PHARMACOPHOBIA- ADDRESSING RISKS, WARNINGS, AND COUNTERFEITS

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DISCLOSURES

- I have no financial disclosures
- Any opinions expressed are my own, and do not represent any government agency
- The use of brand names of medications does not reflect an endorsement of any particular drug product or pharmaceutical manufacturer

CONTRIBUTORS TO PATIENT MEDICATION FEARS

- Clickbait news headlines
- Direct to consumer pharmaceutical advertising with lengthy side effect lists
- Tort lawsuit commercials
- Social Media Misinformation
- Political or ideological views about medications
- General distrust of government agencies

OBJECTIVES

- Review landmark legislation for medication safety in the United States
- Discuss Boxed Warnings and REMS programs, and their impacts to patient care
- Review adverse drug reactions and reporting
- Discuss medication management during a medication recall
- Consider counterfeit medications and their impact on patients

BRIEF HISTORY OF MEDICATION REGULATION IN THE US

- Pure Food and Drug Act of 1906
  - Encouraged by public outcry following the Upton Sinclair novel, *The Jungle*
  - Prohibited medications in interstate commerce from being adulterated or misbranded
  - Did NOT grant authority to ban unsafe medications

Adulterated

- A medication that fails to conform to compendial standards of quality, strength, or purity

Misbranded

- Labeling is false or misleading in any manner related to the drug's identity

SULFANILAMIDE DISASTER

- Bacterial infections were a common cause of death in early 1900s

- Sulfanilamide was discovered and marketed for streptococcal infections
  - Used successfully in tablet form with no ill effects

- S.E. Massengill Company reformulated sulfanilamide as a liquid for children
  - Chief chemist used diethylene glycol as a solvent and flavored with raspberry extract
  - Product is very bitter- diethylene glycol has a sweet taste
  - Internal testing at S.E. Massengill evaluated flavor, color, and smell
  - 240 gallons were manufactured and shipped across the country, labeled as Elixir Sulfanilamide

1. ABOOD, ET AL. PHARMACY PRACTICE AND THE LAW
2. WAX PM. (1995)

SULFANILAMIDE DISASTER

- MDs begin reporting patient deaths to the American Medical Association

- Cause of deaths traced to diethylene glycol
  - An industrial solvent
  - Causes kidney failure with no antidote at the time

- 107 deaths attributed to this product
  - S.E. Massengill stated they could not reasonably predict their product would cause death

- Could not be removed from market for being unsafe, but could be removed for being misbranded
  - Elixirs must contain alcohol- Elixir Sulfanilamide did not
  - S.E. Massengill paid a fine for misbranding violation

1. ABOOD ET AL. PHARMACY PRACTICE AND THE LAW
2. WAX PM (1995).

FOOD, DRUG, AND COSMETIC ACT OF 1938

- The basis for today's medication regulation laws
- Required drug manufacturers to submit a new drug application with safety data to the FDA prior to medication approval
- Tightened requirements for medication labeling- active ingredients must be disclosed on the label
- Medication labels must disclose if a medication is habit forming
- Medication labels must contain adequate directions for use

- Limitations
  - Did not require medications already approved to demonstrate safety
  - FDA only had 60 days to review a medication

1. ABOOD ET AL. PHARMACY PRACTICE AND THE LAW
3. BREN, L (2001).
4. FDA HISTORY MILESTONES

DISASTER AVERTED

- FDA received application for a new drug, Kevadon (thalidomide) in 1960
  - Widely used in Europe for anxiety and insomnia
  - Given to pregnant women to treat morning sickness

- Assigned to reviewer Frances Kelsey at the FDA
  - Required additional safety data after hearing reports of peripheral neuropathy
  - Repeatedly rejected pressure from the drug manufacturer to approve the medication

- Thalidomide linked to severe birth defects in Europe
  - Babies born with phocomelia and other related defects
  - Drug makers rapidly withdrew the drug from European markets

- Led to passage of Kefauver-Harris Amendment in 1962
  - Required medications to be safe AND effective

3. BREN, L. (2001)
4. FDA HISTORY MILESTONES

OTHER SAFETY REGULATIONS

- Poison Prevention Packaging Act of 1970
  - Child resistant packaging on prescription medications

- Antitampering Act of 1983
  - Influenced by The Tylenol Murders
    - Required tamper-evident packaging on OTC medications
  - Made it a Federal Crime to tamper with consumer products

- Waxman-Hatch Amendment of 1984
  - Streamlines approval process for generic medications

- Dietary Supplement Health and Education Act of 1994
  - Dietary supplements are regulated more as foods than as drugs

- Drug Supply Chain Security Act of 2013
  - To maintain integrity of the drug supply in the US

CLINICAL TRIALS PROCESS

Phase I
- Investigational New Drug
- Small group of healthy volunteers
- Mainly to identify adverse effects and pharmacokinetics

Phase II
- Larger group of participants with condition being treated
- Focuses on effectiveness
- Upon completion, FDA meetings to discuss continuing trials

Phase III
- Much larger treatment population
- Continue to prove effectiveness plus determine dosing
- Once complete, New Drug Application filed with FDA for approval

Post-marketing
- Monitor safety reports for adverse events
- Labeling may be updated from post-market data

Typically takes **YEARS** to bring a new medication to market.

Drug makers file for **patent approval** during approval process

Process can be expedited for rare diseases or first-in-class medications at the discretion of the FDA

MEDICATION LABELING

When a medication is approved for the US Market, the FDA reviews the medication labeling and package insert to ensure accuracy and compliance with the Code of Federal Regulations

Over 40 required pieces of information must be included in a medication label, and in a set order

The package insert is typically the most unbiased source of information about any medication

Available for any medication at fda.gov

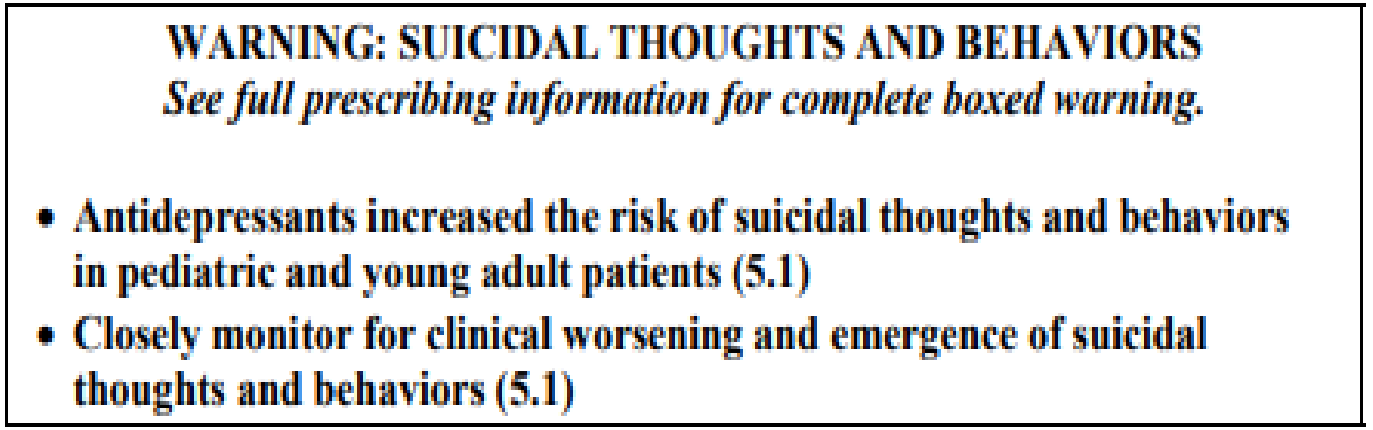
Can be obtained from a pharmacy upon request

6. 21 CFR 201.80

WARNINGS

BOXED WARNINGS (FORMERLY "BLACK BOX WARNINGS")

- The FDA can require a prominent warning on the medication's package insert
  - This warning is listed first on the package insert, inside a box
  - Considered the **most stringent warning** applied to a medication
  - Boxed warnings can be added or removed at any time, pending FDA guidance
  - Over 400 medications carry boxed warnings



WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients (5.1)**
- **Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.1)**

9. DELONG ET AL (2023).

BOXED WARNINGS

Medications can receive boxed warnings if they

- **Produce a serious side effect that can cause death or disability**
- **Have a prescribing restriction**
  - Must be administered in a hospital
  - Require monitoring immediately post administration
  - Prescribed by experienced physician or specific discipline
- **Can have reduced risks by following specific recommendations**
  - Avoiding in patients with certain disease states
  - Avoiding interacting medications
  - Following dosing limits or duration restrictions

7. DUSETZINA ET AL (2011).
8. FORNARO ET AL (2008).

EXAMPLES OF MEDICATIONS WITH BOXED WARNINGS

Fluroquinolone Antibiotics	• Risk of tendon rupture
Opioids	• Risk of misuse and abuse
Atypical antipsychotics	• Risk of psychosis
NSAIDs	• Risk of GI bleed • Risk of serious cardiovascular effects
Chemotherapy agents	• Use by experienced physician • Injection or infusion site reactions

BOXED WARNING LIMITATIONS

Limitations

- Providers can be unaware of boxed warnings
- Can cause "warning fatigue"
- Can cause undue concern in patients
- Can be inappropriately applied to an entire medication class or route of administration

Strengths

- Provide awareness for most important medication risks
- Concise summary of major concerns with a medication

Key Takeaways

- Boxed warnings are warnings, not contraindications
- Can change- stay up to date with frequently prescribed medications
- Remember nuance- statistical significance vs clinical significance

9. DELONG ET AL. (2023).
10. BOXED WARNINGS

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

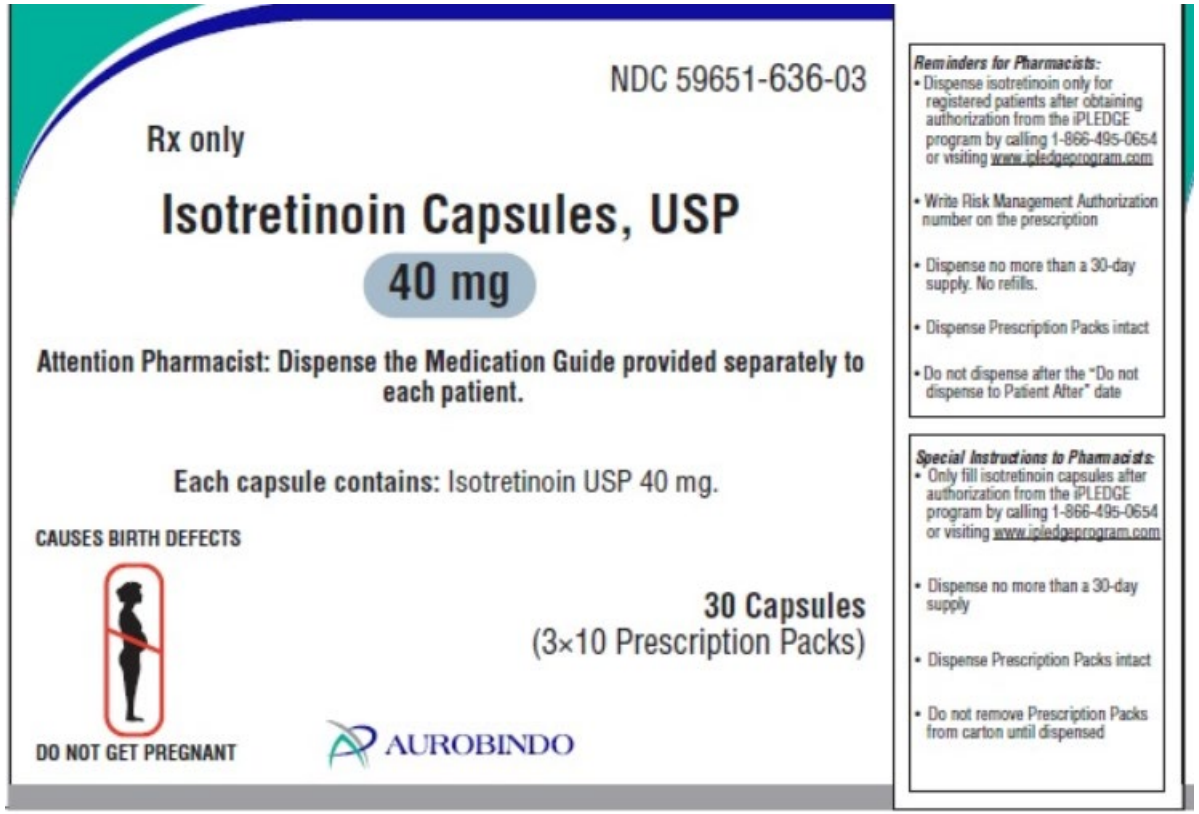
- **Mandated** by the FDA, but **developed** and **implemented** by the medication manufacturer
  - Required if there is a risk that outweighs the benefits of the medication without proper caveats
  - The risk cannot be adequately mitigated by labeling requirements

- If a REMS is necessary, a medication **cannot** be marketed without a REMS in place

- REMS Requirements are varied based on the medication, and may include
  - Provide a medication guide to all patients receiving medication
  - Reporting requirement for lab values
  - Monitoring requirements for infusions or injections
  - Require certification programs for pharmacies or prescribers
  - Medication can only be obtained directly from the pharmaceutical manufacturer

REMS EXAMPLE- IPLEDGE

- Isotretinoin is teratogenic and can cause significant depression
- Providers, pharmacies, and patients must enroll in the iPledge program to prescribe, dispense, and receive isotretinoin products
- **Provider requirements**
  - Provide pregnancy testing
  - In person monitoring for depression
- **Patient requirements**
  - Attend monthly appointments
  - Complete questions on iPledge website
- **Pharmacy Requirements**
  - Obtain authorization to fill Rx from iPledge and document on each Rx



REMS CHANGES

- All REMS information with links to individual REMS programs is available at fda.gov

- **REMS programs added**
  - Opioid analgesics program added in June 2025
    - Providers and pharmacies encouraged to counsel all patients on safe medication use and disposal
    - Providers encouraged to complete opioid REMS Continuing Education
    - Opioid manufacturers required to provide mail-back medication disposal envelopes at no cost to pharmacies

- **REMS programs removed**
  - Clozapine REMS program removed in February 2025
    - No longer required to report ANC levels monthly for clozapine
    - Boxed warning and monitoring parameters still in place
    - Improves access to care

ADVERSE DRUG REACTIONS

"Side effects include the urge to read the side effects list, scaring you into not taking the medication."

ADVERSE DRUG EVENTS/REACTIONS

- **Adverse Drug Event-** any undesired effect that occurs upon taking a drug, may or may not be caused by the drug itself

- **Adverse Drug Reaction-** any undesired effect that occurs upon taking a drug, with specific evidence of being caused by the drug

- Can range from serious (anaphylaxis, Stevens-Johnson syndrome) to mild (nausea, headache, drowsiness)
  - Many adverse drug reactions are a result of the normal pharmacologic effects of the medication
  - Can be very difficult to prove causality between an adverse event and a medication

- Help patients distinguish between **adverse events** and **medication allergies**- especially for antimicrobials!
  - Incorrectly labeled medication allergies are a significant contributor to antimicrobial resistance

- Remember- not all adverse events are bad! We frequently take advantage of **positive** adverse effects.

ADVERSE DRUG EVENTS/REACTIONS

- Present adverse effects carefully to patients to avoid nocebo effect
  - **Nocebo effect**- belief that a medication will cause harm can cause perception of harm
    - The opposite of the placebo effect

- Report adverse events to **FDA Medwatch** database at fda.gov

- Patients or providers can report adverse events
  - Can report even if the medication isn't approved by the FDA
  - Reports are in a searchable database, but must be interpreted cautiously
    - Is extremely difficult to prove causality between a medication and an adverse event

14. CLEVELAND CLINIC (2024). NOCEBO EFFECT

MEDICATION RECALLS

MEDICATION RECALLS

- Can be **requested** by the FDA but cannot be **mandated** by the FDA (except in very specific circumstances)
  - Usually voluntarily initiated by the medication manufacturer

- Patients are typically notified first. Pharmacies receive official recall notices from manufacturers.
  - Typically limited to very specific batches of medications.

- Categorized by patient impact
  - **Class I**- Most stringent. Likely that use or exposure to product could cause harm or death
  - **Class II-** May cause reversible or temporary adverse events with exposure to product. Most common type.
  - **Class III-** Not likely to cause adverse events. Usually minor manufacturing or labeling issues.

15. NATOF, T (2023). FOOD AND DRUG ADMINISTRATION RECALLS

ADDRESSING PATIENT CONCERNS

Verify this is a current, active recall and not an old headline circulating social media

Medication recalls almost NEVER involve every single bottle of a specific medication

In most cases- have the patient contact the pharmacy first to see if their pharmacy was affected

Many recall issues resolved by pharmacy issuing replacement product- may or may not require an additional refill on the Rx

MARKET WITHDRAWALS

- The FDA can request medications be withdrawn from the U.S. Market, and manufacturers can voluntarily withdraw medications from the U.S. Market due to significant safety concerns or new data

- **Vioxx (rofecoxcib)**
  - COX-2 inhibitor- anti-inflammatory with GI protective benefits
  - Pulled from U.S. market in 2004 – risk of heart attack and stroke with higher continued doses
  - Concerns that the manufacturer intentionally withheld safety data from the FDA during approval process

- **Zantac (ranitidine)**
  - H2 receptor antagonist- used for acid reflux. Available in a tablet and a liquid
  - Concerns about a contaminant (NMDA) causing cancer
  - **Clinical pearl**- the Zantac on pharmacy shelves today is a different active ingredient- contains **famotidine** and not **ranitidine**

BUYER BEWARE!

ONLINE PHARMACIES AND COUNTERFEIT MEDICATION

- Use of online pharmacies has increased dramatically since COVID

- According to the Alliance for Safe Online Pharmacies 2023 Consumer Survey
  - Americans are drawn to online pharmacies for cost savings, convenience, or due to product shortages
  - Up to **60%** of surveyed participants would buy medicine online **even if it wasn't regulated** by U.S. Regulators if it was more convenient
  - **47%** of participants would buy prescriptions from a source not approved by U.S. Regulators if it gave them access to a medication they could not get elsewhere
  - **54%** of participants falsely believed any pharmacy advertised online has been approved by the FDA and state regulatory bodies
  - Participants believed the **greatest risk** of purchasing medication online **was not receiving the medication on time**

HIGHER RISK FOR COUNTERFEITS

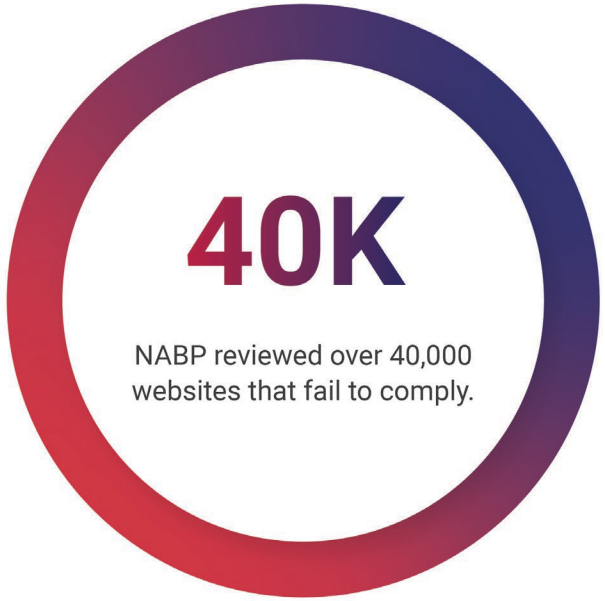
Any "trending" medication based on current events	Illicit substances	Cosmetic injectables	Lifestyle meds	Weight loss injectables
• Ivermectin and hydroxychloroquine during COVID	• Opioids (high risk for fentanyl-laced products) • Benzodiazepines	• Cases involving counterfeit Botox and other dermal fillers	• Sildenafil (Viagra), tadalafil (Cialis) and others	• Plethora of cases involving counterfeit GLP-1s

ONLINE PHARMACIES AND COUNTERFEIT MEDICATION

- **Medication purchased online from illegal online pharmacies**
  - Is often subtherapeutic or completely nontherapeutic
  - Can be adulterated, misbranded, or both
  - Has bypassed U.S. Regulatory standards
  - Temperature sensitive medication protocol is not followed

- **Other risks for consumers**
  - Injection site issues from counterfeit injectables
  - Pay for medication and never receive it
  - Sites sell personal info
  - Complex webs of shell companies- make legal action difficult
  - Difficult to adequately assess adverse drug reactions (unsure what products contain)

SAFE ONLINE PHARMACIES SURVEY



NABP reviewed over 40,000 websites that fail to comply.

Nearly 95% of websites offering prescription-only drugs online operate illegally.

96% of illegal online pharmacies reviewed by NABP did not require a valid prescription for the sale of prescription-only medicine.

24% of Americans who have used an online pharmacy have been exposed to harmful, counterfeit, or substandard medication, according to ASOP.

NABP®

ONLINE PHARMACY RED FLAGS

- No prescription required
- Offering medications that aren't commercially available
- Offers incentives or "bonus pills"
- Only accept cryptocurrency
- No way to verify what pharmacy is shipping the medication
- No way to contact a pharmacist with questions

IS MY ONLINE PHARMACY LEGITIMATE?

- Search the NABP Accredited Digital Pharmacy Search Tool
  - https://nabp.pharmacy/programs/accreditations/digital-pharmacy/accredited-digital-pharmacies/

COMPOUNDED CONFUSION

COMPOUNDING CONUNDRUMS

- Compounding pharmacies **fill gaps** for patients who **cannot** take commercially available forms of medication
  - Allergy to excipients
  - Require other routes of administration
  - Require a dose that cannot be obtained with a commercially available preparation

- Compounded products **are not FDA approved** or tested for safety or effectiveness

- Compounding pharmacies must adhere to stringent regulatory framework
  - Must follow USP requirements
  - **Cannot make medications that are "essentially a copy" of commercially available medications**
    - Limited exceptions for when medications are in shortage
    - Still considered "essentially a copy" if two commercially available preparations are mixed
  - **Cannot manufacture**- must be limited supplies
  - Cannot compound products with investigational drugs

18. MARTHA M, ET AL. PHARMACY TIMES
19. COMPOUNDED WEIGHT LOSS INJECTIONS (2025)

OUTSOURCING FACILITIES- 503B ENTITIES

- Licensed and regulated by the FDA and allowed to distribute medications directly to hospitals and clinics

- Adhere to Good Manufacturing Practices

- **But beware!** Many bad actors taking advantage of consumers
  - Not following Good Manufacturing Practices
  - Advertising direct to consumer for **prohibited products** in the U.S. (like Investigational New Drugs)
  - Sourcing Active Pharmaceutical Ingredients from unregulated suppliers
    - Leads to counterfeit and dangerous medications in the U.S. supply chain
    - **Non-sterile bulk ingredients** used in sterile compounds

18. MARTHA M, ET AL. PHARMACY TIMES

THE FINAL DOSE

01

The U.S. has a significant regulatory framework for medication safety to protect patients

02

Boxed warnings and REMS programs provide additional guidance for higher risk medications

03

Any adverse events from medication should be reported to the FDA Medwatch system

04

Most medication recalls do not require changing a patient's prescription

05

Patients should only receive prescription medication from U.S. licensed pharmacies

QUESTIONS?

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