Medication Safety: New Black Box Warnings & Other Warnings

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Disclosures

• I have no conflicts of interest to disclose
Objectives

Following the presentation, the participant will:
• Be able to list 3 scenarios where a BBW is used.
• Be able to list the common types 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 3 new significant BBW drugs and how to address the BBWs
Introduction

“Cautions” in FDA Labeling
WARNINGS AND PRECAUTIONS

• The WARNINGS AND PRECAUTIONS section of product labeling is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for management.
WARNINGS AND PRECAUTIONS

• The order in which adverse reactions are presented in the WARNINGS AND PRECAUTIONS section should reflect the relative clinical significance of the ADR.

• BOLDING should be limited to one or two sentences.
CONTRAINDICATIONS

• A drug should be contraindicated only in those clinical situations for which the risk from use CLEARLY OUTWEIGHS any possible benefit.
What is a BBW?

Much more than a Precaution;
More than a simple Warning
Less than a Contraindication*

The FDA does allow boxed “Contraindication” – BBC?
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-[(4-Benzyl-2-thiazolyl)ethoxy]-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 $C_{42}H_{30}N_6O_4 \cdot S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 893.11 (fumarate salt). The structural formula is:

[Image of structural formula]
BBW – First Billing
Under Warnings in Lexicomp

**Alert:** U.S. Boxed Warning

**Warnings/Precautions**

*Boxed warnings:*

- Hepatic failure: See “Concerns related to adverse effects” below.
- Pancreatitis: See “Concerns related to adverse effects” below.
- Pregnancy: See “Special populations” below.
The FDA’s “Index to Drug-Specific Info” lists updated BBWs and other safety issues.

http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111085.htm
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
Overview: BBW Used in 3 Situations

1. Random serious ADR
2. Preventable serious ADR
3. Specific restrictions

BBW’s Used in 3 Situations

1. 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.

2. 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.)

3. The drug can be safely used ONLY with certain use restrictions.

Physician’s Duty with BBW’s

1. **Random serious ADR**
   – Inform patient; Weigh risk vs. benefit

2. **Preventable serious ADR**
   – Take action steps to minimize risk

3. **Specific restrictions**
   – Respect the exclusions
   – If there are no other options, inform patient

Case:

Prescribing in Face of a Caution
Patient with known G6PD deficiency requires BACTRIM therapy.
• There are no other options
• But BACTRIM is associated with hemolysis in G6PD.
• Should the prescriber go forward?
• What level of “caution” is given?
  – Is it contraindicated?
Level of Admonition?

• Not a Contraindication
• Not a Warning
• A Precaution – Monitor Response

PRECAUTIONS

General: Prescribing Bactrim (sulfamethoxazole and trimethoprim) tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

BACTRIM should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).
New BBW & Warnings for 2013
Magnesium Sulfate IV

FDA Recommends Against Prolonged Use of Magnesium Sulfate to Stop Pre-term Labor Due to Bone Changes in Exposed Babies

Safety Announcement

[5-30-2013] The U.S. Food and Drug Administration (FDA) is advising health care professionals against using magnesium sulfate injection for more than 5-7 days to stop pre-term labor in pregnant women. This use of the drug is off-label, which means that it is not an FDA-approved use of the drug. Administration of magnesium sulfate injection to pregnant women longer than 5-7 days may lead to low calcium levels and bone problems in the developing baby or fetus, including thin bones, called osteopenia, and bone breaks, called fractures. The shortest duration of treatment that can result in harm to the baby is not known (see Data Summary).

In light of this new safety information about low calcium levels and bone problems in the developing baby, the following information is being added to the drug label for Magnesium Sulfate Injection, USP 50%:

- A new Warning stating that continuous administration of magnesium sulfate injection beyond 5-7 days in pregnancy for the treatment of pre-term labor can cause low calcium levels and bone changes in the baby.
Tolvaptan (Samsca) Liver Injury

- An oral selective vasopression V2-receptor antagonist indicated for the treatment of clinically significant hypervolemic and euvoletic hyponatremia [serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction], including in patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).
- Samsca was approved with a boxed warning that mandates drug initiation and re-initiation should entail close monitoring of serum sodium in a hospital setting. Too rapid correction of hyponatremia can cause osmotic demyelination syndrome which can cause neurological changes and result in coma or death.
Tolvaptan (Samsca) Liver Injury

FDA Drug Safety Communication: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death

Safety Announcement

[04-30-2013] The U.S. Food and Drug Administration (FDA) has determined that the drug Samsca (tolvaptan) should not be used for longer than 30 days and should not be used in patients with underlying liver disease because it can cause liver injury, potentially requiring liver transplant or death. Samsca is used to treat low sodium levels in the blood. An increased risk of liver injury was observed in recent large clinical trials evaluating Samsca for a new use in patients with autosomal dominant polycystic kidney disease (ADPKD)³ (See Data Summary). FDA has worked with the manufacturer to revise the Samsca drug label to include these new limitations.

The Samsca drug label has been updated to include the following information:

- Limitation of the duration of Samsca treatment to 30 days. (Dosage and Administration and Warnings and Precautions sections)
- Removal of the indication for use in patients with cirrhosis, a condition that involves scarring of the liver due to injury or long-term disease. Use of Samsca in patients with underlying liver disease, including cirrhosis, should be avoided because the ability to recover from liver injury may be impaired. (Indications and Usage and Use in Specific Populations sections)
Blue Skin with Ezogabine

Facts about Potiga

• Approved as adjunctive (added on to other anti-seizure medications) treatment of partial-onset seizures in adult patients 18 years and older.
• From marketing in April 2012 through February 2013, approximately 10,900 prescriptions were dispensed\(^1\) and approximately 2,900 patients received a dispensed prescription for ezogabine from outpatient retail pharmacies.

http://www.fda.gov/Drugs/DrugSafety/ucm349538.htm
Blue Skin with Ezogabine

FDA Drug Safety Communication: Anti-seizure drug Potiga (ezogabine) linked to retinal abnormalities and blue skin discoloration

Safety Announcement

[04-26-2013] The U.S. Food and Drug Administration (FDA) is warning the public that the anti-seizure medication Potiga (ezogabine) can cause blue skin discoloration (See photos in Appendix 1) and eye abnormalities characterized by pigment changes in the retina. FDA does not currently know if these changes are reversible. All patients taking Potiga should have a baseline eye exam, followed by periodic eye exams. FDA is working with the manufacturer to gather and evaluate all available information to better understand these events. FDA will update the public when more information is available.

Pigment changes in the retina have the potential to cause serious eye disease with loss of vision. It is not yet known whether the retinal pigment changes caused by Potiga lead to visual impairment, although several patients have been reported to have impaired visual acuity.

The skin discoloration in the reported cases appeared as blue pigmentation, predominantly on or around the lips or in the nail beds of the fingers or toes, but more widespread involvement of the face and legs has also been reported. Scleral and conjunctival discoloration, on the white of the eye and inside eyelids, has been observed as well. The skin discoloration generally occurred after four years of treatment with Potiga, but has appeared sooner in some patients (See Data Summary). In some cases, retinal abnormalities have been observed in the absence of skin discoloration.
Pre-Cancerous Lesions + Pancreatitis

FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes

[3-14-2013] The U.S. Food and Drug Administration (FDA) is evaluating unpublished new findings by a group of academic researchers that suggest an increased risk of pancreatitis, or inflammation of the pancreas, and pre-cancerous cellular changes called pancreatic duct metaplasia in patients with type 2 diabetes treated with a class of drugs called incretin mimetics. These findings were based on examination of a small number of pancreatic tissue specimens taken from patients after they died from unspecified causes. FDA has asked the researchers to provide the methodology used to collect and study these specimens and to provide the tissue samples so the Agency can further investigate potential pancreatic toxicity associated with the incretin mimetics.

Drugs in the incretin mimetic class include exenatide (Byetta, Bydureon), liraglutide (Victozta), sitagliptin (Januvia, Janumet, Janumet XR, Juvisync), saxagliptin (Onglyza, Kombiglyze XR), alogliptin (Nesina, Kazano, Oseni), and linagliptin (Tradjenta, Jentadueto). These drugs work by mimicking the incretin hormones that the body usually produces naturally to stimulate the release of insulin in response to a meal. They are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

FDA has not reached any new conclusions about safety risks with incretin mimetic drugs. This early communication is intended only to inform the public and health care professionals that the Agency intends to obtain and evaluate this new information. FDA will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report.

FDA previously warned the public about postmarketing reports of acute pancreatitis, including fatal and serious nonfatal cases, associated with the use of the incretin mimetic drugs exenatide and sitagliptin. A recently published study that examined insurance records also found the use of exenatide or sitagliptin could double the risk of developing acute pancreatitis.1 The Warnings and Precautions section of the drug labels and the patient Medication Guides for incretin mimetics contain warnings about the risk of acute pancreatitis. FDA has not previously communicated about the potential risk of pre-cancerous findings of the pancreas with incretin mimetics. Further, FDA has not concluded these drugs may cause or contribute to the development of pancreatic cancer.
QT and Azithromycin

FDA Drug Safety Communication: Azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms

Safety Announcement

[3-12-2013] The U.S. Food and Drug Administration (FDA) is warning the public that azithromycin (Zithromax or Zmax) can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias. This communication is a result of our review of a study by medical researchers as well as another study by a manufacturer of the drug that assessed the potential for azithromycin to cause abnormal changes in the electrical activity of the heart.

The azithromycin drug labels have been updated to strengthen the Warnings and Precautions section with information related to the risk of QT interval prolongation and torsades de pointes, a specific, rare heart rhythm abnormality. Information has also been added regarding the results of a clinical QT study which showed that azithromycin can prolong the QTc interval. (see Data Summary)
Health care professionals should consider the risk of fatal heart rhythms with azithromycin when considering treatment options for patients who are already at risk for cardiovascular events (see Additional Information for Health Care Professionals below). FDA notes that the potential risk of QT prolongation with azithromycin should be placed in appropriate context when choosing an antibacterial drug: Alternative drugs in the macrolide class, or non-macrolides such as the fluoroquinolones, also have the potential for QT prolongation or other significant side effects that should be considered when choosing an antibacterial drug.

FDA released a statement on May 17, 2012, about a New England Journal of Medicine (NEJM) study that compared the risks of cardiovascular death in patients treated with the antibacterial drugs azithromycin, amoxicillin, ciprofloxacin (Cipro), and levofloxacin (Levaquin), or no antibacterial drug.¹ The study reported an increase in cardiovascular deaths, and in the risk of death from any cause, in persons treated with a 5-day course of azithromycin (Zithromax) compared to persons treated with amoxicillin, ciprofloxacin, or no drug. The risks of cardiovascular death associated with levofloxacin treatment were similar to those associated with azithromycin treatment.
Zolpidem Dosing and Driving

Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)

Safety Announcement

[1-10-2013] The U.S. Food and Drug Administration (FDA) is notifying the public of new information about zolpidem, a widely prescribed insomnia drug. FDA recommends that the bedtime dose be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Today’s announcement focuses on zolpidem products approved for bedtime use, which are marketed as generics and under the brand names Ambien, Ambien CR, Edluar, and Zolpimist.

FDA is also reminding the public that all drugs taken for insomnia can impair driving and activities that require alertness the morning after use. Drowsiness is already listed as a common side effect in the drug labels of all insomnia drugs, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia drugs can experience impairment of mental alertness the morning after use, even if they feel fully awake.
Zolpidem Dosing Changes

Ambien (zolpidem tartrate tablets)

2 DOSAGE AND ADMINISTRATION

The dose of Ambien should be individualized

2.1 Dosage in Adults
The recommended dose for adults is 10 mg once daily immediately before bedtime. The total Ambien dose should not exceed 10 mg per day. Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness [see Warnings and Precautions (5.1)]. The total dose of Ambien should not exceed 10 mg once daily immediately before bedtime.

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMBIEN safely and effectively. See full prescribing information for AMBIEN.

Ambien (zolpidem tartrate) tablets C-IV
Initial US Approval: 1992

-------------------RECENT MAJOR CHANGES-------------------
Dosage and Administration (2) 4/2013
Dosage and Administration, Dosage in Adults (2.1) 4/2013
Warnings and Precautions (5) 4/2013

-------------------INDICATIONS AND USAGE-------------------
Ambien, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Ambien has been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)
5 WARNINGS AND PRECAUTIONS

5.1 CNS Depressant Effects and Next-Day Impairment

Ambien, like other sedative-hypnotic drugs, has central nervous system (CNS) depressant effects. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. Dosage adjustments of Ambien and of other concomitant CNS depressants may be necessary when Ambien is administered with such agents because of the potentially additive effects. The use of Ambien with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended [see Dosage and Administration (2.3)].

The risk of next-day psychomotor impairment, including impaired driving, is increased if Ambien is taken with less than a full night of sleep remaining (7- to 8 hours); if a higher than the recommended dose is taken; if co-administered with other CNS depressants; or if co-administered with other drugs that increase the blood levels of zolpidem. Patients should be cautioned against driving and other activities requiring complete mental alertness if Ambien is taken in these circumstances [see Dosage and Administration (2) and Clinical Studies (14.3)].
FDA is also warning that patients who take the sleep medication zolpidem extended-release (Ambien CR) —either 6.25 mg or 12.5 mg—should not drive or engage in other activities that require complete mental alertness the day after taking the drug because zolpidem levels can remain high enough the next day to impair these activities. This new recommendation has been added to the Warnings and Precautions section of the physician label and to the patient Medication Guide for zolpidem extended-release (Ambien CR).
Valproic Acid Risks to Fetus

FDA Drug Safety Communication: Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children

Safety Announcement

[05-06-2013] The U.S. Food and Drug Administration (FDA) is advising health care professionals and women that the anti-seizure medication valproate sodium and related products, valproic acid and divalproex sodium, are contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. Based on information from a recent study, there is evidence that these medications can cause decreased IQ scores in children whose mothers took them while pregnant.\(^1\) Stronger warnings about use during pregnancy will be added to the drug labels, and valproate’s pregnancy category for migraine use will be changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug).
Valproic Acid Risks to Fetus

With regard to valproate use in pregnant women with epilepsy or bipolar disorder, valproate products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable. Valproate products will remain in pregnancy category D for treating epilepsy and manic episodes associated with bipolar disorder.

With regard to women of childbearing age who are not pregnant, valproate should not be taken for any condition unless the drug is essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking valproate products should use effective birth control.

FDA is working with manufacturers to change the drug labels for valproate products with this updated risk information. FDA continues to evaluate information about the potential risks of valproate use during pregnancy and will update the public as more information becomes available.
Certain BBWs Are Linked to “REMS”

- An FDA mandate for post-marketing safety requirements
BBWs IN PATIENT CARE
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
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)

Commentary

“It appears that when there are specific, clear recommendations about what to do, when and how often, adherence to BBW warnings is high.

When monitoring or contraindication advice is not specific, the adherence observed in this and other studies is low.

The BBW is intended to represent the best public health and practice recommendations based on the available science. When, however, the evidence-base supporting how often laboratory monitoring should be performed is lacking (as one example), and there is no choice other than to provide non-specific recommendations, it should come as no surprise that actual practices vary widely.
Study 2

Adherence to Black Box Warnings for Prescription Medications in Outpatients

Karen E. Lasser, MD, MPH; Diane L. Seger, RPh; D. Tony Yu, MD, MPH; Andrew S. Karson, MD, MPH; Julie M. Fiskio, BS; Andrew C. Seger, PharmD; Nidhi R. Shah, MD, MPH; Tejal K. Gandhi, MD, MPH; Jeffrey M. Rothschild, MD, MPH; David W. Bates, MD, MSc

• 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

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