Black Box Warnings and Prescribing: What the APRN Needs to Know and Do

Kim Giberga MSN ARNP FNP-C RNPh
President, Excellence in Advanced Practice 02/2017

Boeing 777
- 0.4% planes have been involved in an accident that damaged the plane so further flight was not possible.
- The 2015 global jet accident rate (measured in hull losses per one million flights) was 0.32, the equivalent of one major accident for every 3.1 million flights.
- In the 21 years since the plane entered service, only six Boeing 777s have been written off, because of fire, crashes, or disappearances.

Boeing 777 Safety Back-ups
- 2 engines
- Computerized piloting systems
- Human pilot

Being admitted to the hospital is dangerous

Hospital Visits
- 37.5 million people admitted in 2008 in US.
- 800,000 deaths inpatient US hospital deaths in 2000.
- 91% of these due to ADRs estimated
- 72% these were avoidable

Air Travel
- 631,939,829 flights in US in 2010
- In 2017, no deaths due to commercial air travel in the US. Including cargo planes and props 79 deaths in the US (incl Puerto Rico)

Another way to look at it....

Most dangerous Profession in 2016: logging.
- 135.9 fatal injuries per 100,000 workers
- 0.14% fatality rate

Annual Hospitalizations in the US
- 524,160 deaths per 37,500,000 hospital visits
- 1.4% fatality rate
**Black Box Warnings**

- Black box warnings are the strictest labeling requirements that the FDA can mandate for prescription drugs.

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

Sertraline prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL is not approved for use in patients with dementia-related psychosis. (5.1)
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**History**

- First implemented in 1979, black box warnings highlight serious and sometimes life-threatening adverse drug reactions within the labeling of prescription drug products.
- These safety concerns are generally identified through the FDA’s Adverse Event Reporting System and Office of Surveillance and Epidemiology, which evaluates post-market safety data.
- Sometimes, however, a black box warning is handed down right at the time when a new drug is approved.

**How Common is This?**

- 1 million outpatient prescriptions 40% medications had a black box warning.
- 7% of medication prescriptions were written in violation of a black box warning.

**So.....?**

- Although black box warnings are not necessarily absolute contraindications, providers and pharmacists should be aware of these safety concerns when counseling patients.
- Count on the pharmacist, the television or friends and neighbors educating your patients if you do not.
- Increase patient compliance and protect yourself, document this warning was considered and labs will be monitored, or benefits outweighed risks etc. whatever you are doing to mitigate risk.

**Make sure you know if your EMR shows warnings**
Athena Doesn’t

Epocrates Does

Patient Provider Relationship

- This is an area we need to discuss with our patients to ensure they are
  - Knowledgeable
  - Prescribing Safely
  - Considering Risk/Benefit
  - Develop trust in our relationships with our patients

Metronidazole...really?

3 Times Black Box Warnings Are Used

1. They are used when an adverse reaction is so serious in comparison to the drug’s benefits that consideration is essential when assessing the risks versus benefits of the drug.
   - These warnings are typically used for potentially permanently disabling or fatal reactions.
     - For example, the risk of anaphylaxis with iron dextran injection justifies its use only when anemia is severe and refractory to oral therapy.

2\textsuperscript{nd} Instance

2. Boxed warnings are applied to drugs with the potential for serious adverse reactions that may be prevented or reduced in severity by appropriate prescribing or monitoring.

- This may include specific monitoring:
  - Labs: liver function tests for valproic acid (Depakene)
  - OR Patient Selection: avoidance of angiotensin-converting enzyme (ACEI’s) inhibitors in pregnant women.

3\textsuperscript{rd} Instance

3. The FDA issues boxed warnings for drugs with mandatory restrictions to ensure safe use.

- In this case the FDA approved the drug with restrictions to ensure safe use because FDA believes the drug can be safely used only if distribution or use is restricted
  - Patient selection
  - Managing concomitant therapy
  - Addition of another drug
  - Avoiding use in certain situations
- Example: providers must complete a certification program before prescribing isotretinoin (formerly Accutane).
- Example: chemotherapeutic agents, may be administered only in supervised or inpatient settings.

Should I prescribe medications with black box warnings?

- Yes, when...
  - the benefit outweighs the risk.
  - If there are no other good alternatives

When you do....

- Chart notes that the warning was reviewed with pt. and Be SPECIFIC...
  - For example with anticoagulant therapy: Reviewed SERBs including:
    - increased risk of bleeding with pt and pt verbalizes understanding, will report to ER with coffee grounds in emesis, jelly in stool, MVA or fall or other injury

When you do...

- Include thoughtful response to black box warning in plan of care that includes benefit and risks:
  - Fluoroquinolones: urinary culture shows pseudomonas resistant to everything except Cipro...Pt prescribed Cipro per results of urinary culture, reviewed risks of tendon rupture, possible, rare CNS side effects with pt. Pt will abstain from high impact sports for 12-26 weeks following Cipro, will call if any sensory/motor changes.'

Classes and Individual Drugs

- Some boxed warnings apply to individual drugs, and others apply to entire classes (i.e. fluoroquinolones)
### Common drug classes with Boxed Warnings

- Antidepressants
- Antipsychotics
- Atypical Antipsychotics
- Fluoroquinolones
- ACEIs
- ARBs
- Loop Diuretics
- Beta blockers

### Rivaroxaban (Xarelto), Apixaban (Eliquis) Fondaparinux (Arixtra)

#### Tx Discontinuation
- Increased thrombotic event and stroke risk when D/C rivaroxaban before completion of tx course; if must D/C rivaroxaban for reasons other than pathological bleeding or completion of tx course, consider administering another anticoagulant

#### Epidural/Spinal Hematoma Risk
- Epidural/spinal hematoma risk after neuraxial anesthesia or spinal puncture in anticoagulated pts; hematoma may result in long-term or permanent paralysis; incr. risk if indwelling epidural catheter use, concomitant use of drugs affecting hemostasis incl. NSAIDs, platelet inhibitors, or other anticoagulants, traumatic or repeated epidural or spinal puncture hx, spinal deformity, or spinal surgery hx; consider benefit vs. risk before neuraxial intervention in anticoagulated pts or planned anticoagulation for thromboprophylaxis; while optimal timing to minimize risk is unknown, delay epidural catheter removal >18h (for pts 60-76 yo, delay removal >26h) after last rivaroxaban dose and delay rivaroxaban >6h after catheter removal; delay rivaroxaban 24h if traumatic puncture occurs; monitor sx neurologic impairment, treat urgently if needed

### Anticoagulant Therapy

- **Document:**
  - PT denies recent injury, no epistaxis, no GI bleeding, no blood noted in stool or hematuria. Pt will call clinic STAT should this change. Pt understands the risks associated with anticoagulant therapy and will report to ER if injury/MVA occurs.
  - Pt understands will not take OTC NSAID's or ASA without approval from Prescribing provider.
  - Pt understands the need for monitoring and agrees to be compliant with monitoring and will be available for follow-up.

### Clopidogrel

- Does anyone know the Black Box Warning on Clopidogrel?

#### Diminished Antiplatelet Effect in CYP2C19 Poor Metabolizers

- Clopidogrel antiplatelet effect dependent on conversion to active metabolite by CYP450 enzymes, principally CYP2C19;
  - pts homozygous for nonfunctional alleles of CYP2C19 gene (CYP2C19 poor metabolizers) formed less active metabolite and had reduced anti-platelet activity at recommended doses;
  - CYP2C19 genotype tests are avail. to identify CYP2C19 poor metabolizers
  - Consider using other platelet P2Y12 inhibitor tx in CYP2C19 poor metabolizers
CYP2C19 Poor Metabolizers

- 3–5% of Caucasians and 15–20% of Asian populations are poor metabolizers with no CYP2C19 function
- 10% of drugs
  - PPI’s
  - Antiseizure drugs such as mephenytoin
  - Antimalarial proguanil
  - Anxiolytics Diazepam (Valium), lorazepam (Ativan), oxazepam (Serax), and temazepam (Restoril)

Promethazine

- Respiratory Depression:
  - contraindicated in pts <2 yo due to cases of resp. depression, some fatal incidents, at wide-range of wt-based doses;
  - 2 yo and older, use w/ caution at lowest effective dose, avoid combo w/ other resp. depressant drugs
- Severe Tissue Injury, Gangrene: promethazine injection can cause severe chemical irritation and tissue damage including burning, pain, thromboembolitis, tissue necrosis and gangrene regardless of administration route; may result from perivascular extravasations, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration; some cases require surgical intervention

Promethazine

1. Don’t give by IV
2. Don’t give with other respiratory depressants
3. Don’t give to under 2yo.
4. If you do carefully consider other options and document why this is the best choice for this patient.

Case Study

- 32 yo female presents for spontaneous bruising for 5 years on lower extremities.
- Pt hx of bipolar on lamotrigine, risperidone
- PCP has been evaluating for >1 year no conclusive results
- Labs WNL, further labs done x 3 sets (pt not sure what was done each time) TSH mildly abnormal 4.5-4.8 resolved with low dose synthroid.
- Social history: mother of 1 ½ year old twins, does not work outside the home

On Further Questioning....

- US screening shows no vessel abnormalities under bruises.
- Further questions: has been on risperidone 6 months, lamotrigine for 5 years, shortly after started lamotrigine developed bruising.

Lamotrigine Causes Serious Skin Reactions

- Lamotrigine (Lamictal) is an antiepileptic drug indicated for the treatment of epilepsy and bipolar disorder.
- Lamotrigine has a black box warning for causing cases of life-threatening serious rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and/or rash-related death.
- The rate of serious rash has been greater in pediatric patients than adults.
- Additional factors that may increase the risk of rash include co-administration with valproate and exceeding the recommended initial dose or dose escalation of Lamotrigine.
Lamotrigine Cont.

• Although Lamotrigine may also cause benign rashes, the prescribing information states that it is not possible to predict which rashes will prove to be serious or life-threatening. Therefore, the medication should be discontinued at the first sign of rash, unless it is clearly not drug-related.

Stevens-Johnson

• Type of severe hypersensitivity reactions involving the skin and mucous membranes.
• Early symptoms include fever and flu-like symptoms: cough, headache, arthralgias, malaise
• A few days later the skin begins to blister and slough forming painful raw areas.
• Complications include dehydration, sepsis, pneumonia, ocular involvement, and multiple organ failure, potentially fatal.
• Toxic epidermal necrolysis (TEN) >30% BSA.

How Common is This?

• The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately
  • 0.3% to 0.8% in pediatric patients
  • 0.08% to 0.3% in adults
If pt. develops rash while on lamotrigine...

- A rash that is confluent and widespread OR purpuric or tender
- With any prominent involvement of neck or upper trunk; any involvement of eyes, lips, mucus membranes etc.
- With any associated fever, malaise, pharyngitis, anorexia, or lymphadenopathy
- With abnormal laboratory tests: CBC, liver function, kidney function tests

Yes, this lamotrigine associated rash could be SJS....now what?

- Stop lamotrigine (and valproate if administered)
- If pt calls to report rash via phone have pt come in to office promptly to evaluate.
- Monitor and investigate organ involvement (hepatic, renal, hematologic) – CBC, CHEM12
- Patient may require hospitalization.
- Monitor patient very closely and discontinue lamotrigine.

Case Study

- 56 yo inpatient female hx of depression, multiple suicide attempts lamotrigine added to other sertraline and buspirone. Lamotrigine added 25mg PO QD gradually increased to 50mg PO QD over 2 week taper.
- Her anxiety and depressive symptoms showed significant improvement on this combination and she started feeling almost back to her normal self so discharged.
- 16 days after d/c developed conjunctivitis, 3-4 days later develops erosions of the oral mucous membranes, papules – bullae on hands and feet start sloughing on Day 4. ER-ICU stopped lamotrigine, General recovery after 14 days, a few more weeks for full ophthalmic recovery.

Combination Oral Contraceptives

- Warning: Smoking and Cardiovascular Events
  - Cigarette smoking increases risk of serious cardiovascular side effects from combination OCPs;
  - Increased risk w/ age (particularly for women >35 yo) and w/ number of cigarettes smoked
  - Contraindicated in smokers >35 yo
  - Combination oral contraceptives such as Alesse, Beyaz, Loestrin, Ocelia, Yaz, and Zarah include an estrogen and a progestin to prevent pregnancy.
  - Risk increases with age and number of cigarettes smoked.

What is the risk?

- The use of combined oral contraceptives (COCs) is associated with approximately
  - 2x Arterial Risk
    - The risk of myocardial infarction does not correlate to the length of therapy and disappears after treatment termination.
  - 4x increased relative risks of venous thromboembolic events
    - The highest risk of venous thromboembolism occurs in the first year of use.
    - If they make it to 4 years without VTE, the risk is reduced to only 2.76x.
    - Stopped WHI branch early researching COC’s.

Age as a Risk Factor

- Current users of Combined Oral Contraceptives, >35 years estimated increased risk of Venous thromboembolism
  - 2.5x increased risk in <35 years COCs non-users.
  - 10x increased risk >35 and COCs users.
The Tobacco Risk Factor

- COCs users, who are current smokers
  - 10x increased risk of myocardial infarction.
  - 3x increased risk of stroke.

Combination Oral Contraceptives

- So a patient over 35 who smokes...
  - Options:
    1. Alternative OCP progestin
    2. Don’t prescribe
    3. Thoughtful prescribing — document why alternatives failed and that pt was counselled on CV events and risk mitigated via?
      1. Do you want to know their family hx of heart disease
      2. Cardiac eval?
      3. Framingham score documented
      4. If pt is tobacco user, will PT attempt to stop tobacco use/decrease number of cigarettes smoked?

Estrogen: Black Box Warning I

- Endometrial Cancer Risk:
  - unopposed estrogen use incr. risk if intact uterus
  - adding progestin may decr. risk of endometrial hyperplasia (possible precursor to endometrial CA)
  - use adequate diagnostic measures such as endometrial sampling to rule out malignancy if undiagnosed persistent or recurrent abnormal genital bleeding

Estrogen: Black Box Warning II

- Cardiovascular and Other Risks
  - estrogens +/- progestins not indicated for cardiovascular dz or dementia prevention
  - Increased risk of stroke and DVT [from WHI estrogen-alone sub-study] and MI, stroke, PE/DVT, and invasive breast CA [from WHI estrogen/progestin sub-study] in postmenopausal women
  - Increased risk of probable dementia in postmenopausal women 65 yo and older on a WHI regimen x4 - 5y
    - WHI regimens = conj. estrogens 0.625 mg/day w/ or w/o medroxyprogesterone 2.5 mg/day, other doses or estrogen/progestin combos not studied, but assume similar risk.

Estrogen

- Document:
  - SERB’s reviewed with pt the risk for cardiovascular events, consider documenting Framingham Risk Score, Personal/Fam HX CVD. PT will call with abnormal/unexpected uterine bleeding, fam hx breast cancer,
  - Use lowest effective estrogen dose, shortest duration based on individual tx goals and risks

Contraception

- For every pt...
  - Document:
    - SERB’s reviewed with pt, pt voices understanding and has had all questions answered.
    - PT has no known 1st degree fam hx of VTE
    - PT denies tobacco use
    - PT will report to ER with CP, SOB
    - PT will call provider with unexplained leg pain or swelling
Case Study: Fluoroquinolones

• 42yo female presents to ER cc: generalized pain, medical hx notable only for current UTI with ciprofloxacin on Day 1 treatment. Clinical examination unremarkable.
• PT reassured and advised to finish the 5-days antibiotics. Her symptoms persisted 3 weeks and she was referred for a rheumatological opinion.
• She described feeling that the tendons of her hands, left knee and left ankle were “inflamed”. She had morning stiffness lasting 30 minutes and the pain was worse at the end of the day. She had pain on walking and performing simple tasks with her hands. There was no joint swelling and she denied other symptoms. She used ibuprofen as required for symptom control.

Examination of the hands revealed tenderness of the flexor and extensor tendons with poor grip secondary to pain. The patellar and Achilles tendons were tender to palpation but no swelling was detected. There was no swelling or tenderness of her peripheral joints.
• Labs revealed normal inflammatory markers, renal and liver biochemistry and CBC. Autoimmune serology was negative.
• Ultrasound examination of her Achilles tendons showed no evidence of a tendon tear or rupture.

A diagnosis of ciprofloxacin-related tendinopathy was made.
• She was treated with ibuprofen PRN and PT
• Her symptoms improved after 3 weeks and completely resolved after 4 months.

In July 2008, the FDA issued a boxed warning describing an increased risk of tendinopathy and tendon rupture in patients taking fluoroquinolone antibiotics. The risk is greatest for:
• Adults older than 60 years
• Patients taking corticosteroids
• Transplant recipients.
• The accompanying product information counsels prescribers to consider alternatives in patients with multiple risk factors for tendon rupture and to discontinue use in patients who develop tendon pain or inflammation during treatment.

Avoid in Myasthenia Gravis
• fluoroquinolones may exacerbate muscle weakness in pts w/ myasthenia gravis

Fluoroquinolones: BBW’s Besides Tendinopathies

Reserve Fluoroquinolone Use
• for pts w/ no alternative tx options for acute bacterial sinusitis or acute bacterial exacerbation of chronic bronchitis

Fluoroquinolones: Not so Fun Facts

1. As of February 2014, about 45,000 individual cases of fluoroquinolone damage has been reported to the FDA.
2. The FDA states that only 1%-5% of the actual number of adverse reactions that occur are reported
3. Estimates 4 out of 100,000 will have tendon rupture.
4. Achilles is most often tendon damaged
5. Tendon rupture/tendonitis Levaquin >Cipro
6. Most ruptures occur towards end of 7-10 day course of antibiotics but can be as early as few hours after first dose up to 6 months after antibiotic therapy is completed.
Fluoroquinolones

- Few studies done to assess numbers affected: One population-based case-control study found that 5,958 patients need to be treated with fluoroquinolones to cause one case of Achilles tendon rupture.
- The number needed to harm (NNH)
  - decreases with concomitant corticosteroid use (NNH = 979)
  - and age greater than 60 years (NNH = 1,638)
- Tendon injury can occur as early as two hours after the first dose and as late as six months after treatment ends.

Symptoms of Fluoroquinolone Associated Tendinopathy

- The most common presenting complaint of fluoroquinolone-associated tendinopathy is acute onset pain
- Other symptoms include swelling, warmth, tenderness, erythema or itchiness over tendon sites and functional disability. Bilateral involvement is common.
- Clinical findings include tendon swelling, thickening or edema

Fluoroquinolones more....

- According to the package labeling, fluoroquinolones should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon.
- Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and then contact their health care provider about potentially switching to a different antimicrobial drug class.

Fluoroquinolones and How They Work

- Fluoroquinolones inhibit two bacterial enzymes, DNA gyrase and topoisomerase IV, which have essential and distinct roles in DNA replication.
- The quinolones bind to the complex of each of these enzymes with DNA; the resulting complexes, including the drug, block progress of the DNA replication enzyme complex.
- Ultimately, this action results in damage to bacterial DNA and bacterial cell death.
- Thus, fluoroquinolones are bactericidal agents.
- FQ’s are the only antibiotics that directly inhibit DNA synthesis.

Fluoroquinolones: The Saga Continues

- In 2013, FDA increased warning to include risks of potentially irreversible peripheral neuropathy, has led to disabilities.
- Neurology journal published a study in 2014, researchers evaluated a large group of male subjects and were able to determine that the risk of peripheral neuropathy was actually doubled in those individuals who had been placed on fluoroquinolone antibiotics.
- In 2016, FDA warning revised: “These medicines [FQ’s] are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient.

FQ Tendinitis vs. Tendinitis

- Tendinitis: inflammation of tendon
- FQ tendinitis:
  - FQ’s may cause nutritional depletion esp. Magnesium
  - FQ’s can cause mitochondrial damage/decrease in mitochondrial numbers
  - FQ’s can cause damage to DNA –things don’t heal properly
  - Because these changes aren’t corrected when antibiotic clears, tendinitis, CNS side effects may last for years

http://n.neurology.org/content/83/14/1261.short
Fluoroquinolones: The Saga Continues

- In 2017, as part of our ongoing review of fluoroquinolone antibiotics, FDA is informing the public that patient cases identified by the FDA and findings from published studies currently do not support reports that these medicines may result in detachment of the retina in the eyes, or bulges or tears in the aorta blood vessel called aortic aneurysm and aortic dissection. We will continue to assess safety issues with fluoroquinolones and will update the public if additional actions are needed.

http://n.neurology.org/content/83/14/1261.short

Fluoroquinolones July 10, 2018

- New class-wide warning that must be included on the label but is NOT black box, regarding:
  - Mental health side effects
  - Include Disturbances in Attention, Disorientation, Agitation, Nervousness, Memory impairment and delirium
  - Potential hypoglycemia reactions
  - Hypoglycemic Coma
  - FAERS 67 pts, 20 were not on any DM meds; 13 of the 67 died.
  - Elderly and People on ANY diabetes medications.
  - Suggestion: Have pts on DM meds and FQ’s increase bg monitoring. Review symptoms of hypoglycemia with all pts.

Fluoroquinolones: Most commonly Used For:

- UTI's
- Sinusitis
- Pneumonia
- Do you want to use this in pts. with myasthenia gravis? MS? Neuropathies?
  - Diabetes
  - Peripheral Neuropathy
  - Venous
  - Medication Induced
  - Idiopathic

Fluoroquinolones: Recommendations for Athletes

- Athletes should reduce training volume by 60% during first 7 days of therapy.
- Resume high intensity activities 2-4 weeks post end of FQ therapy.
- No competitions during this time.
- Pain over tendon esp Achilles 6 months after FQ therapy should have us exam done.
- Return to play depends upon clinical response and averages 6 to 12 weeks

Actos and Avandia Cause or Exacerbate Congestive Heart Failure

- Pioglitazone (Actos) and Rosiglitazone (Avandia) are thiazolidinediones indicated for the treatment of type 2 diabetes mellitus.
- Black Box Warning: thiazolidinediones cause or exacerbate CHF, observe pts closely after tx initiation or dose incr. for s/x incl.
  - excessive, rapid wt gain,
  - dyspnea, and/or edema
  - manage CHF based on current care standards if s/x develop and consider D/C or dose reduction
  - contraindicated in pts w/ NYHA Class II-IV CHF and not recommended in pts w/ symptomatic CHF

Pioglitazone (Actos) and Rosiglitazone (Avandia)

- If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the medications must be considered.
- New Rx’s and refills
  - Assess and document SOB, sleep laying down or with pillows, talking in complete sentences, peripheral edema
  - Do you want to document history or lack of history of htn, compliance with htn meds? Make sure weight is documented and reviewed every visit.
  - SERB’s reviewed including pt will report any SOB, changes in stamina, fatigue, peripheral edema
Liraglutide (Victoza)

- Thyroid C-cell Tumor Risk
- Contraindicated in pts with history of or family history of medullary thyroid carcinoma (MTC) or in pts w/ multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Document and counsel pts on potential MTC risk and thyroid tumor sx (e.g., neck mass, dysphagia, dyspnea, persistent hoarseness)

Canagliflozin (Invokana)

- Lower Limb Amputation Risk
- 2x increased risk of leg and foot amputations in pts w/ type 2 DM w/ established cardiovascular disease or those at risk.
- Toe and midfoot amputations most frequent, though leg amputations observed; some pts had multiple amputations, some involving both limbs.
- Document and consider risk factors incl. prior amputation hx, PAD, neuropathy, diabetic foot ulcers prior to tx start; monitor for infection, new pain or tenderness, sores or ulcers involving lower limbs; D/C if complications occur

Antipsychotics

- Haloperidol
- Loxapine
- Mellaril (thioridazine)
- Moban (molindone)
- Navane (chlorophenazine)
- Prolixin (fluphenazine)
- Serentil (mesoridazine)
- Stelazine (trifluoperazine)
- Triafon (perphenazine)
- Thorazine (chlorpromazine)

- Atypical antipsychotics
- Abilify (aripiprazole)
- Clozaril (clozapine)
- Geodon (ziprasidone)
- Risperdal (risperidone)
- Seroquel (quetiapine)
- Zyprexa (olanzapine)

Atypical Antipsychotics Increase Risk of Death in Elderly Patients with Dementia-Related Psychosis

- In 2005, the FDA issued a black box warning for atypical antipsychotics, including quetiapine (Seroquel), olanzapine (Zyprexa), and risperidone (Risperdal), stating that elderly patients with dementia-related psychosis who are treated with these drugs face an increased risk of death.
- Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed that drug-treated patients had between 1.6 to 1.7 times the risk of death of placebo-treated patients. Although the causes of death varied, most appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Antipsychotics: Quetiapine, Risperidone, Haloperidol, Olanzapine

- Black Box Warning: Increased mortality in elderly patients with dementia-related psychosis
- Monitor patients for improvement of dementia-related target symptoms.
- Antipsychotics are to be used for the shortest duration at the lowest dose possible in older adults with dementia.
- The need for a gradual dose reduction should be re-assessed periodically.

Antidepressants Raise Suicidality Risk

- In 2004, the FDA issued a black box warning for all antidepressants indicating an association with an increased risk of suicidal thinking, feeling, and behavior in young individuals.
- Meta-analyses of 372 randomized clinical trials involving nearly 100,000 participants, which showed that the rate of suicidal thinking or suicidal behavior was 4% among patients assigned to receive an antidepressant, compared with 2% among those assigned to receive placebo.
- Subsequent age-stratified analyses showed that this increased risk was significant only among children and adolescents younger than 18 years, as there was no evidence of increased risk among adults older than 24 years, including those older than 65 years.
**Antidepressants and Suicide: More Info....**

- Patients of all ages who are started on antidepressant therapy should be monitored closely for emergence and worsening of suicidal thoughts and behaviors.
- Additionally, families and caregivers should be advised of the need for close observation and communication with the prescriber.
- The FDA’s decision to implement this black box warning was controversial.

**Antidepressants**

- Document negative for suicidal ideation (after evaluating) reviewed increased risk of SI with pt, pt will call or report to ER with suicidal ideation. Risk of increased suicidal ideation and warning signs of suicide reviewed with ______Sally, pt mother, Sarah LVN pt caretaker, Robert Pt spouse, by pt cell phone 01/12/18 10:06am.

**Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers**

- Enalapril, Lisinopril, Irbesartan, valsartan, losartan
- Warning: Injury or death to developing fetus
- If this is the best medication to give to woman of childbearing years, document method of birth control being used, patient agrees before attempting to conceive medication therapy will need to be re-evaluated

**Beta-Blockers**

- Metoprolol, atenolol, propranolol,
- Warning: Exacerbation of Angina and risk of MI with abrupt discontinuation
- Discuss and Document: SERB's reviewed with patient, pt. understands this medication can not be abruptly stopped. Pt will contact provider if before discontinuing this medication.
- Consider: Documenting personal history, fam hx of cardiac disease, Framingham score. Do you want to prescribe in one month or 90 days for this one?
- Taper this medication to d/c if possible.

**Loop Diuretics**

- Furosemide, bumetanide
- Warning: Volume and electrolyte depletion
- Individualize dose.
- Document: Schedule to monitor labs, Reviewed with patients risk and symptoms of orthostatic hypotension, low potassium (weakness, N/V/D, fatigue, palpitations, ) pt with call office with any of these symptoms.
- Geriatric patients will be at increased risk of falls first two days after initiation and dosage adjustment.
**Decision Making Fatigue**

- Doctors were 13 percent more likely to prescribe an antibiotic in the 13th appointment of a day and 19 percent more likely by the 24th appointment. The data mirrors similar 2014 findings published in JAMA Internal Medicine and recently summarized in the New York Times.
- Is this decision making fatigue or talking with patient all day fatigue?
- We need to be more vigilant as the day progresses and make more of an effort later in the day.

**Remember...**

- Despite any warning, black box or otherwise, all of these medications remain viable treatment options with appropriate patient selection.
- Ultimately, providers must decide whether to prescribe drugs with boxed warnings.
- Reconsider samples.
- Consider electronic prescriptions.

**Asiana Airlines**

- July 2013
- First fatal accident since aircraft put on the market in 1995
- Of the 307 people aboard, two passengers died at the crash scene, and a third died in a hospital several days later; all three of them were teenage Chinese girls. Another 187 individuals were injured, 49 of them seriously.
- 117 people walked away with no injuries.
Resources

There is growing interest in making evidence-based information about drugs available to prescribers, patients, and policy makers.

One such initiative, the Drug Effectiveness Review Project (DERP), is a collaboration between several states, the Oregon Evidence-Based Practice Center, and the Center for Evidence-Based Policy. DERP issues systematic reviews of drug effectiveness and safety (http://www.ohsu.edu/drugeffectiveness).

These reviews are used by the Consumers Union to produce Consumer Reports Best Buy Drugs for patients (http://www.consumerreports.org/health/best-buy-drugs/index.html).

Resources such as DERP can provide providers with the evidence and context needed to confidently evaluate new drugs, drugs with boxed warnings, and their alternatives.

Thank You!

• Kim Giberga
• Giberga@sbcglobal.net

Works Cited


