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Boxed Warnings

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Conflicts of Interest

- I have no conflicts of interest related to this topic except,
  - I am a friend of Andrew Mulberg (FDA)
  - I shared a sandwich with Richard Vesely (EMA)

Mission of the FDA

- "FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devises, our nation's foods supply, cosmetics, and products that emit radiation"

FDA Approval Process

- Evaluation of new drugs
  - Phase 1: Volunteers without the disease to assess safety and dose ranging
  - Phase 2:Individuals with the disorder to assess efficacy, dosing and safety
  - Phase 3: Patients are treated to evaluate safety and efficacy in blinded, randomized, placebo-controlled trial
- Indentifying Rare events (<1:5,000) may not occur in Phase 3.
  - Post-approval (phase 4): MedWatch
  - MedWatch at www.accessdata.fda.gov/scripts/medwatch

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Black Box or Boxed Warning

Warning placed on the package insert by the U.S. Food and Drug Administration signifying that a drug has a significant risk of serious adverse advents.

"Learn to know the **Dark Side** of the Force …"
D. Vater

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Examples of boxed warnings in the past decade

- Antidepressant medications: suicidal tendencies in children
- Celebrex (celecoxib): cardiovascular and GI risks
- Depo-Provera: bone loss
- Warfarin: fatal hemorrhage
- Methylphenidate: cardiovascular risk. Pediatric Advisory Committee rejected the warning for cardiac and psychiatric events
- Fluoroquinolone:tendon ruptures and tendinitis
  - Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin,ofloxacin
- Meloxicam (non-steroidal anti-inflammatory): Cats

CDER 2006 Meeting Documents". U.S. Food and Drug Administration. February 1, 2007. Retrieved 2007-08-15. FDA orders 'black box' label on some antibiotics". *CNN*. 2008-07-08. Retrieved 2008-07-08.

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When to Use a Boxed Warning (I)

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug
  - Anti-TNF agents:hepatocellular T cell lymphoma

7

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When to Use a Boxed Warning (II)

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)
  - Avoid concomitant use of azathioprine or 6-mercaptopurine with anti-TNF agent in boys and young men. Change in clinical practice.

8

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Anti-TNF Agents

Infections: Tuberculosis, invasive fungal infections: histoplasmosis, coccidiodomyocisis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis.

Hepatosplenic T-cell Lymphoma: progression of disease to death. Majority adolescent or young adult males. All patients received an immunomodulator—azathioprine or 6-MP.

9

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When to Use a Boxed Warning (III)

- FDA approved the drug with the restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.
  - Restricted use
    - Natalizumab (progressive multifocal leukoencephalopathy—usually leads to death or severe disability)
    - Thalidomide (birth defects)

10

BOXED WARNING: Fluoroquinolones

- Fluoroquinolone products may exacerbate muscle weakness in persons with myasthenia gravis. Avoid fluoroquinolone products in patients with known history of myasthenia gravis
- **WARNINGS AND PRECAUTIONS**
- **Exacerbation of myasthenia gravis**
- Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis.

11

Risk of fluoroquinolone-associated Myasthenia Gravis Exacerbation February 2011 Label Changes for Fluoroquinolones

- Avelox (moxifloxacin hydrochloride) tablets and Avelox (moxifloxacin hydrochloride in NaCl injection) I.V.
- Cipro (ciprofloxacin hydrochloride) Tablets, Oral Suspension, IV and Cipro XR (ciprofloxacin extended-release tablets)
- Noroxin (norfloxacin) Tablets
- Levaquin (levofloxacin) Tablets, Oral Solution and Injection
- Proquin XR (ciprofloxacin) Extended-Release Tablets
- Floxin (ofloxacin) Tablets
- Factive (gemifloxacin mesylate) Tablets

12

BOXED WARNING

- **WARNING:**
- **Fluoroquinolones, including ciprofloxacin, 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**

13

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Impact of Boxed Warnings

- Effects of Boxed Warning on prescribing practices
  - Does the warning impact use?
    - Rosiglitazone use decreased by 70% related to media exposure and scientific publications
    - Pioglitazone received a similar warning, but did not have the same media exposure and use did not decrease
- Physician-patient interaction may not be driving practice

14 Cohen A, et al. Diabetes care 2010;33:823-825.

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Lessons Learned

- Pay attention to Boxed Warnings
- Communicate these findings with your patients discussing not only the risks but also the benefits
- MedWatch is a failed system
- We need much better safety registries for children who are not “little adults”

15

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