

The Prescription

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Transdermal Fentanyl Patches and Heat-Associated Toxicities

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Between the months of January 2006 and March 2006, 1220 adverse drug events involving the use of transdermal drug delivery systems were reported to the FDA. Of these episodes, 3.7% were related to fentanyl transdermal patches of which 4.3% resulted in death.¹ One of the most serious complications of opiate overdose is respiratory depression, a condition which can lead to death if not recognized and reversed in a timely manner. Unintentional exposure of the patch or person to heat has resulted in several cases of fentanyl overdose, many of which could have been prevented if patients and practitioners had been educated on the appropriate use of the patch.

In one case, a 17-year-old who had been prescribed fentanyl for pain after a dental procedure was found dead on a heated waterbed. In another instance, a 42-year-old female had an upper-body warming blanket placed over a 75 mcg/hr fentanyl patch during surgery. She subsequently developed respiratory depression.² Finally, a 44-year-old man treated with a 75mcg/hr patch for HIV neuropathy went to camp and was involved in several outdoor activities upon arrival. By the fourth day he felt tired, and his speech began to slur. After all other diagnoses were excluded; the patient was treated for opioid toxicity. He was restarted on his previous dose of fentanyl with no further complications.³

In an effort to limit interpatient variation, the rate of fentanyl administration through the transdermal system is limited by passive cutaneous diffusion through the membrane of the patch. Therefore, it is the membrane, not patient's skin, which should determine the patient's exposure to fentanyl. The system consists of a protective liner, adhesive, release membrane, reservoir, and backing (Figure 1).

The reservoir contains a concentrated amount of fentanyl in alcohol and hydroxyethyl cellulose. The alcohol in the patch increases the drug flux of fentanyl through the skin.² Fentanyl accumulates in the upper skin layers and a depot is formed. Intracutaneous blood flow carries the drug from the depot to the systemic blood flow.^{4,5}

Normal serum concentrations of fentanyl range from 0.3-2.5 ng/mL, depending on dose, metabolism, weight, skin thickness and integrity. Hypoventilation can occur at doses >2 ng/mL in patients who are opioid naïve, have pulmonary conditions, or are taking concomitant medications that cause respiratory depression.² When body temperatures rise, blood flow may increase through the drug depot in the skin. A 25% increase in fentanyl blood levels is expected with a rise of 3°C in body temperature.²

Other reports estimate a 1/3 increase in fentanyl blood levels at a body temperature of 40°C (104°F).⁴ In addition, Doppler flowmetry demonstrates a 10-15 times increase in cutaneous blood flow when skin temperature increases from 32°C to 40°C.⁶ When heat is applied directly to the patch, similar results may occur due to an increase in release of medication from the transdermal system.

If a fentanyl transdermal patch heat-associated toxicity is suspected, the patch should be removed immediately and an opiate antagonist such as naloxone should be administered. It takes approximately 17 hours to decrease serum drug levels by 50% after removal of the patch. Repeat dosing of naloxone may be required because of its short half-life along with the delay of decrease in serum fentanyl concentrations. It is important to keep in mind that withdrawal symptoms may occur, and pain may return during this process. The patch may be reinitiated at the previous dose used and counseling on the effect of heat on the transdermal system performed.

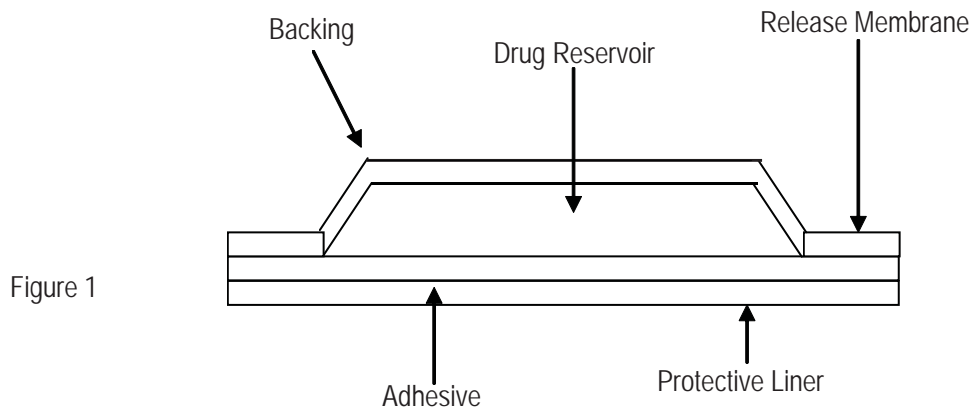


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Transdermal Fentanyl Patches and Heat-Associated Toxicities

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There are a number of preventative methods to avoid heat-associated toxicities and other adverse effects (Table 1). Respiratory depression is the most dangerous side effect of fentanyl overdose. The ultimate goal in preventing heat-associated toxicities that result in respiratory depression is avoiding changes in skin temperature from both internal and external sources. Heat-associated toxicities should be managed immediately with careful avoidance of overcorrection resulting in withdrawal symptoms or breakthrough pain. All three of the case reports mentioned could have been prevented with appropriate patient and practitioner education.



<i>Objects and Activities to Avoid While Wearing a Fentanyl Patch</i>
*Heating beds or electronic blankets
* Heat lamp
* Saunas
* Hot tubs
* Heated water beds
* Overheating from outdoor activities
* Fever (contact physician)
* Applying to damaged skin
* Shaving hair at application site (may clip hair)
* Improper disposal
* Using damaged patches
* Wiping alcohol, lotions, soaps, or oils on the application site

Table 1

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Opiate Safety

By Chris Winfield, PharmD Intern

As more and more prescribers gain experience with the use of opiate analgesics, it is reasonable to expect that problems due to this increased use will rise as well. Complications as simple as increased constipation rates, dizziness, confusion and death are possible with a litany of events in between. Costs and length of stay in the hospital are also affected by the use of opiates. In a study released in March of this year by *Annals of Pharmacotherapy*, it was found that in surgical patients the use of opiates increases a patient's stay in the hospital up to a day, and increases costs by hundreds of dollars. Increased frequency of adverse events and medication interactions are an unfortunate by-product of greater usage; however, since the culprit is known we can implement measures to prevent many of these complications.

There are many causes for the errors that arise from the use of opioid analgesics. One of the more common mishaps is the confusion between morphine and hydromorphone. The confusion comes from the belief that hydromorphone is the generic for morphine. In actuality, morphine is the generic name for many products including Avinza[®], MS Contin[®], Kadian[®] and others. Hydromorphone is the generic name for Dilaudid[®]. These two medications, though both opiate analgesics, are designed for use in different situations. Confusing the two could lead to serious adverse effects for patients. These medications are sometimes switched inadvertently when they are placed on shelves near each other. For this reason, it is recommended to keep them separated in such a way as to avoid accidentally using one instead of the other. This is recommended both in pharmacies and in emergency kits on the floors. Additionally, using the brand name Dilaudid[®] on the order for hydromorphone can greatly reduce the amount of errors.

Another modality of opiate related errors is the misprogramming of infusion pumps. By inputting the incorrect rates it is likely that a patient will receive either too much of a medication, leading to possible respiratory depression, confusion, or even death; too little of a medication which would not provide the patient with adequate pain control.

New devices are currently available that are designed to compensate for this problem, but they are not in widespread use as of yet and they can be inadvertently overridden to an incorrect rate by the operator. Therefore, it is essential to always double check infusion rates just to be sure that there will be no harm to patients.

Unfamiliarity with IV-to-oral conversions of opioids is also a common origin of errors with this class of medications. Similarly, unfamiliarity with equiesic doses between the different opioids is common and can lead to adverse effects. By converting a dose incorrectly, again either too much or too little of the medication may be administered, leading to the same effects previously mentioned. Tables explaining the conversion factors between the different opiates are available through the UHS Clinical Intranet that will help in the conversion. Page three contains a table that can be found as a pocket guide under the "Guidelines" section on the UHS Clinical Intranet. Again, double check results just to be sure.

As with all other medications, abbreviations should not be used if at all possible. MgSO₄ (magnesium sulfate) can easily be mistaken for MSO₄ (morphine sulfate). It is also possible that the "g" could get "lost in translation" leading to a mix-up between the two agents. For this reason, it is recommended that abbreviations for these two drugs never be used. It is a very simple step to take when writing orders and other communications, and yet it is one that historically has caused many errors. Furthermore, both are included in the "UHS Prohibited Abbreviations" list.

Using a concentrated formulation in place of a conventional strength formulation is another method that may also lead to errors with opioid administration or dosing. For obvious reasons, this is a problem that can cause serious complications, and yet can be easily avoided in most situations. By stocking different concentrations clearly labeled and separated from each other, errors can be significantly reduced.

Recognizing an adverse effect early in its progression is another key element to improving patient outcomes. Most all patients on opiate therapy need to be on a stool softener and mild stimulate to prevent constipation and possible impactions. This is due to opiates suppressing GI motility and secretions. With doses too high, respiratory depression can occur and is one of the more common adverse events. The typical characteristic of this is hypoventilation. There are many other adverse events that may occur while on opiate therapy. Early recognition of these effects can greatly improve a patient's disposition.

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EQUIANALGESIC DOSE CHART

- Equianalgesic means approximately the same pain relief
- This chart is a guideline. Doses and intervals between doses are titrated to individual's response.
- This chart is helpful when switching from one drug to another or from one route of administration to another
- Dosages in this chart are not necessarily starting doses. They suggest a ration for comparing the analgesia of one drug to another.
- The longer the patient has been receiving opioids, the more conservative the starting doses of a new opioid.

OPIOID ANALGESICS	PARENTERAL (IM/SQ/IV) OVER ~ 4 HRS	ORAL (PO) OVER ~ 4 HRS	ONSET (MINUTES)	PEAK (MINUTES)	DURATION (HOURS)	HALF-LIFE (HOURS)	COMMENTS
Morphine	10mg	30mg	5-10 (IV) 10-20 (IM/SQ) 30-60 (PO)	15-30 (IV) 30-60 (IM/SQ) 60-90 (PO)	3-4 (IV) 3-4 (IM/SQ) 3-4 (PO)	2-4	Active metabolite M6G can accumulate with repeated dosing in pts. with renal failure.
Codeine		200mg NR	30-60 (PO)	60-90 (PO)	3-4 (PO)	2-4	Usually compounded with non-opioid e.g., Tylenol #3.
Fentanyl	100µg/hr IV & transdermal (TD) = 4mg/hr Morphine IV/IM/SQ: 1µg/hr TD = Morphine 2 mg/24hr PO		1-5 (IV) 7-15 (IM) 12-16 (TD)	3-5 (IV) 10-20 (IM) 24 hrs (TD)	0.5-4 (IV) 0.5-4 (IM) 48-72 (TD)	3-4 (IV/IM) 13-24 (TD)	A steady state, slow release of Fentanyl from storage in tissues can result in a prolonged half-life of up to 12 hours.
Hydrocodone (Vicodin or Lortab)		30mg NR	30-60 (PO)	60-90 (PO)	4-6 (PO)	4	
Hydromorphone (Dilaudid)	1.5mg	7.5mg	5 (IV) 10-20 (IM) 15-30 (PO)	10-20 (IV) 30-90 (IM) 30-90 (PO)	3-4 (IV) 3-4 (IM) 3-4 (PO)	2-3	Useful alternative to Morphine.
Methadone (Dolophine)	10mg	See Comments column	10 (IV) 10-20 (IM/SQ) 30-60 (PO)	Unknown (IV) 60-120 (IM/SQ) 60-120 (PO)	4-8 (IV) 4-8 (IM/SQ) 4-8 (PO)	12-190	Complex conversion Consult pharmacy or APS
Oxycodone (Percocet, Tylox)		20mg	30-60 (PO)	60-90 (PO)	3-4 (PO)	2-3	
Buprenorphine (Buprenex)	0.4mg		5 (IV) 10-20 (IM)	10-20 (IV) 30-60 (IM)	3-4 (IV) 3-6 (IM)	2-3	
Butorphanol (Stadol)	2mg		5 (IV) 10-20 (IM)	10-20 (IV) 30-60 (IM)	3-4 (IV) 3-4 (IM)	3-4	
Nalbuphine (Nubain)	10mg		5 (IV) <15 (IM/SQ)	10-20 (IV) 30-60 (IM)	3-4 (IV) 3-4 (IM/SQ)	5	
Pentazocine (Talwin)	30mg	90mg	5 (IV) 15-20 (IM/SQ) 15-30 (PO)	15 (IV) 60 (IM/SQ) 60-180 (PO)	3-4 (IV) 3-4 (IM/SQ) 3-4 (PO)	2-3	Adjust dose for renal or hepatic impairments

NR = not recommended

Opiate therapy is a necessary and beneficial therapy in many patients. However, it is not without its pitfalls.

By being educated on the possible adverse events that may occur, it is possible to greatly increase quality of life for our patients, decrease their length of stays at the hospital, and decrease both patient costs and the costs to the system.

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New FDA Drug Approvals in 2006

Drug Name	Approval Status	Drug Class	Indication	MOA
Ranexa® (Ranolazine)	January 2006	ER anti-ischemic/ anti-anginal	Chronic angina in patients who have failed first line therapy	Ranexa's mechanism of action has not been fully characterized. It is suspected that the drug exerts some of its effects by eliciting changes in cardiac metabolism.
Sutent® (sunitinib)	January 2006	Receptor tyrosine kinase inhibitor	Gastrointestinal stromal tumors (GIST) that are refractory to or have relapsed following treatment with imatinib; and advanced renal cell carcinoma (RCC)	Sutent is designed to inhibit multiple receptor tyrosine kinases, including platelet-derived growth factor receptors (PDGFR-alpha and PDGFR-beta), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). A number of these kinases have been implicated in tumor growth, pathologic angiogenesis, and cancer metastasis.
Vivaglobin® (subcutaneous immunoglobulin)	January 2006	Immunoglobulin	Primary immunoglobulin deficiency	SCIG (subcutaneous immunoglobulin) supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The exact mechanism by which immunoglobulins yield a therapeutic effect in a variety of diseases, including immune deficiency states and autoimmune disorders, is not well understood. The pooled heterogenous IgG present in SCIG provides antibodies capable of altering toxins and microbes so that they are more readily and more efficiently engulfed by phagocytes. The passive immunity imparted by SCIG is capable of attenuating or preventing infectious diseases or deleterious reactions from toxins, mycoplasma, parasites, bacteria, and viruses.
Eraxis® (anidulafungin)	February 2006	Echinocandin semi-synthetic lipopeptide	Candidemia; intra-abdominal abscess and peritonitis caused by Candida species; and esophageal candidiasis	Anidulafungin is a semi-synthetic echinocandin designed to inhibit glucan synthase, an enzyme present in fungal (but not mammalian) cells. Inhibition of glucan synthase disrupts formation of 1,3-B-D-glucan, an essential component of the fungal cell wall.
RotaTeq®	February 2006	Live pentavalent vaccine	Rotavirus vaccine	RotaTeq provides immunity by creating an immunologic response against the G1, G2, G3, G4, and G6 rotavirus capsid proteins as well as attachment proteins P1A and P7. The rotavirus vaccine replicates in the intestine and induces immunity. Immunity provides protection from rotavirus induced gastroenteritis which leads to a severe and sometimes fatal diarrhea, especially in children under two years of age.
Myozyme® (alglucosidase alfa)	April 2006	Enzyme replacement	Pompe disease (GAA deficiency)	Myozyme is designed to act as an exogenous source of GAA, acting to correct GAA deficiency that is the hallmark of Pompe disease. Myozyme binds to mannose-6-phosphate receptors on the cell surface via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

Amitiza® (lubiprostone)	May 2006	CIC-2 chloride channel activator	Chronic idiopathic constipation	Amitiza activates CIC-2, a chloride channel present in the apical membrane of the intestine in a protein kinase A-independent fashion, thereby increasing secretion of chloride-rich intestinal fluid. This in turn increases intestinal motility, reducing symptoms of chronic constipation and increasing stool passage.
Azilect® (rasagiline)	May 2006	MAO-B inhibitor	As monotherapy in early Parkinson's Disease, combination therapy with levodopa in advanced Parkinson's	The precise mechanisms of action of rasagiline are unknown. One mechanism is believed to be related to its MAO-B inhibitory activity, which causes an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.
Chantix™ (varenicline)	May 2006	Nicotinic acetylcholine receptor agonist	Smoking cessation	Chantix competitively inhibits the ability of nicotine to bind to and activate the alpha-4 beta-2 receptor.
Dacogen® (decitabine)	May 2006	Nucleoside analog	Myelodysplastic Syndromes	Dacogen is an analogue of the nucleoside 2'-deoxycytidine. It is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. DNA hypomethylation is achieved at concentrations below those required to significantly inhibit DNA synthesis, which may promote restoration of function to genes associated with control of cellular differentiation and proliferation. Cytotoxicity in rapidly dividing cells may also result from covalent adducts between DNA methyltransferase and decitabine incorporated into DNA.
Zostavax® (live herpes zoster vaccine)	May 2006	Attenuated herpes vaccine	Herpes zoster prevention for adults >60 years old	The herpes zoster virus vaccine boosts VZV-specific cell-mediated immunity, which is thought to be the mechanism by which it protects against herpes zoster and its complications.
Gardasil® (HPV Vaccine)	June 2006	Recombinant vaccine	In the prevention of conditions caused by HPV types 6, 11, 16 and 18 infections. These include cervical cancer, genital warts (condyloma acuminata), and precancerous or dysplastic lesions.	Gardasil delivers HPV-6, -11, -16 and -18 L1 protein, conferring protection against these HPV strains, presumably through induction of humoral immune response. These strains are responsible for the majority of cases of cervical cancer, AIS, CIN and VIN, and for a number of cases of VaIN and genital warts.
Lucentis® (ranibizumab)	June 2006	Recombinant humanized IgG1 kappa isotype monoclonal antibody	Neovascular ("wet") age-related macular degeneration (AMD)	Lucentis binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF110. This binding activity prevents the interaction of VEGF-A and its angiogenic receptor targets VEGFR1 and VEGFR2. Lowering VEGFR1 & VEGFR2 activation reduces endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Prezista® (darunavir)	June 2006	HIV-1 protease inhibitor (PI)	HIV-1 infections in combination with ritonavir and other antiviral agents in treatment-experienced patients.	Prezista is an inhibitor of HIV-1 protease, designed to selectively inhibit the cleavage of HIV encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.
Sprycel® (dasatinib)	June 2006	Tyrosine kinase inhibitor	Chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib.	Sprycel is believed to bind to multiple conformations of ABL kinase. It has been shown to inhibit multiple tyrosine kinases at nanomolar concentrations, including BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRB
Elaprase™ (idursulfase)	July 2006	Enzyme replacement	Hunter syndrome	This enzyme cleaves the terminal 2-O-sulfate moieties from the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. Due to the missing or defective iduronate-2-sulfatase enzyme in patients with Hunter's Syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction and organ system dysfunction. Treatment of Hunter's Syndrome patients with Elaprase provides exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow specific binding of the enzymes to the M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated GAG.
Noxafil® (posaconazole)	September 2006	Triazole antifungal agent.	Prophylaxis of invasive Aspergillus and Candida infections	Noxafil is a triazole antifungal agent. It blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of the enzyme lanosterol 14a-demethylase and accumulation of methylated sterol precursors.
Helidac® (Bismuth Subcitrate Potassium; Metronidazole; Tetracycline)	September 2006	Anti-infective	H. pylori and duodenal ulcer	This combination is to be used in conjunction with omeprazole to eradicate H. pylori in infected individuals.
Vectibix™ (Panitumumab)	September 2006	Monoclonal Antibody	Metastatic Colon Cancer	In vitro assays and in vivo animal studies have shown that panitumumab inhibits the growth and survival of cancer cells that display an excess of the expression of EGFR (human epidermal growth factor receptor).
Verdeso® (desonide)	September 2006	Topical Corticosteroid	Mild to moderate atopic dermatitis	Verdeso Foam is a topical corticosteroid which are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. These proteins are believed to control the biosynthesis of potent mediators of inflammation, such as prostaglandins and leukotrienes, by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Januvia™ (sitagliptin)	October 2006	Intranasal glucocorticoid	Allergic rhinitis	Glucocorticoids are naturally occurring hormones which suppress or inhibit inflammation or the immune response of many cell types and mediators. These include mast cells, eosinophils, neutrophils, macrophages, and lymphocytes as well as histamine, eicosanoids, leukotrienes, and cytokines. Cis-ciclesonide is an active metabolite of ciclesonide with anti-inflammatory activity 120 times greater than the parent compound.
Omnaris™ (ciclesonide)	October 2006	Intranasal glucocorticoid	Allergic rhinitis	Glucocorticoids are naturally occurring hormones which suppress or inhibit inflammation or the immune response of many cell types and mediators. These include mast cells, eosinophils, neutrophils, macrophages, and lymphocytes as well as histamine, eicosanoids, leukotrienes, and cytokines. Cis-ciclesonide is an active metabolite of ciclesonide with anti-inflammatory activity 120 times greater than the parent compound.
Zolinza™ (vorinostat)	October 2006	Synthetic antineoplastic	Persistent or recurrent cutaneous T-cell lymphoma	Vorinostat is a potent histone deacetylase (HDAC) inhibitor. Vorinostat inhibits HDAC1, HDAC2, HDAC3, and HDAC6 enzymes. Histone deacetylases are the enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. Overexpression of HDACs or an abnormal recruitment of HDACs to oncogenic transcription factors is present in some cancer cells. This causes hypoacetylation of core nucleosomal histones resulting in a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity produces an accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation. In many different malignant cell lines, HDAC inhibitors have been shown to activate differentiation, inhibit the cell cycle, and induce apoptosis.
Tyzeka™ (telbivudine)	November 2006	Synthetic thymidine nucleoside analogue	Hepatitis B	Telbivudine works by inhibiting HBV DNA polymerase. Telbivudine is phosphorylated by cellular kinases to the active triphosphate form, telbivudine 5'-triphosphate, which inhibits HBV DNA polymerase by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine 5'-triphosphate into viral DNA causes DNA chain termination, which results in inhibition of HBV replication.
Invega™ (paliperidone)	December 2006	Atypical Antipsychotic	Schizophrenia	Paliperidone is the major active metabolite of risperidone. Its effects are shown by D2 and 5HT2A receptor antagonism.

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