IMPORTANT DRUG WARNING

Black Box Warnings

A to Z

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Objectives

Following the presentation, the participant will:

• Be able to quantify the typical frequency of prescribing drugs that have a black box warning (BBW)
• Be able to list the common categories of prescribing practices in violation of BBWs
• Be able to navigate and use the FDA’s on-line tool for communicating new drug safety information
• Be able to identify 10 significant BBW drugs and how to avoid the BBWs
INTRODUCTION
What is a BBW?

**BOX WARNING**

**HEPATOTOXICITY:**
Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity. Especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When Depakote is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

**TERATOGENICITY:**
Valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, the use of Depakote tablets in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., migraine) is contemplated. See warnings, information for patients. A patient information leaflet describing the teratogenic potential of valproate is available for patients.
BBW – More than a Precaution; Less than a Contraindication

US FDA Labeling Cautions

• **Precaution**: Consideration must be taken in special situations/patient groups

• **Warning**: Serious adverse events that have been observed and potential safety hazards
  – A “Black Box Warning” or “Boxed Warning” is the strongest warning the FDA issues

• **Contraindication**: Drug should not be used in a specific situation because risk much greater than possible benefit
BBW Used in 3 Situations

- There is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug.
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (patient selection, monitoring, avoiding interactions, etc.)
- The drug can be safely used ONLY with certain use restrictions.

An FDA mandate for post-marketing safety requirements
Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

SEROQUEL (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzothiazole)2-[1,4]thiazepin-11-yl]-1-piperazineyl]ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is C_{42}H_{50}N_{6}O_{4}S_{2}C_{4}H_{4}O_{4} and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:
BBW – First Billing
Under Warnings in Lexicomp
BBWs IN PATIENT CARE
What % of Drugs Carry a BBW?

<5%?
5-10%?
~20%?

25 Years of Drug Development; Amit Kalgutar, PhD, Pfizer Global Research and Development (2010)
What % of Pts Take a BBW Drug?

~10%?
~20%?
~40%?

Study 1

- **Retrospective review of 1 million outpatient Rx claims for 216 specific BBW drugs (1999-2001)**
  - XL % outpatients receive a prescription that carries a black box warning

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FDA drug prescribing warnings: is the black box half empty or half full?

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Inna Dashevsky MSc\(^{1,2}\), Marsha A. Raebel PharmD\(^{2,5}\), Susan E. Andrade ScD\(^{2,6}\),
Jennifer Elston Lafata PhD\(^{2,7}\), Robert L. Davis MD, MPH\(^{2,8}\), Jerry H. Gurwitz MD\(^{2,6}\),
Stephen B. Soumerai ScD\(^{1,2}\) and Richard Platt MD, MS\(^{1,2,3}\)
What BBWs Are Most Common?

1. Do not co-administer with interacting drug
2. Monitor to prevent possible adverse effects
3. Warning against rapid discontinuation
4. **Only** use drug for specific indications
5. Do **NOT** use drug in certain indications

What BBW Violations Are Most Common?

1. Co-administer with interacting drug
2. Omitting initial lab test for safety monitoring
3. Failing to test for pregnancy

BBW for Co-Administering With Interacting Drug

• **10% in Violation**
  – ketorolac
    • Contraindicated with other NSAID for GI risk
  – methotrexate
    • Decreased renal clearance (toxicity) and increased GI toxicity when co-administered with NSAIDs, esp high dose MTX
  – itraconazole
    • Co-administration with certain QT prolonging drugs
  – ritonavir
    • Co-administration with certain QT prolonging drugs, sedative hypnotics or ergot alkaloids

BBW for Initial Lab Test

• 50% in Violation
  – valproic acid (LFT)
  – carbamazepine (CBC + platelets),
  – isoniazid (AST or ALT in pts >35 yrs old),
  – triamterene and amiloride (serum K)

BBW for Initial Pregnancy Test

• 0.3% in Violation
  – Retinoids:
    • isotretinoin (Accutane®) & acitretin (Soriatane®)
  – methotrexate
  – leflunomide (Arava®)
    • antiproliferative used in Rheum. arthritis
  – ACE Inhibitors
  – PO misoprostol (Cytotec®)
  – megestrol (Megace®)
    • synthetic progestogen
  – ribavirin/interferon (Hep C)

• Retrospective review of 324,548 outpatients in 50 Boston-area ambulatory care practices with EMR
  – E-prescribing with limited clinical decision support (allergy, dose)
  – EMR contained demographics, medical problem list, patient medication lists, and lab test results

• 33778/324548 (10.4%) got a BBW drug

Lasser et al, Harvard Medical School
Arch Intern Med. 2006;166:338-344.
Findings

• 2354/33778 (7%) received a prescription in violation of a BBW
  – Seven drugs accounted for 3/4ths of the BBW violations.
    • lithium, carbamazepine, valproate, metformin, propoxyphene, triamterene, azathioprine
  – Inadequate laboratory monitoring was common
    • lithium 69.1% failure rate
    • carbamazepine 24.5% failure rate
    • valproate 30.1% failure rate
  – Drug-disease state interactions were common

Lasser et al, Harvard Medical School
Arch Intern Med. 2006;166:338-344
BBW Overlooked

- lithium – monitor lithium levels
- carbamazepine – monitor for hematologic toxicities
- valproate – monitor LFT’s
- metformin – monitor serum creatinine
- triamterene – monitor potassium levels
- azathioprine – monitor for hematologic toxicities

Lasser et al, Harvard Medical School Arch Intern Med. 2006;166:338-344
High Risk Patients for BBW Violations

- Pts ≥75 yrs old
- ≥4 medications and
- ≥7 medical problems

Lasser et al, Harvard Medical School Arch Intern Med. 2006;166:338-344
Real ADE’s from Real BBW

• A subset of 575 records were reviewed for ADE’s
  – 4 related ADE’s were noted
    • 3 serious, 1 significant
  – 92 potential ADE’s noted
    • 18 potentially fatal or life-threatening

Lasser et al, Harvard Medical School
Arch Intern Med. 2006;166:338-344
Revisiting the Numbers

• 10% of drugs carry a BBW
• 10 - 40% of patients receive one or more BBW drugs
• In patients receiving a BBW drug, about 1-50% may be in violation of the BBW.
KEEPING UP WITH BBWs
Any drug’s BBW can be found in its FDA-approved package insert or Lexicomp.
The FDA’s “Index to Drug-Specific Info” lists updated BBWs and other safety issues.
The FDA’s “Drug Safety Communications” Webpage Lists the “Latest Safety Information”


“MACE occurring within 30 days of treatment discontinuation: Chantix =0.31% Placebo= 0.21% in a meta-analysis (NS)”. 
Black Box Warnings
(& Other Concerns)
A-Z
Which “A” Drug to Choose?

Abacavir sulfate
Abilify (aripiprazole)
AbobotulinumtoxinA
Accolate (zafirlukast)
Accupril (quinapril)
Accutane (isotretinoin)
Aceon (perindopril)
Acetaminophen
AcipHex (rabeprazole sodium)
Actimmune (interferon gamma-1b)
Actonel (risedronate)
Actoplus Met (pioglitazone)
Actos (pioglitazone)
Adalimumab
Adenosine
Advair Diskus (fluticasone propionate; adderall (amphetamine salts)
Alemtuzumab
Aleve (naproxen sodium)
Alimta (pemetrexed)
Alli (orlistat)
Almotriptan malate
Alosetron hydrochloride
Altace (ramipril)
Ambien (zolpidem tartrate)
Amerge (naratriptan)
Amiodarone
Amiodarone/Simvastatin
Amnesteem (isotretinoin)
Amphetamine salts
Anaprox (naproxen sodium)
AndroGel 1%
Anzemet (dolasetron mesylate)
Aprotinin
Aranesp (darbepoetin alpha)
Arava (leflunomide)
Aredia (pamidronate)
Arformoterol tartrate
Aripiprazole
Aspirin
Atacand (candesartan)
Atomoxetine
Avalide (irbesartan/hydrochlorothiazide)
Avandamet (rosiglitazone)
Avandaryl (rosiglitazone)
Avandia (rosiglitazone)
Avapro (irbesartan)
Avastin (bevacizumab)
Avelox (moxifloxacin)
Axert (almotriptan malate)
Azor (olmesartan/amlodipine)
ACE inhibitors and ARBs

Fetal Harm

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ZESTRIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor drug during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.
**BLACK BOX WARNING**

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, AND OTHER BLOOD DYSCRASIAS. SULFONAMIDES, INCLUDING SULFONAMIDE CONTAINING PRODUCTS SUCH AS TRIMETHOPRIM/SULFAMETHOXAZOLE, SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious blood disorder (see **PRECAUTIONS**). Clinical signs, such as rash, sore throat, fever, arthralgia, pallor, purpura, or jaundice may be early indications of serious reactions.
CONTRAINDICATIONS
BACTRIM is contraindicated in …
• patients with documented megaloblastic anemia due to folate deficiency
• pregnant patients and nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus.
• in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.
Biphosphonates

Safety Announcement

[10-13-2010] The U.S. Food and Drug Administration (FDA) is updating the public regarding information previously communicated describing the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis. This information will be added to the Warnings and Precautions section of the labels of all bisphosphonate drugs approved for the prevention or treatment of osteoporosis.

The bisphosphonates affected by this notice are only those approved to treat osteoporosis, including Fosamax, Fosamax Plus D, Actonel, Actonel with Calcium, Boniva, Atelvia, and Reclast (and their generic products).

FDA is looking at safety data past the 3-5 year time frame of original clinical trials.
Botox®

• New warning about unintended spreading of paralytic action beyond intended area (2009)
  – Hospitalization and death occurred mostly in children treated for cerebral palsy-associated limb spasticity (off-label)
  – Probably related to overdose
BOTOX® Cosmetic
(onabotulinumtoxinA)
for injection

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc. 2525 Dupont Dr., Irvine, CA 92612

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of BOTOX® Cosmetic and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have occurred at doses comparable to those used to treat cervical dystonia and at lower doses.
Beta-Lactam Antibiotics

- A careful inquiry into allergy hx
- Cross-hypersensitivity has been clearly documented and can occur in up to 10% of patients

**WARNINGS**

BEFORE THERAPY WITH FORTAZ IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO FORTAZ OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.
### Similar Side Chain Tables

**from Pediatrics 2005;115:1048–1057**

<table>
<thead>
<tr>
<th>TABLE 6. Chemical Structures of 7-Position Side Chains of Penicillins and Cephalosporins</th>
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<tbody>
<tr>
<td><strong>Similar Structure/Possible Cross-Reactivity With Group</strong></td>
</tr>
<tr>
<td>Related</td>
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<tr>
<td>Penicillin G</td>
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<tr>
<td>Cephaloridine</td>
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<td>Cephalothin</td>
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<td>Cefoxitin</td>
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<tr>
<th>TABLE 7. Chemical Structures of 3-Position Side Chains of Penicillins and Cephalosporins</th>
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<tr>
<td><strong>Similar Structure/Possible Cross-Reactivity Within Group</strong></td>
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<tr>
<td>Related</td>
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<tr>
<td>Cephradine</td>
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<td>Cefadroxil</td>
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<td>Cephalexin</td>
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# OPIOID Cross Allergies

<table>
<thead>
<tr>
<th>CLASS MEMBERS &amp; SUBCLASSES</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylpiperidines</td>
<td></td>
</tr>
<tr>
<td>• Meperidine (Demerol)</td>
<td></td>
</tr>
<tr>
<td>• Diphenoxylate (Lomotil)</td>
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<tr>
<td>• Fentanyl; Sufentanil; Alfentanil</td>
<td>Cross-reactions between the 2 natural opiates (morphine and codeine) common</td>
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<tr>
<td>Phenylheptanones (diphenylheptanes)</td>
<td></td>
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<tr>
<td>• Methadone</td>
<td></td>
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<tr>
<td>• Propoxyphene (Darvocet)</td>
<td>Cross-reactions between the 2 opiates within a chemical class are common.</td>
</tr>
<tr>
<td>Phenanthrenes</td>
<td></td>
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<tr>
<td>• Morphine (natural)</td>
<td></td>
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<tr>
<td>• Codeine (natural)</td>
<td></td>
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<tr>
<td>• Hydromorphone (Dilaudid)</td>
<td></td>
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<tr>
<td>• Hydrocodone (Vicodin)</td>
<td></td>
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<tr>
<td>• Oxycodone (Percocet)</td>
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<tr>
<td>• Oxymorphone; Buprenorphine</td>
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<tr>
<td>• Butorphanol; Nalbuphine</td>
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<tr>
<td>• Pentazocine; Levorphanol</td>
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Rather than being truly allergic, some patients are merely sensitive to the histamine-releasing chemical effects of opioids. Most common with IV or epidural morphine and meperidine.

**ALTERNATIVES:** Nonnarcotic analgesics should be considered.
# NSAID Cross Allergies

<table>
<thead>
<tr>
<th>CLASS</th>
<th>CLASS MEMBERS</th>
<th>NOTES</th>
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<tbody>
<tr>
<td>NSAIDs</td>
<td><strong>Non-selective COX inhibitors</strong>&lt;br&gt;• aspirin&lt;br&gt;• ketorolac (Toradol)&lt;br&gt;• ibuprofen (Motrin)&lt;br&gt;• naproxen (Aleve)&lt;br&gt;• &amp; other NSAID's</td>
<td>Cross-reactions are near 100% because allergic symptoms are caused by the action of the NSAID drug, rather than the molecular structure. The newer COX2 inhibitors (such as Celebrex) may be tolerated by certain patients, but this should only be confirmed by a specialist. <strong>Alternatives:</strong> Tylenol is generally tolerated; consider opioids.</td>
</tr>
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<td></td>
<td><strong>Selective COX 2 inhibitors</strong>&lt;br&gt;• celecoxib (Celebrex)</td>
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-CAINE Cross Allergies

<table>
<thead>
<tr>
<th>CLASS MEMBERS &amp; SUBCLASSES</th>
<th>NOTE</th>
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<tbody>
<tr>
<td>AMIDES</td>
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<tr>
<td>• lidocaine</td>
<td>True allergies to a local anesthetic are rare.</td>
</tr>
<tr>
<td>• bupivacaine (Marcaine)</td>
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<tr>
<td>• prilocaine (Emla)</td>
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<tr>
<td>• ropivacaine (Naropin)</td>
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<tr>
<td>ESTERS</td>
<td></td>
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<tr>
<td>• cocaine</td>
<td></td>
</tr>
<tr>
<td>• procaine (Novocain)</td>
<td>Patients who are allergic to ESTER local anesthetics should be treated with a preservative-free AMIDE local anesthetic.</td>
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<tr>
<td>• chloroprocaine</td>
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<tr>
<td>• tetracaine (Pontocaine)</td>
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Procaine penicillin carries a double-risk of cross-reactions.
Cefepime (and other beta-lactams)

Safety Announcement

[6-26-2012] The U.S. Food and Drug Administration (FDA) is reminding health care professionals about the need to adjust the dosage of the antibacterial drug cefepime in patients with renal (kidney) impairment. There have been cases of a specific type of seizure called nonconvulsive status epilepticus associated with the use of cefepime, primarily in patients with renal impairment who did not receive appropriate dosage adjustments of cefepime. The Warnings and Precautions and Adverse Reactions sections of the cefepime label are being revised to highlight this risk.

– Possible manifestations of neurotoxicity include confused state, dysarthria, somnolence, psychosis, myoclonus, seizures, and sometimes, coma.

 Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia (see PRECAUTIONS).
Cefipime & Ceftazidime (Chow et al)

- Mean age of 54 patients
  - cefepime (61 yrs), ceftazidime (65 yrs)
- Confusion was the chief symptom
  - cefepime (93%), ceftazidime (91%)
- Myoclonus was subsequently detected
  - cefepime (29%), ceftazidime (50%)
- The median interval between symptom onset and diagnosis of neurotoxicity
  - cefepime (5 days), ceftazidime (3 days)
EEG patterns of AB Neurotoxicity

• Encephalopathic State (cefepime > ceftazidime)
  – EEGs showed loss of background activity, increased slow rhythms in the theta and delta range, and triphasic waves.
  – Symptoms abated with discontinuation of the drug rather than because of any change in degree of uremia.

• EEG Epileptic Activity (cefepime > ceftazidime)
  – Epileptiform discharges such as polyspike discharges, rhythmic slow waves, or irregular spikes or sharps, which initially might be confined to one region and become more widespread, subsequently spreading to both cerebral hemispheres.
  – Spike and wave discharges were suppressed after intravenous administration of benzodiazepines.
  – EEG changes were accompanied by either overt convulsions or continuous subclinical seizures.
    • Nonconvulsive status epilepticus
      – Characterized by prolonged clouding of consciousness and confusion associated with persistent epileptiform discharges seen on EEG in the absence of motor convulsive activity.
      – cefepime group (35%) and 75% of the ceftazidime group (75%)
Ciprofloxacin

- increased risk of tendinitis and tendon rupture, a serious injury that could cause permanent disability (July 2008.)
  - Do not rigorously exercise during the healing process

**WARNING:**
Fluoroquinolones, including CIPRO®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

(esp. patients > 60 yrs old + 30-40 yo runner
Pts with prior tendon damage or hypomagnesemia probably due to Mg++ chelation at the tendon (similar to chelation with divalent cations in the gut) or oxidative damage.
Ofloxacin > ciprofloxacin
Ciprofloxacin

Maybe Myasthenia Gravis

**Post-Marketing Adverse Event Reports:** The following adverse events have been reported from worldwide marketing experience with quinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug. Agitation, agranulocytosis, albuminuria, anaphylactic reactions (including life-threatening anaphylactic shock), anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure (including fatal cases), hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus,
Antibiotics and Myasthenia

2. ANTIBIOTICS

These are used to prevent and treat bacterial infections. One group (A), which contains six members, affects transmission between nerve and muscle, and therefore can make MG worse. They are chiefly given by injection, and you are therefore most likely to come across them in hospital. You are more likely to encounter those in groups B, which are usually given as tablets, often for chest infections, but which are much less likely to upset your MG, and C, which are commonly used for bladder and kidney infections. Group D is now used very rarely.

Group E (one member) are antibiotics which have been shown to have serious side effects, and which must not be prescribed to myasthenics.

- A.
  - Gentamicin Genticin, Genticin Ear/Eye drops, Cidomycin Injection, Cidomycin Ear/Eye drops/ointment
  - Amikacin Amikin
  - Netilmicin Netilin
  - Tobramycin Nebcin
  - Streptomycin
  - Kanamycin Kannasyn

- B.
  - Tetracycline Achromycin, Kustamycin, Tetrabid, Tetrachel, Deteclo, (Mystecin).
  - Doxycycline Nordox, Vibramycin,
  - Limecycline Tetrapsal 300
  - Minocycline Minocin MR
  - Oxytetracycline Terramycin

- C.
  - Ciprofloxacin Ciproxin
  - Acrosoxin Eradicin
  - Cinoxacin Cinobac
  - Nalidixic Acid Micral, Negram, Uriben
  - Norfloxacin Utor
  - Ofloxacin Tarvid

- D.
  - Polymixin B
  - Colistin Colomycin Injection

- E.
  - Telithromycin Ketek (see HERE for further information).
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)
Colistimethate (Colistin) IV

Overdosage can result in renal insufficiency, muscle weakness, and apnea (see OVERDOSAGE section). See PRECAUTIONS, Drug Interactions subsection for use concomitantly with other antibiotics and curariform drugs.

Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnea and neuromuscular blockade following administration of colistimethate sodium. Therefore, it is important to follow recommended dosing guidelines. See DOSAGE AND ADMINISTRATION section for use in renal impairment.
Contrast Media - Iodinated

• Precaution:
  – Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease).
  – Dehydration in these patients seems to be enhanced by the osmotic diuretic action of contrast agents. 

*Patients should be well hydrated prior to and following administration of any (iodinated) contrast medium*
Dabigatran (Pradaxa®)  

Serious Bleeding

FDA has not changed its recommendations regarding Pradaxa.

- Healthcare professionals who prescribe Pradaxa should carefully follow the dosing recommendations in the drug label, especially for patients with renal impairment... to reduce the risk of bleeding.
- Patients with atrial fibrillation should not stop taking Pradaxa without first talking to their healthcare professional.
- Stopping use of anticoagulant medications such as Pradaxa can increase the risk of stroke. Strokes can lead to permanent disability and death.

Note: False elevation of PT
Daptomycin (Cubicin®)

Eosinophilic Pneumonia

---

**WARNINGS AND PRECAUTIONS**

- Anaphylaxis/hypersensitivity reactions (including life-threatening): Discontinue CUBICIN and treat signs/symptoms. (5.1)

- Myopathy and rhabdomyolysis: Monitor CPK levels and follow muscle pain or weakness; if elevated CPK or myopathy occurs, consider discontinuation of CUBICIN. (5.2)

- Eosinophilic pneumonia: Discontinue CUBICIN and consider treatment with systemic steroids. (5.3)

- Peripheral neuropathy: Monitor for neuropathy and consider discontinuation. (5.4)

---

Note: False elevation of PT
7.1 HMG-CoA Reductase Inhibitors

In healthy subjects, concomitant administration of CUBICIN and simvastatin had no effect on plasma trough concentrations of simvastatin, and there were no reports of skeletal myopathy [see Clinical Pharmacology (12.3)].

However, inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of creatine phosphokinase (CPK). In the Phase 3 S. aureus bacteremia/endocarditis trial, some patients who received prior or concomitant treatment with an HMG-CoA reductase inhibitor developed elevated CPK [see Adverse Reactions (6.1)]. Experience with the coadministration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited; therefore, consideration should be given to suspending use of HMG-CoA reductase inhibitors temporarily in patients receiving CUBICIN.

Note: False elevation of PT
Dronedarone (Multaq®)

Liver Failure

Safety Announcement

[1-14-2011] The U.S. Food and Drug Administration (FDA) is alerting healthcare professionals and patients about cases of rare, but severe liver injury, including two cases of acute liver failure leading to liver transplant in patients treated with the heart medication dronedarone (Multaq).

Dronedarone is a drug used to treat abnormal heart rhythm in patients who have had an abnormal heart rhythm (atrial fibrillation or atrial flutter) during the past 6 months. Dronedarone can reduce the risk of being hospitalized for these heart problems. Since dronedarone's approval in July 2009 through October 2010, around 492,000 dronedarone prescriptions were dispensed and around 147,000 patients filled dronedarone prescriptions at outpatient retail pharmacies in the United States.\(^1\) Additional usage can occur in the hospital setting.

Dronedarone was approved with a Risk Evaluation and Mitigation Strategy (REMS) with a goal of preventing its use in patients with severe heart failure or who have recently been in the hospital for heart failure. In a study of patients with these conditions, patients given dronedarone had a greater than two-fold increase in risk of death.
Epoetin and Darbopoetin

Renal failure
• CRF patients experienced greater risks for death and serious CV events when administered ESAs to target higher vs lower Hgb levels.
• Must individualize dosing to achieve and maintain Hgb levels within the range of 10 to 12 g/dL.

Perisurgery
• Epoetin increased the rate of DVTs in patients not receiving prophylactic anticoagulation. Consider DVT prophylaxis.

CV Events

Cancer
• ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical CAs when dosed to target a Hgb of ≥ 12 g/dL.
• Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
• Discontinue following the completion of a chemotherapy course.
• Use the lowest dose needed to avoid RBCs transfusions.

Survival
Fentanyl Transdermal System (marketed as Duragesic) Information

FDA ALERT 7/15/2005; Update 12/21/2007: This update highlights important information on appropriate prescribing, dose selection, and the safe use of the fentanyl transdermal system.

In July 2005, FDA issued a Public Health Advisory and Information for Healthcare Professionals that emphasized the appropriate and safe use of the fentanyl transdermal system (fentanyl patch), marketed as Duragesic and generics). Despite these efforts FDA has continued to receive reports of death and life-threatening adverse events related to fentanyl overdose that have occurred when the fentanyl patch was used to treat pain in opioid-naïve patients and when opioid-tolerant patients have applied more patches than prescribed, changed the patch too frequently, and exposed the patch to a heat source.
Fentanyl Patch

The US FDA and ISMP have identified U.S. patient deaths when contraindications to fentanyl transdermal patch have NOT been followed.

Overlooked Contraindications

Contraindicated in the management of acute or post-operative pain.
Contraindicated in patients whose pain has NOT required at least one week of scheduled round-the-clock high doses of strong opioid.

– Prescribers must consult the approved conversion chart

Additional Dangers

Inadequate patient monitoring at peak effect (12-24 hr p application)
Not removing the previous patch when a new patch is applied
Accelerated release from the patch if heat is accidentally applied
Due to prolonged half-life, multiple doses of naloxone may be needed in overdose
Notable Fentanyl Patch Cases

• 17-year-old who had been prescribed fentanyl for pain after a dental procedure was found dead on a heated waterbed.

• 42-year-old female had an upper-body warming blanket placed over a 75 mcg/hr fentanyl patch during surgery – developed respiratory depression.

Gadolinium-Based MRI contrast

Nephrogenic Systemic Fibrosis

Safety Announcement

[09-09-2010] The U.S. Food and Drug Administration (FDA) is requiring changes in the drug label for gadolinium-based contrast agents (GBCAs) to minimize the risk of nephrogenic systemic fibrosis (NSF), a rare, but serious, condition associated with the use of GBCAs in certain patients with kidney dysfunction. GBCAs are intravenous drugs used in diagnostic imaging procedures to enhance the quality of magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA). (See Approved Gadolinium-Based Contrast Agents below).

The revised labeling will enhance the safe use of GBCAs, by recommending that healthcare professionals:

• Not use three of the GBCA drugs--Magnevist, Omniscan, and Optimark-- in patients with AKI or with chronic, severe kidney disease. These three GBCA drugs are contraindicated in these patients.
CONTRAINDICATIONS

GLUCOPHAGE and GLUCOPHAGE XR are contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).

Surgical procedures—GLUCOPHAGE (metformin hydrochloride) or GLUCOPHAGE XR (metformin hydrochloride) therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient’s oral intake has resumed and renal function has been evaluated as normal.
Glucophage®, metformin
Glucophage®

• Very rare - - 3 cases/100,000
  – Primarily in DM with renal insufficiency
• Avoid in hepatic disease (CLlactate)
• Key Points
  – Regular monitoring of CLcr key
  – Holding during periods of hypoxemia or dehydration
    • surgery, sepsis
  – Initial symptoms are non-specific
    • Malaise, myalgias, respiratory, somnolence, GI symptoms
      – While GI symptoms are common with initiation, watch out for “late”
  – Hypothermia, hypotension, & bradyarrhythmias follow
  – Life-threatening
Do not take GLUCOPHAGE or GLUCOPHAGE XR if you:

- have kidney problems
- have liver problems
- have heart failure that is treated with medicines, such as Lanoxin® (digoxin) or Lasix® (furosemide)
- drink a lot of alcohol. This means you binge drink for short periods or drink all the time
- are seriously dehydrated (have lost a lot of water from your body)
- are going to have an x-ray procedure with injection of dyes (contrast agents)
- are going to have surgery
- develop a serious condition, such as heart attack, severe infection, or a stroke
- are 80 years or older and you have NOT had your kidney function tested

Tell your doctor if you are pregnant or plan to become pregnant. GLUCOPHAGE and GLUCOPHAGE XR may not be right for you. Talk with your doctor about your choices. You should also discuss your choices with your doctor if you are nursing a child.
Haloperidol (Haldol®)

Body as a Whole
Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with haloperidol. (See WARNINGS for further information concerning NMS.)

Cardiovascular Effects
Tachycardia, hypotension, hypertension, and ECG changes including prolongation of the Q-T interval and ECG pattern changes compatible with the polymorphous configuration of torsades de pointes.
Several drugs have been withdrawn from the U.S. market or have received black box warnings due to their potential to cause QT interval prolongation that leads to fatal ventricular arrhythmias and sudden cardiac death.

<table>
<thead>
<tr>
<th>Antiarrhythmics</th>
<th>Antimicrobials</th>
<th>Antidepressants</th>
<th>Antipsychotics</th>
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<tr>
<td></td>
<td>Itraconazole</td>
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</tbody>
</table>

- Quinine
- AmphoB prior to Azole
- propoxyphene
Inhaled Long-Acting Beta-Agonists (Salmeterol & Formoterol)

• may increase the chance of severe asthma episodes and death when those episodes occur (2005)
  – Wean patients as possible
[09-25-2009]
FDA is revising the prescribing information for Januvia (sitagliptin) and Janumet (sitagliptin/metformin) to include information on reported cases of acute pancreatitis in patients using these products.

Sitagliptin, the first in a new class of diabetic drugs called dipeptidyl peptidase-4 (DPP-4) inhibitors, is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Eighty-eight post-marketing cases of acute pancreatitis, including two cases of hemorrhagic or necrotizing pancreatitis in patients using sitagliptin, were reported to the Agency between October 16, 2006 and February 9, 2009. Based on these reports, FDA is working with the manufacturer of sitagliptin and sitagliptin/metformin to revise the prescribing information to include:
Keppra®, levetiracetam

Suicidal Behavior and Ideation and Antiepileptic Drugs

Update 5/5/2009:

AED class label changes

Manufacturers of antiepileptic drugs (AEDs) or anticonvulsant drugs will update product labeling to include a warning about an increased risk of suicidal thoughts or actions and will develop a Medication Guide to help patients understand this risk. These changes affect all approved AEDs except those indicated only for short-term use.

Drugs with updated labels

The approved AEDs affected by these safety label changes are Carbatrol, Celontin, Depakene, Depakote ER, Depakote sprinkles, Depakote tablets, Dilantin, Equetro, Felbatol, Gabitril, Keppra, Keppra XR, Klonopin, Lamictal, Lyrica, Mysoline, Neurontin, Peganone, Stavzor, Tegretol, Tegretol XR, Topamax, Tranxene, Tridione, Trileptal, Zarontin, Zonegran, and generics. FDA approved updated labeling for these drugs on April 23, 2009.
Lansoprazole and other PPI’s

Fracture

[05-25-2010] The U.S. Food and Drug Administration (FDA) is revising the prescription and over-the-counter (OTC) labels for a class of drugs called proton pump inhibitors to include new safety information about a possible increased risk of fractures of the hip, wrist, and spine with the use of these medications.

Proton pump inhibitors work by reducing the amount of acid in the stomach. Nexium, Dexam, Prilosec, Zegerid, Prevacid, Protonix, Aciphex, and Vimovo are available by prescription to treat conditions such as gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, and inflammation of the esophagus. Prilosec OTC, Zegerid OTC, and Prevacid 24HR are sold over-the-counter (OTC) for the treatment of frequent heartburn.

The new safety information is based on FDA’s review of several epidemiological studies that reported an increased risk of fractures of the hip, wrist, and spine with proton pump inhibitor use. Some studies found that those at greatest risk for these fractures received high doses of proton pump inhibitors or used them for one year or more (see Data Summary section). The majority of the studies evaluated individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group.

While the greatest increased risk for fractures in these studies involved people who had been taking prescription proton pump inhibitors for at least one year or who had been taking high doses of the prescription medications (not available over-the-counter), as a precaution, the "Drug Facts" label on the OTC proton pump inhibitors (indicated for 14 days of continuous use) also is being revised to include information about this risk.
PPI’s & Fracture

In these studies:

- Six reported an increased risk of fractures with the use of proton pump inhibitors \(^1,^2,^3,^5,^6,^7\).
- Exposure to proton pump inhibitors ranged from a period of 1 to 12 years, depending on the study.
- The emergence of fractures varied among studies; with one study reporting an increase in fractures with use of proton pump inhibitors in the previous year \(^2\) and another study finding an increase after 5 to 7 years of proton pump inhibitor use\(^3\).
- The increased risk of fractures was primarily observed in older individuals.
- Two studies reported an increase in fractures with higher doses of proton pump inhibitors \(^2,^5\).
- Two studies reported an increase in fractures with longer duration of use \(^2,^3\).
- One study did not find a relationship between proton pump inhibitor use and fractures \(^4\). This study limited the study population to those without major risk factors for fracture.

In the largest meta-analysis to date, a 25% increased risk was noted (Ditah et al)
FDA is providing additional information about the reports of serotonin syndrome. **Not all serotonergic psychiatric drugs have an equal capacity to cause serotonin syndrome with linezolid.**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Found in Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>paroxetine</td>
<td>Paxil, Paxil CR</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>Luvox, Luvox CR</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>Prozac, Symbyax</td>
</tr>
<tr>
<td>sertraline</td>
<td>Zolort</td>
</tr>
<tr>
<td>citalopram</td>
<td>Celexa</td>
</tr>
<tr>
<td>escitalopram</td>
<td>Lexapro</td>
</tr>
<tr>
<td>vilazodone¹</td>
<td>Viibryd</td>
</tr>
</tbody>
</table>

¹Although the FDA has not received cases of serotonin syndrome to date involving vilazodone, the pharmacology of this drug places it in the SSRI category and suggests that it possesses a risk comparable to that of the SSRIs.

All others “unclear”
Metoprolol (Lopressor®) w/Clonidine

Rebound Withdrawal Hypertension

If a patient is treated with clonidine and Lopressor concurrently, and clonidine treatment is to be discontinued, Lopressor should be stopped several days before clonidine is withdrawn. Rebound hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.
Metoprolol (Lopressor®) and other BB

Abrupt Cessation

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician’s advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.
Midodrine (ProAmatine®) for Orthostatic Hypotension

- FDA recently notified manufacturers of their proposal to withdraw product approval for midodrine.
  - The FDA's proposed action was based on the lack of required post-marketing data confirming the clinical benefit of the drug.
- A key point is that FDA's announcement did not represent the actual withdrawal of the medication from the market.
  - It represented a step in the regulatory process –more data about the benefits of midodrine would help doctors and patients understand who can benefit from the drug and how best to use it.
- Shire has requested a public hearing in response to FDA's proposal to withdraw midodrine.
  - That hearing will provide an opportunity for the company to present the agency with data supporting the clinical benefit of the drug and for an advisory committee to review those data.
Naproxen

• Preliminary data from the ADAPT trial (Alzheimer’s Disease Anti-Inflammatory Prevention) indicated an apparent increase in reports of cardiovascular and cerebrovascular adverse events among the participants taking naproxen when compared with those on placebo.
  – For OTC use, patients should not exceed 2 tablets (440 mg) in any 8 to 12 hour period and should not exceed 3 tablets (660 mg) in a 24-hour period.
  – For prescription use, naproxen should always be prescribed within the recommended dosing range of 250 mg to 500 mg twice a day. (per FDA)
Omeprazole

FDA reminder to avoid concomitant use of Plavix (clopidogrel) and omeprazole

Please note this is not a Drug Safety Communication, rather just a reminder of our recommendations from the previous DSC. It is posted on the Plavix Information page.

The U.S. Food and Drug Administration (FDA) is reminding the public that it continues to warn against the concomitant use of Plavix (clopidogrel) and omeprazole because the co-administration can result in significant reductions in clopidogrel's active metabolite levels and antiplatelet activity. This information was added to the drug label of Plavix in November 2009, and has been the source of continued discussion in the medical literature.¹

Pantoprazole (Protonix) or antacid may be an alternative. Pantoprazole is a weak inhibitor of CYP2C19 and has less effect.

Proton Pump Inhibitors
Avoid concomitant use of Plavix with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Plavix [see Drug Interactions (7.1) and Dosage and Administration (2.4)].
A recently completed clinical study suggest that a 32 mg single intravenous dose of ondansetron (Zofran, ondansetron hydrochloride, and generics) may affect the electrical activity of the heart (QT interval prolongation), which could pre-dispose patients to develop an abnormal and potentially fatal heart rhythm known as Torsades de Pointes.

GlaxoSmithKline (GSK) has announced changes to the Zofran drug label\(^2\) to remove the 32 mg single intravenous dose
Oxycodone

The concomitant use of OxyContin with all cytochrome P450 3A4 inhibitors such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse effects and may cause potentially fatal respiratory depression. Patients receiving OxyContin and a CYP3A4...

...should be carefully monitored with the dose titrated as needed.
Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

- "Mr. Heath Ledger died as the result of acute intoxication by the combined effects of oxycodone, hydrocodone, diazepam, temazepam, alprazolam, and doxylamine," We have concluded that the manner of death is accident, resulting from the abuse of prescription medications."
  - New York City Medical Examiner
- “Heath's accidental death serves as a caution to the hidden dangers of combining prescription medication, even at low dosage."
  - Mr. Ledger’s publicist
Penicillin

Bicillin® L-A
(penicillin G benzathine injectable suspension)
Disposable Syringe
for deep IM injection only

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.
Bicillin Events

- In 1996, inadvertent intravenous administration of Pen G benzathine in a 10-fold overdose in a Colorado hospital caused death in neonate.
  - "Hoping to spare the infant unnecessary punctures, the nurses began investigating whether they could give the drug intravenously instead of intramuscularly. After research, they incorrectly concluded that they could."
Quetiapine (Seroquel®)

**WARNING:** INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full Prescribing Information for complete boxed warning.

- Antipsychotic drugs are associated with an increased risk of death (5.1)
- Quetiapine is not approved for elderly patients with Dementia-Related Psychosis (5.1)

**WARNING:** SUICIDALITY AND ANTIDEPRESSANT DRUGS See full Prescribing Information for complete boxed warning.

- Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders (5.2)

Carries an indication for treating depression with mania
Quetiapine (Seroquel®)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. SEROQUEL (quetiapine) is not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.1)].
Rifampin

Administration of rifampin with other medications metabolized by hepatic enzymes alters the metabolism of these other drugs. Rifampin induces CYP metabolism, thus decreasing the plasma concentration and efficacy, of the following drugs: theophylline; azole antifungals; antiarrhythmic agents (disopyramide, mexiletine, propafenone, quinidine, and tocainide); antidiabetic agents (chlorpropamide, glyburide, and tolbutamide); chloramphenicol; coumarin anticoagulants; digoxin; corticosteroids; methadone; phenytoin; and verapamil. Rifampin also induces the metabolism and decreases the enterohepatic cycling of estrogen-containing oral contraceptives, causing a decrease in hormone levels and contraceptive efficacy.[24]
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<tr>
<th>1A2</th>
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<th>2D6</th>
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<td>Prednisone</td>
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<td>Ritalin</td>
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<td>Troglitazone</td>
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Rosiglitazone (Avandia®)

- Avandia® (rosiglitazone) and Actos® pioglitazone carry an increased risk of heart failure
  - Observe patient carefully
  - Not recommended in symptomatic HF
- A meta-analysis of 42 trials showed that rosiglitazone also carries risk of heart attack if patients already have heart disease or are at high risk of suffering a heart attack. (November 2007.)
Rosiglitazone (Avandia®)

• REMS: UPDATED 02/04/2011
• FDA notified healthcare professionals and patients that information on the cardiovascular risks (including heart attack) of rosiglitazone has been added to the physician labeling and patient Medication Guide.
  – This information was first announced by FDA on September 23, 2010 as part of new restrictions for prescribing and use of this drug a heart attack.
Rosiglitazone (Avandia®) REMS

- FDA will require that GSK develop a REMS.
- Under the REMS, Avandia will be available to new patients only if they are unable to achieve glucose control on other medications and are unable to take Actos (pioglitazone).
- Current users of Avandia who are benefiting from the drug will be able to continue using the medication if they choose.
- Physicians will have document patient eligibility.
- Patients will have to review statements describing the CV concerns and acknowledge they understand the risks.
- FDA anticipates that the REMS will limit use of Avandia significantly.
Sertraline (Zoloft®) & all Antidepressants

- **Suicidality** in children, adolescents (2004)
- **Suicidality in young adults** (2007)
  - < 25 years old

- Monitor for agitation
- Educate family members
- Dispense small quantities

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**20th Century Changes In Youth Suicide Rates**

*United States, Ages 15-24*

- [Graph showing suicide rates from 1900 to 2000](chart).

Sertraline (Zoloft®) & all SSRIs

Serotonin Syndrome

Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT (sertraline hydrochloride), a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.

The concomitant use of Zoloft with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS – Potential for Interaction with Monoamine Oxidase Inhibitors.)
Sertraline (Zoloft®) & all SSRIs

Serotonin Syndrome

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Zoloft treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.
# Drugs That Increase Serotonin

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
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<tr>
<td>Metabolic serotonin precursor</td>
<td>L-tryptophan</td>
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<tr>
<td>Inhibit serotonin metabolism</td>
<td>MAOIs</td>
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<tr>
<td>Increase serotonin release</td>
<td>amphetamines</td>
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<td></td>
<td>lithium</td>
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<td>MDMA (Ecstasy)</td>
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<td>Inhibit serotonin reuptake</td>
<td>cocaine</td>
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<td>dextromethorphan</td>
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<td>merperidine</td>
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<td>SSRIs</td>
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<td>tricyclic antidepressants</td>
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<td>trazodone</td>
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<td>venlafaxine</td>
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<td>serotonin receptor agonists</td>
<td>buspirone</td>
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<td>dopamine agonists</td>
<td>lysergic acid diethylamide (LSD)</td>
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<td>l-dopa</td>
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& linezolid
TNF blockers are approved for the treatment of one or more of a number of immune system diseases including juvenile idiopathic arthritis (JIA), rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn’s disease, and ankylosing spondylitis.

Information on Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi)

FDA ALERT [8/4/2009]:
FDA is requiring the manufacturers of TNF blockers to update the Boxed Warning in the prescribing information to alert healthcare professionals of an increased risk of lymphoma and other malignancies in children and adolescents treated with TNF blockers.

In addition to the updated Boxed Warning, FDA is requiring several other changes to the prescribing information for TNF blockers to warn of and mitigate the risks associated with these drugs. These changes are based on additional safety reviews and include a(n):

- Update to the Warnings section describing reported cases of leukemia in adults, adolescents, and children. Changes to the Warnings section of the labeling will also include additional information on malignancies in children and adolescents (see also Boxed Warning information above).
Ultram®, tramadol

WARNINGS
Seizure Risk
Seizures have been reported in patients receiving ULTRAM® within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of ULTRAM® above the recommended range. Concomitant use of ULTRAM® increases the seizure risk in patients taking:

- Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or
- Other opioids.

Administration of ULTRAM® may enhance the seizure risk in patients taking:

- MAO inhibitors (see also WARNINGS, Use with MAO Inhibitors and Serotonin Re-Uptake Inhibitors),
- Neuroleptics, or
- Other drugs that reduce the seizure threshold.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In ULTRAM® overdose, naloxone administration may increase the risk of seizure.
**Ultram®, tramadol**

**Drug Interactions**

**CYP2D6 and CYP3A4 Inhibitors**

Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**), such as quinidine, fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), and ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol increasing the risk for serious adverse events including seizures and serotonin syndrome.
Viagra®, Sildenafil and other ED drugs

NTG & isosorbide products + ED drug -> excess cyclic guanosine monophosphate -> extreme hypotension

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

Hypotension
After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered.

- Single 100 mg oral dose given to healthy normal volunteers – results in peak level of 440 ng/mL, 24 hour trough = 2 ng/mL
- In the following patients:
  - age >65,
  - hepatic impairment (e.g., cirrhosis),
  - severe renal impairment (e.g., CRCL <30 mL/min), and
  - concomitant use of potent cytochrome P450 3A4 inhibitors

...plasma levels at 24 hours are 3 to 8 times higher than those seen in healthy volunteers.

- Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely co-administered at this time point.
A meta-analysis of 9 studies including 2775 patients (99% Caucasian) was performed to examine the clinical outcomes associated with CYP2C9 gene variants in warfarin-treated patients. 3 studies assessed bleeding risks; 8 studies assessed daily dose requirements.

- The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles.

- Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the homozygous CYP2C9*1 pts

- For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the homozygous CYP2C9*1 pts
Warfarin

• In an observational study, the risk of achieving INR >3 during the first 3 weeks of warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype.
  – The relative risk of overanticoagulation as measured by INR >3 during the first 2 weeks of therapy was approximately doubled for those patients classified as *2 or *3 compared to patients who were homozygous for the *1 allele.4
Warfarin

Microemboli & Purple Toes

• Anticoagulation therapy with COUMADIN may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the “purple toes syndrome.”
  – Discontinuation of COUMADIN therapy is recommended when such phenomena are observed.
Warfarin

- Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including:
  - purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion.
  - The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver.
  - Some cases have progressed to necrosis or death.
Purple toes syndrome is a complication of oral anticoagulation characterized by a dark, purplish or mottled color of the toes, usually occurring between 3 to 10 weeks, or later, after the initiation of therapy with warfarin.

Major features of this syndrome include purple color of plantar surfaces and sides of the toes that blanches on moderate pressure and fades with elevation of the legs; pain and tenderness of the toes; waxing and waning of the color over time.

While the purple toes syndrome is reported to be reversible, some cases progress to gangrene or necrosis which may require debridement of the affected area, or may lead to amputation.
Xenical®, Alli®, orlistat

Safety Announcement

[05-26-2010] The U.S. Food and Drug Administration (FDA) has approved a revised label for Xenical to include new safety information about cases of severe liver injury that have been reported rarely with the use of this medication. The agency is also adding a new warning about rare reports of severe liver injury to the OTC Drug Facts label for Alli and is working with the manufacturer to ensure that consumers can understand this new warning.

Xenical and Alli are medications used for weight-loss that contain different strengths of the same active ingredient, orlistat. Xenical (orlistat 120 mg) is available by prescription and Alli (orlistat 60 mg) is sold over-the-counter without a prescription.

This new safety information, originally announced in August 2009, is based on FDA's completed review that identified 13 total reports of severe liver injury with orlistat; 12 foreign reports with Xenical and 1 U.S. report with Alli (see Data Summary).
Yasmin® (drospirenone+ethinyl estradiol)

Hyperkalemia

YASMIN contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. YASMIN should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium, should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin–II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs.
Zyvox®, linezolid

**Monoamine Oxidase Inhibition:** Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

**Adrenergic Agents:** A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content (see **PRECAUTIONS, Information for Patients**).

A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects (see **PRECAUTIONS, Drug Interactions**). A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg q12h...
Questions?

END