

The Institute for Safe Medication Practices (ISMP) expanded on the subject of inappropriate prescribing to opiate-naïve patients in the June 28, 2007 issue, emphasizing the indications, safety, and dosing limitations of fentanyl transdermal patches. Specifically to pharmacists, it states the prescribing indication, along with patient information on opiate tolerance and pain characteristics, should be obtained before dispensing transdermal fentanyl.⁴

Currently, a Black Box Warning exists stating the fentanyl transdermal patch (Duragesic®) is indicated only for the management of persistent, moderate-severe chronic pain in opioid-tolerant patients uncontrolled by other agents (i.e. NSAIDs, other opioid combination products, or immediate-release opioids, along with adjuvant therapy).⁵ Opioid-tolerant patients are generally considered those prescribed routine, around-the-clock narcotics.³ Specifically, opioid tolerance can be defined as those taking opiates for one week or longer consisting of at least 60 mg of morphine, 30 mg of oral oxycodone, 8 mg of oral hydromorphone, or another opiate equianalgesic dose, daily.⁴

Common adverse reactions to opioid use, especially in the elderly, include sedation, nausea/vomiting, constipation, impaired psychomotor function, and respiratory depression. With the exception of constipation, these events can be limited by using lower doses with longer intervals and proper titrations.⁶

Transdermal fentanyl poses a notable risk of life-threatening hypoventilation, typically preceded by oversedation. In nonopioid-tolerant patients, use of even low-dose transdermal fentanyl may result in respiratory depression and death. Consequently, it is contra-indicated in the management of mild-intermittent pain (i.e. PRN basis), acute pain (headaches), post-operative pain (including outpatient and day surgeries), and opiate-naïve patients.⁷ To prevent these adverse events, careful attention should be allocated to the titration and dose conversion guidelines of the transdermal fentanyl patch.³

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Fentanyl Patches

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Once the fentanyl patch is applied, depot accumulation occurs within the subcutaneous tissue, and peak serum concentrations are typically achieved between 24-72 hours, with many reaching steady-state plasma concentrations (C_{ps}) after sequential applications of the second and third patches. Serum fentanyl concentration is proportional to the transdermal drug delivery rate, dependent upon the individual's skin permeability, and clearance (primarily hepatic).^{7,8} Therapeutic concentrations are reached in about 13 hours, with a mean half-life of 17 hours.^{5,7,8} Unfortunately, there is a substantial delay in the onset of fentanyl therapy, and titration of transdermal fentanyl is a slow process.

During administration of the initial patch, short-acting oral or parenteral pain medications can be given to prevent any pain exacerbation.^{4,9} The initial dose should be selected according to the patient's current opioid regimen (i.e. daily dose, potency, and opioid tolerance), the dosing guidelines (found in the package insert), and the current clinical status of the patient.^{4,5,7} Initial doses can be converted from equianalgesic tables. Table 1 displays a simplistic method for converting the total daily dose of oral or parenteral opioids to fentanyl.⁷ These starting doses are conservative to reduce the risk of overdoses occurring on the first dose, with 50% of patients usually requiring a dose increase.^{4,7}

Conversely, if the medication or dosing is not found in Table 1, calculate the previous 24-hour analgesic requirement of the patient, and convert it to the amount of equianalgesic morphine dose listed in Table 2. Once the total daily morphine dose is established, use Table 3 to locate the corresponding fentanyl dose. Remember, the doses in these tables are conservative, and therefore, should not be used to convert the dose of fentanyl to other analgesic therapies. Doing so may overestimate the dose of the new medication.⁷

Fentanyl doses may be titrated upwards based on the supplemental opioid-analgesic therapy using the ratio of 45 mg/day of oral morphine to every 12.5 mcg/h increase in fentanyl

dose. Moreover, after the initial dose, increase no more frequently than three days before applying the second titrated dose. Six days may be required for patients to reach equilibrium on each subsequent new dose, so increase no more frequently than every two applications thereafter. Upon sustaining a therapeutic dose, the fentanyl transdermal patch should be administered every 72 hours.^{4,7}

Lastly, consider concomitant administration of CYP3A4 inhibitors, including ketoconazole, itraconazole, clarithromycin, nelfinavir, nefazadone, etc. These medications inhibit fentanyl clearance resulting in increased plasma concentrations and possible adverse events. Upward titration and dosage adjustments should be cautioned and monitored closely.¹⁰

WHO's Pain Relief Ladder

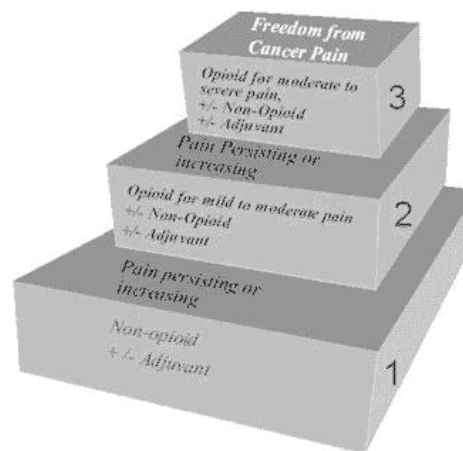


Figure 1: WHO's Pain Relief Ladder

DOSE CONVERSION GUIDELINES

Current Analgesic	Daily Dosage (mg/d)			
Oral morphine	60-134	135-224	225-314	315-404
IM/IV morphine	10-22	23-37	38-52	53-67
Oral oxycodone	30-67	67.5-112	112.5-157	157.5-202
IM/IV oxycodone	15-33	33.1-56	56.1-78	78.1-101
Oral codeine	150-447	448-747	748-1047	1048-1347
Oral hydromorphone	8-17	17.1-28	28.1-39	39.1-51
IV hydromorphone	1.5-3.4	3.5-5.6	5.7-7.9	8-10
IM meperidine	75-165	166-278	279-390	391-503
Oral methadone	20-44	45-74	75-104	105-134
IM methadone	10-22	23-37	38-52	53-67
	↓	↓	↓	↓
Recommended DURAGESIC® Dose	25 mcg/h	50 mcg/h	75 mcg/h	100 mcg/h

Table 1: Initial dose conversion of common opiates to transdermal fentanyl (Duragesic®).

Fentanyl Patches

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Name	EQUIANALGESIC POTENCY CONVERSION	
	Equianalgesic Dose (mg)	
	IM	PO
Morphine	10	60 (30)
Hydromorphone (Dilaudid®)	1.5	7.5
Methadone (Dolophine®)	10	20
Oxycodone	15	30
Levorphanol (Levo-Dromoran®)	2	4
Oxymorphone (Numorphan®)	1	10 (PR)
Meperidine (Demerol®)	75	—
Codeine	130	200

IM = Intramuscular; PO = Oral; PR = Rectal

Table 2: 24-hour analgesic requirement conversion to morphine. All IM and PO doses are equivalent to 10 mg of IM morphine in analgesic effect. The conversion of 10 mg IM morphine to 30 mg of PO morphine is based on clinical experience. The conversion of 10 mg IM morphine to 60 mg PO morphine is based on a potency study in acute pain.⁷

RECOMMENDED INITIAL DURAGESIC® DOSE BASED UPON DAILY ORAL MORPHINE DOSE	
Oral 24-hour Morphine (mg/day)	DURAGESIC® Dose (mcg/h)
60-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

Table 3: Total daily morphine dose and corresponding transdermal fentanyl (Duragesic®) dose.

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An Ounce of Prevention is Worth a Pound of Cure

By Megan McKee, PharmD

We all know the saying “an ounce of prevention is worth a pound of cure,” and we lecture about preventative healthcare on a daily basis. Why is it then, that less than 50% of all healthcare workers did not receive their flu vaccines last year? According to the Centers for Disease Control Practices Advisory Committee, all healthcare workers (including full-time, night, weekend, and temporary staff) need to be vaccinated annually to protect against influenza.¹ In fact, last year the Joint Commission implemented a standard to require all healthcare organizations to offer free influenza vaccines to their staff, volunteers, students, and any other individuals with direct patient contact.¹ As healthcare professionals, we must lead by example, and that means ensuring all of our vaccines are up-to-date.

With the latest H1N1 pandemic, today's focus is on prevention and the value of immunizations. While certain immunizations remain standard, questions among healthcare providers and patients have been raised about the need to promote administration of other vaccines such as Zostavax® (a live attenuated zoster vaccine) and Gardasil® (human papilloma vaccine). As a provider, it is necessary to educate your patients and be prepared to answer their questions about the recent reports and numbers. This summary will address some of the billing issues associated with Zostavax® and the safety concerns surrounding Gardasil®.

According to the latest report from the Centers for Disease Control, more than 43 million adults over the age of 60 are at risk for developing herpes zoster.² Herpes zoster, a manifestation also known as shingles, occurs due to a reactivation of the varicella zoster virus. It manifests as a rash in a single dermatome accompanied by unilateral pain. The most common complication of the virus is the development of postherpetic neuralgia which increases with advancing age.³ Currently, there are three vaccines that contain the live virus, existing in varying concentrations: Varivax®, ProQuad®, and Zostavax®. Zostavax® is at least 14 times the potency of a single antigen varicella vaccine.

A large multicenter study (The Shingles Prevention Study) demonstrated that use of the zoster vaccine reduced the burden of illness due to herpes zoster by 61.1% ($p < 0.001$); reduced the incidence of postherpetic neuralgia by 66.5% ($p < 0.001$); and reduced the incidence of herpes zoster by 51.3% ($p < 0.001$).⁴ Unfortunately, the truth is that only 1.9% of adults over the age of 60 have actually been immunized for the disease.⁵

While Zostavax® is currently available across the US, one of the obstacles facing providers and patients alike is obtaining funding sources. In 2003, the Medicare Prescription Drug Improvement and Modernization Act required that certain immunizations be covered under Medicare Part B.¹ For example, Part B covers the vaccine and administration fees for influenza, pneumococcal, and hepatitis B. Today, Part D is required to absorb the costs of all commercially available vaccines unless they are covered under Part B. In addition, the Centers for Medicare and Medicaid Services (CMS) recommend that providers submit one claim for both the cost of the vaccine and the cost of the administration.

However, the billing scenario is not always so simple. When vaccines are administered in an out-of-network office, physicians are required to bill the patients for the entire charges, and then patients have to follow up with paper claims for reimbursement of the vaccine cost. This is also difficult because the assorted Part D sponsors have different administration fees and various billing schemes.

As of January of 2008, administration fees and costs may both be covered under Part D. In a recent *Pharmacy Today*, providers confirm that Zostavax® is eligible for reimbursement by more than 90% of Part D plans.¹ A resource for both providers and patients is the “Medicare Part D Formulary Finder Tool” which can provide insight as to what vaccines are covered and what restrictions are currently in place.¹

(<http://formularyfinder.medicare.gov/formularyfinder/slectstate.asp>)

Earlier this year, the National Foundation of Infectious Diseases released a survey showing that, aside from the flu, most adults have trouble naming diseases that vaccinations can protect against.² According to the survey, only 4% of adults were aware a vaccine could help prevent shingles. Knowing the numbers at risk, and now being aware of the supportive funding available through Medicare, it is necessary to advise all of your patients over the age of 60 about the benefits of Zostavax®.

In addition to addressing some of the billing concerns of Zostavax® it is worthwhile to discuss the controversy surrounding Gardasil®. Gardasil® is an inactivated vaccine that protects against four different types of human papilloma virus (HPV). It was released by the FDA in 2006 following many studies in women between the ages of 9 and 26. Today the vaccine is recommended in girls' ages 11 or 12, but can be administered up to the age of 26.⁶

As of June 2008 the Vaccine Adverse Event Reporting System (VAERS) recorded 9,749 adverse events following the HPV vaccination. While this number does seem daunting it is important as a provider to keep in mind that 94% of these were not serious, and the remaining 6% is much less than the average number of serious reports for other vaccines (averaging 10-15%). To date there have been 21 reports of death following the vaccine Gardasil® (out of 16 million administered); however, no investigations of the deaths has established a causal relationship.⁶

Recent reports suggest that the vaccine series, which costs about \$360 per person, may not be worth the price. Even though the vaccine can provide protection, there is no proof it will ultimately reduce the rates of cervical cancer. Indeed, such statistics may scare patients, but it is necessary to discuss with them both the costs and benefits of vaccination. For further information refer to: <http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm>.

As we prepare for influenza season, it is important to think about all of the vaccines your patients might need. There are many resources available to better understand the vaccines, the costs, and the risks associated with immunizations. Share these resources with your patients and make them aware of the value immunization.

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TABLE 1. Types of Vaccinations in the United States^{5,8}

Type of Vaccine	Vaccines in the US	Contraindications
LIVE: A vaccine that is produced by modifying a virus or bacteria to produce immunity. These vaccines must replicate to be effective and require proper handling and storage.	Herpes zoster Measles Rotavirus Typhoid oral Vaccinia (small pox) Influenza Mumps Rubella Varicella Yellow Fever	<ul style="list-style-type: none"> • Anaphylactic reaction to any previous dose of vaccine or its components • Pregnancy • Immunosuppression • Active, untreated tuberculosis • Must separate from the administration of antibodies, blood products and immune globulins
INACTIVE: A vaccine that is composed of all or a fraction of a virus or bacterium that is inactivated. These vaccines are not alive and cannot replicate.	Anthrax Diphtheria Haemophilus influenzae Type B Hepatitis A Hepatitis B Human Papillomavirus Influenza Japanese encephalitis Meningococcal (conjugate and polysaccharide) Pertussis, acellular Pneumococcal polysaccharide Pneumococcal conjugate Polio Rabies Tetanus toxoid Typhoid injectable	<ul style="list-style-type: none"> • Anaphylactic reaction to any previous dose of vaccine or its components • Encephalopathy within 7 days of previous DTaP or DTP

For the most updated schedules of vaccinations for children and adults refer to: <http://www.immunize.org/cdc/schedules/>.

The fact remains that vaccinations are one of the top medical advances in the past century, and we should take advantage of their protective benefits. Be wise and get immunized!

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Methadone: Risks of QT Prolongation and Arrhythmia

By Tina Chang, PharmD Intern

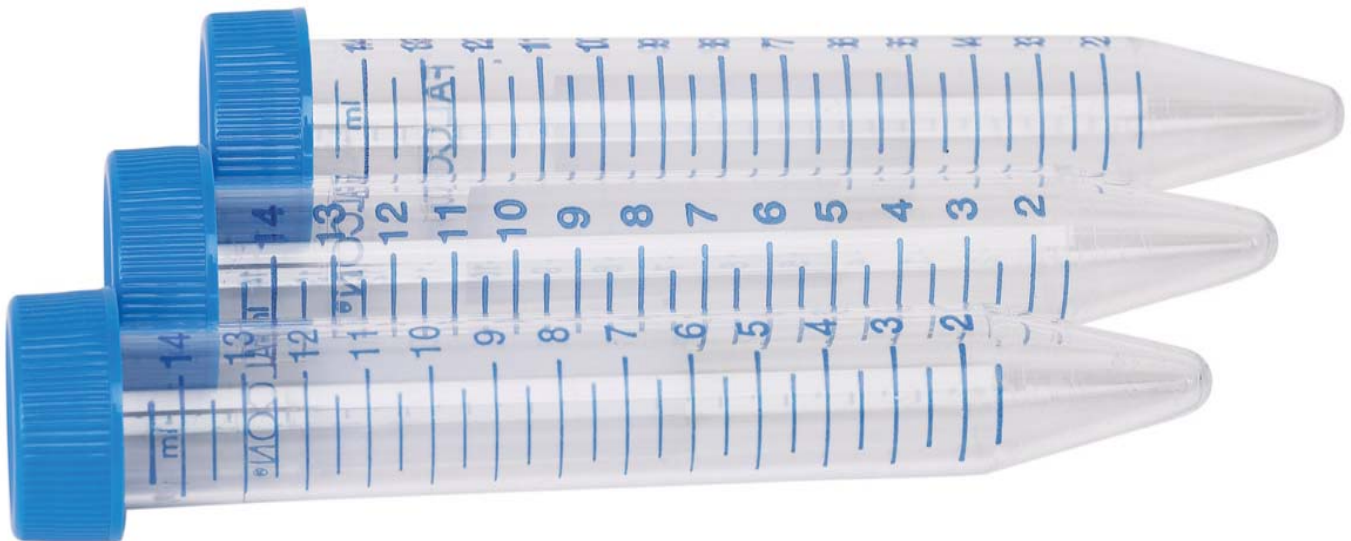
Methadone is indicated for pain and maintenance treatment of opioid addiction.^{1,2} Illicit opiates, like heroin, bind to CNS opioid receptors, and methadone, an opioid agonist, acts on the same receptors. Methadone differentiates itself because it does not produce euphoria, but facilitates weaning of illicit drugs by suppressing withdrawal symptoms and cravings. It is an inexpensive medication with the attractive pharmacological properties of good oral absorption and prolonged duration of action (thus permitting once-a-day dosing). Although methadone has a major role in opioid addiction maintenance treatment, it is not without risks. These risks include prolonged QTc (rate-corrected QT interval), drug interactions, and complicated pharmacokinetics, all of which open up possibilities for accidental overdose or arrhythmias.^{3,4}

Prolonged QTc refers to a larger than normal time interval between repolarization and depolarization of the heart ventricles.⁵ When this occurs, the risk increases for torsades de pointes (TdP), a dangerous arrhythmia. The threshold for QTc interval prolongation is 450 msec and the threshold for arrhythmia risk is >500 msec. Causes of QT prolongation include stroke, brain injury, and eating disorders, but the most common culprits are medication adverse effects and electrolyte imbalances. Methadone induces long QT syndrome (LQTS), and other medications with this similar association are listed in table 1. Because of its cardiac effects, the FDA issued a safety alert to physicians, and a manufacturer's black box warning ensued.

Before prescribing methadone, healthcare providers should inform patients of the risks of arrhythmias and perform thorough patient histories of structural heart disease, arrhythmia, and the primary symptoms in LQTS (syncope, palpitations, seizures, sudden cardiac death). QT prolongation risk factors

should be evaluated (see table 2). It is recommended to obtain a pretreatment electrocardiogram (ECG) to measure the QTc interval and perform periodic ECG readings during the treatment course. Due to the dose-dependent relationship of methadone and QT interval, the lowest effective methadone dose should be used. Additional ECG is preferred at high methadone dosages (>100 mg/d). If a measured QTc interval lies between 450 and 500 msec, careful monitoring is advised. If the QTc interval surpasses 500 msec, reducing the methadone dose, discontinuing treatment, or adjusting the patient's other medications (QT-prolonging medications or medications affecting serum potassium levels) are appropriate options depending on the clinical context.

Numerous medications interact with methadone, resulting in either increases or decreases in its levels.⁶ Not only are QT-prolonging agents a concern, medications that are inhibitors or inducers of hepatic cytochrome metabolism can be dangerous when used in conjunction with methadone. Cytochrome enzymes 3A4, 2B6, and to a lesser degree, 2D6, metabolize methadone. Inducers of hepatic enzymes increase methadone metabolism and thus decrease drug effects. Inhibitors of hepatic enzymes prevent drug degradation and increase methadone's effects. Patient populations that are elderly, hepatically impaired, or renally impaired may have increased levels of methadone due to decreased metabolism and/or elimination. With those functions impaired, methadone can accumulate to toxic levels and lead to accidental overdose or cardiac problems. Another significant interaction is with other sedative medications such as benzodiazepines, barbiturates, or alcohol, which may cause deadly respiratory depression, CNS sedative effects, or drug overdose.



Methadone's tricky pharmacokinetics complicate dosing, titration, and conversion. The pharmacokinetics are influenced by bodily fat stores, urine pH, expression and binding of metabolic enzymes, and genetic variability. Because the factors that affect pharmacokinetics are so individualized, personalized dosing and titration is essential for optimized therapy. Methadone is a fat-soluble and highly protein-bound medication so it accumulates in fat stores and slowly releases into the bloodstream overtime. Unpredictable clearance coupled with a long mechanism of action can make methadone very hazardous, especially since these pharmacological properties are poorly understood. Different doses are used for addiction maintenance therapy, but the usual range is 80 to 120 mg by mouth per day. Studies have demonstrated considerable variability in the effective doses which prevent euphoric effects, reduce cravings, and avoid withdrawal symptoms. The recommended titration schedule is to adjust doses every 3-5 days at the minimum. Currently, no guidelines exist for methadone dosing conversion to other analgesic medications and vice versa. Typically, an equianalgesic dose ratio is used to calculate the appropriate doses when switching from one opioid medication to another to achieve the same analgesic effect. The relative analgesic equivalency

when converting from and to methadone is dependent on the previous opioid doses. Although there is a lack of standard conversion ratios, common dose conversion ratios from oral morphine to methadone are 4:1, 5:1, or 10:1. The parenteral to oral ratio for methadone is 1:2.

Methadone is a beneficial medication with unique pharmacological features that give it a niche in treating pain and opioid addiction. However, healthcare professionals and patients should familiarize themselves with the risks associated with methadone use. It can cause prolonged QTc which increases the risks of dangerous arrhythmias, and also interacts with other prescribed drugs, such as those that also affect the QTc interval and those that inhibit or induce cytochrome metabolism. With comprehensive patient history reviews, medication evaluations, and appropriate ECG screenings, morbidity and mortality related to these risks can be averted. Given that its complex pharmacokinetics generate significant variability, dosing regimens should be tailored to each individual patient. Methadone can have fatal consequences, and while it has indispensable uses, it should be managed carefully by health care providers who have full clinical knowledge of both the drug's potential effects as well as their patients' heart issues.

Table 1: Drug interactions⁶

Factors that decrease methadone effects/increase methadone metabolism	Factors that increase methadone effects/decrease methadone metabolism	QT prolonging medications
CYP3A4 inducers: -ANTICONVULSANTS: carbamazepine, phenobarbital, phenytoin -ANTIBIOTICS: rifampin, rifabutin -ANTIRETROVIRALS: abacavir, amprenavir, nevirapine -st john's wort -methadone	CYP3A4 inhibitors: -ANTIFUNGALS: fluconazole, ketoconazole -SSRIs: fluvoxamine, fluoxetine -ANTIBIOTICS: erythromycin -PROTEASE INHIBITORS: ritonavir, indinavir, saquinovir -grapefruit juice	-ANTIARRHYTHMIC MEDICATIONS: quinidine, procainamine, amiodarone, sotalol -NONSEDATING ANTIHISTAMINES: terfenadine, astemizole -MACROLIDE ANTIBIOTICS: erythromycin, clarithromycin, azithromycin -ANTIPSYCHOTICS: haloperidol, risperidone -SSRI ANTIDEPRESSANTS -CISAPRIDE -COCAINE
CYP2B6 inducers: -rifampin -phenobarbital -carbamazepine -ritonavir -efavirenz -phenytoin -artemisinin	CYP2B6 inhibitors: -haloperidol -paroxetine -sertraline -nelfinavir -ritonavir -ticlopidine -clopidogrel	

Table 2

Risk factors for prolonged QT
-electrolyte abnormalities (hypokalemia, hypomagnesemia) -structural heart disease (left ventricular dysfunction) -genetic predisposition (prolonged QTc interval at baseline) -other drugs which prolong the QT interval -FH of long QT syndrome -female gender -bradycardia -starvation (anorexia nervosa) -hypothyroidism -stroke

**Data from UpToDate©5

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