Overview of Mental Health Medications for Children and Adolescents

Module 1

General Information about Medications

Pharmacology

- Interaction of biologically active agents
- Multidisciplinary
  - Chemistry
  - Physiology
  - Pathology
  - Biochemistry
- Psychopharmacology – interaction of drugs in the brain

Pharmacological Revolutions Affecting Modern Attitudes About Medications

- Vaccines
- Antibiotics
- Psychopharmacologic drugs
- Oral contraceptives

Risk:Benefit

USE OF ANY DRUG CARRIES A RISK

HARMLESS = USELESS

What is a prescription?

- Medication order
- Drugs or substances written on prescriptions

Prescription Only Drugs

- Federal government determines which drugs require a prescription
  - Federal Food, Drug, and Cosmetic Act
- States decide on who can prescribe

Legal Prescribers in Georgia

* Physicians (MD, DO)
* Dentists (DDS, DMD)
* Podiatrists (DPM)
* Veterinarians (DVM)
* Optometrists (OD) – Limited
* Physician's assistants (PA)- Limited
* Nurse practitioners (NP, APN) – Limited

Drug Classes

* Prescription only drugs
* Controlled substances
* Non-prescription drugs (OTC)

OTC

* Medications used to treat conditions that do not necessarily require a health care professional
* Higher safety standard
* Can be a lower dose of the prescription medication

Herbals, Vitamins, Minerals, Food Supplements

- Safety and efficacy not evaluated by FDA
- Cannot state that they are used to treat a condition
- Many state that they are "clinically tested or have IRB approval"
- FDA can remove from market

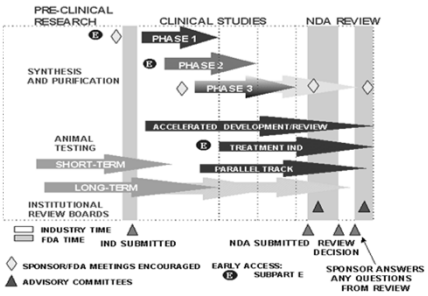
Expiration Date

- Specifies the date the manufacturer guarantees full potency and safety
- Most medications still effective
- Exceptions (loss of potency)
  - Nitroglycerin
  - Insulin
  - Some antibiotics
- Exceptions (toxicity)
  - Tetracycline

Generic Drugs

- Same as brand name in dosage, safety, strength, how it is taken and intended use
- FDA requires all generic drugs be safe and effective
- Less expensive - less cost in development
- Trademark laws in the US do not allow generic drugs to look exactly like the brand-name drug

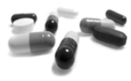
Drug Development Process



http://www.fda.gov/cder/handbook/develop.htm

FDA Approval

- Not a guarantee of efficacy and safety over the life of the drug
- Approval based on indication and dosing described in the NDA



The Case for Generics

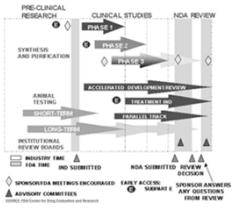
- Considered a major remedy to offset rising health care costs
- In 2002, FDA estimated a savings of approximately $57 billion/yr
- Each 1% increase in generic drug use could save $1.32 billion/yr

http://www.fda.gov/cder/ogd/02-10_BCBS_gjb/sld003.htm

15

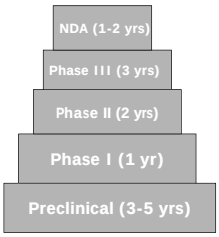
History of Generic Drugs

- Prior to 1984, generic drugs were evaluated on safety and efficacy studies that were required for branded drugs
- Small percentage of generic drugs prescribed

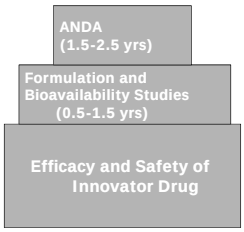


Branded vs Generic Drug Development

Branded Drug



Generic Drug



FDA Requirements for Generics

- Contains identical amounts of same active drug as brand
- Same route of administration
- Same indications
- Same dosage form

FDA Requirements for Generics

- Ratio of active:inactive ingredients must be the same as brand
- Bioequivalent
- Compared to a single reference listed drug (RLD)

19

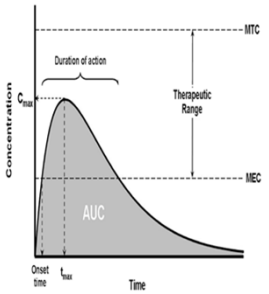
Bioequivalence

- In vivo bioavailability of generic does not differ significantly from the reference listed drug
- Typically determined in 24-36 healthy adult subjects after a single oral dose

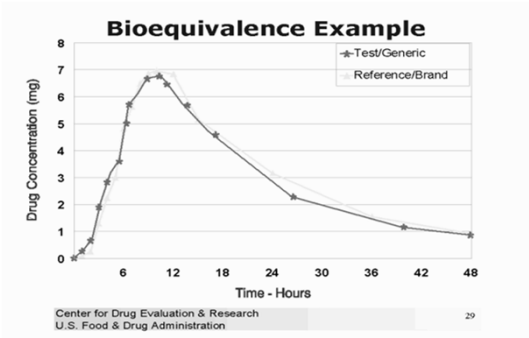
20

Bioequivalence

- Two absorption parameters determined
  - AUC
  - C_{max}
- 90% confidence intervals for AUC and C_{max} must fall within 80-125% of the branded drug



21



http://www.fda.gov/cder/ogd/02-10_BCBS_gjb/sld029.htm

22

Drug Receptors

- Site of drug or chemical interaction
- Receptor recognizes specific structural chemical signal
- Drug-receptor interaction is coupled with an effector mechanism to evoke a response
- Anatomic localization of receptors is one determinant of drug selectivity

23

Drug Receptor Interactions

- Agonist – binds to receptor and produces a response
- Antagonist – binds to receptor but does not initiate a response

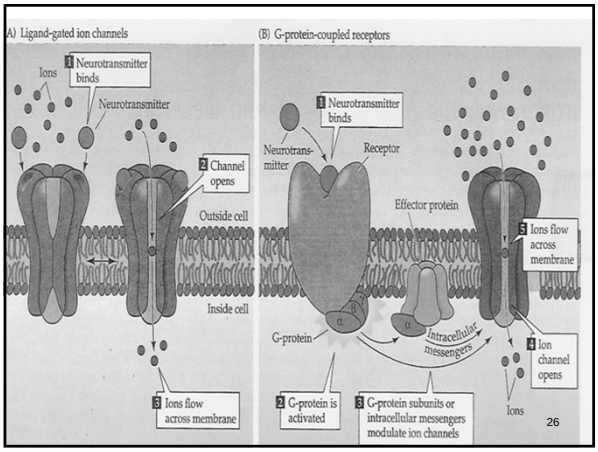
24

Drug Receptor Interaction

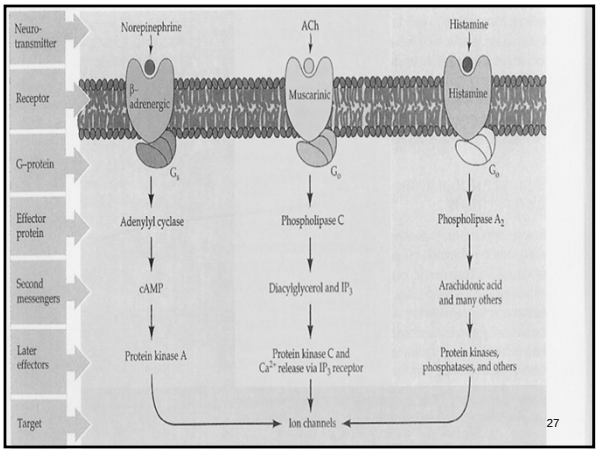
$$\text{Drug [D]} + \text{Receptor [R]} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{DR}$$

K_1 = rate of association
K_2 = rate of dissociation
At equilibrium $k_1 = k_2$

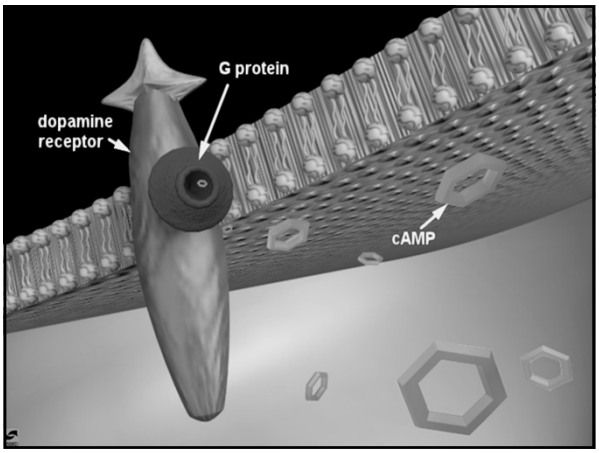
25



26



27



Receptor Downregulation

- Desensitization or refractoriness
- Occurs after continued receptor stimulation
- Effect diminishes after repeated stimulation to the same concentration of drug
- Can be clinically relevant (bronchodilators, SSRIs)

29

Receptor Supersensitivity

- Follows reduction in the chronic level of receptor stimulation
- Can result from long term administration of antagonists
- Can result from synthesis of new receptors

30

Additive Effects, Synergism, Potentiation

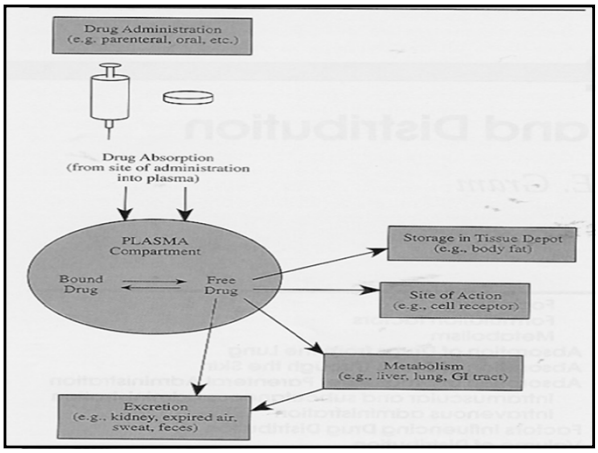
- Additivity – combined effects equal the algebraic sum of individual responses (1+1=2)
- Synergism – combined effects are greater than the sum of effects (1+1=3)
- Potentiation – one drug appears to have no effect when given alone but increases the potency of another drug

31

Pharmacokinetics (ADME)

- Absorption
- Distribution
- Metabolism
- Excretion

32



Drug Metabolism

- Major mechanism of termination of action
- Many times determines:
  - Duration
  - Intensity of drug action
- Generally, metabolites are:
  - Less active pharmacologically
  - More polar

34

Factors Affecting Drug Metabolism

- Age
- Nutrition
  - Protein/essential fatty acid deficiency
  - Chronic alcohol ingestion
  - Grapefruit juice
- Pharmacogenetics
- Co-morbid conditions

35

Factors Affecting Drug Metabolism

- Hormones
  - Estrogens/progesterone
  - Thyroxine
- Other drugs
  - Competition for metabolic enzymes
  - Enzyme induction
  - Enzyme inhibition

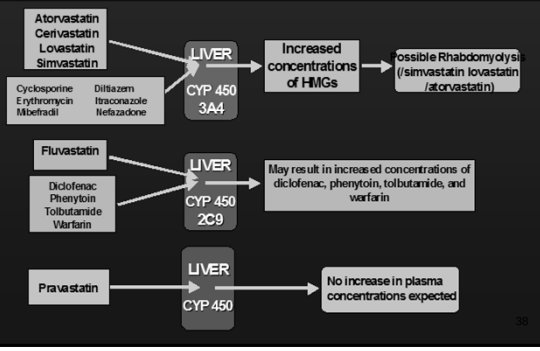
36

Drug Interactions

- Altered absorption from site of administration
- Altered protein binding
- Altered renal excretion
- Inhibition of metabolism
- Induction of metabolism

37

Drug-Drug Interactions Resulting From Liver Metabolism of HMGs



38

Substrates and Inhibitors for Cytochrome P450

CYP1A2		CYP2C9	
Substrates	Inhibitors	Substrates	Inhibitors
Caffeine	Cimetidine	Amitriptyline	Cimetidine
Clozapine	Ciprofloxacin	Imipramine	Co-Trimox
Tacrine	Diltiazem	Ibuprofen	Disulfiram
Theophylline	Erythromycin	Diclofenac	Fluconazole
R-Warfarin	Fluvoxamine	Phenytoin	Metronidazole
	Tacrine	Tolbutamide	**Fluvastatin**
		S-Warfarin	

39

Substrates and Inhibitors for Cytochrome P450

CYP2D6		CYP3A4	
Substrates	Inhibitors	Substrates	Inhibitors
Desipramine	Fluoxetine	Alprazolam	Cimetidine
Imipramine	Paroxetine	Diazepam	Erythromycin
Flecanide	Haloperidol	Triazolam	Clarithromycin
Risperidol	Thioridazine	Terfenadine	Fluconazole
Metoprolol	Quinidine	Astemizole	Ketoconazole
Propranolol	Amiodarone	Nefazodone	Norfluoxetine
Venlafaxine		Verapamil	Nefazodone
Propafenone		**Atorvastatin**	Diltiazem
		Cerivastatin	Mebefradil
		Lovastatin	Grape Fruit Juice
		Simvastatin	Omeprazole
			Cyclosporin

40

Pharmacogenetics

- Genetic factors can influence
  - Efficacy
  - Potential for adverse drug effects
- Factors other than genetics which influence drug response
  - Age
  - Gender
  - Disease/co-morbid conditions
  - Drug interactions

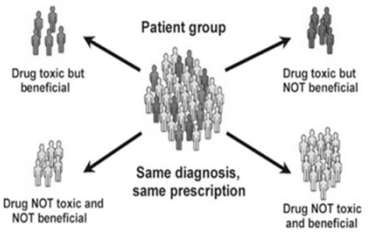
41

Pharmacogenetics

- Genetic variations can be involved in:
  - Effector tissue response (receptors, enzymes)
  - Metabolic processes
  - Excretory processes
- Pharmacogentics originated from the observation of variations in metabolism
  - Patients exhibited either very high or very low plasma or urinary drug concentrations

42

Consequences of Pharmacogenetics

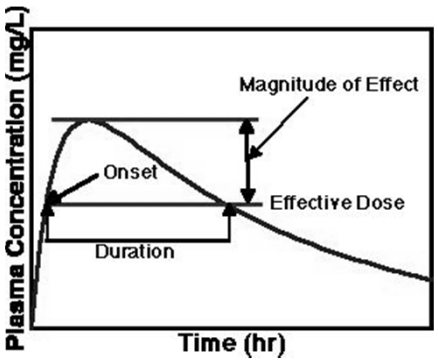


43

Half-life

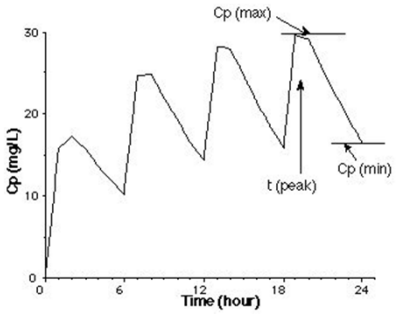
- Often related to drug's duration of action
- Can be used to determine dosing interval

44



45

Multiple Doses



46

Drug Interactions

- Altered absorption from site of administration
- Altered protein binding
- Altered renal excretion
- Inhibition of metabolism
- Induction of metabolism

47

Adverse Drug Reaction (ADR)

- An effect which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy (defined by WHO)
- Type A ADR
  - Exaggerated extensions of the primary or secondary pharmacologic activity
  - Dose dependent
- Type B ADR
  - Idiosyncratic reactions
  - Generally immunologic or allergic
  - Generally independent of dose or route of administration

48

Adverse Drug Reaction (ADR)

- More common in age extremes
- Women reported to have 50% higher rate than men
- Patients with past history of reactions to medications are more apt to experience ADRs

49

Product Label

- Important information for health care providers
- Content based on information from manufacturer
- Approved by FDA

Anatomy of Product Label

- Description
  - Chemical class
  - Chemical description
  - Contents of product
- Clinical Pharmacology
  - Pharmacodynamics
  - Pharmacokinetics (ADME)
  - Special populations
  - Clinical efficacy

Anatomy of Product Label

- Indications and usage
- Contraindications
- Warnings
- Precautions
  - General
  - Information for patients
  - Lab tests
  - Drug interactions
  - Carcinogenesis, mutagenesis
  - Reproductive toxicity
  - Pediatric
  - Geriatric

Anatomy of Product Label

- Adverse Reactions
  - Incidence in clinical trials
  - Adverse events occurring at an incidence of 1% or more
  - Other adverse events
- Drug Abuse and Dependence
- Overdosage

Anatomy of Product Label

- Dosage and Administration
- How supplied
- Animal Toxicology
- Product photos

Old Label Format

- Complex and difficult to find answers to specific questions of prescriber
- Approval date not included
- Did not indicate whether any recent changes to labeling occurred

New Label Format- Highlights Section

- Overview of drugs benefits and risks
- Contents section with easy to use reference to detailed safety and efficacy information

New Label – Highlights Section

- Limitations statement
- Product name and date of initial US approval
- Boxed warning
  - Bullet lists

New Label – Highlights Section

- Recent major changes
- Indications and usuage
  - Bullet list
  - Pharmacological classification to relate mechanism of action
- Dosage and administration

New Label – Highlights Section

- Contraindications (no relative contraindications)
- Warnings/precautions
  - Abbreviated summary of most clinically significant adverse reactions and what to do
  - Monitoring parameters

New Label – Highlights Section

- Adverse reactions
  - Most common adverse reactions and percentage of occurrence
  - Information on how to report
- Drug interactions
  - Clinically significant interactions
  - Nature of the reaction

New Label – Highlights Section

- Use in specific populations
- Patient counseling information statement

Example of Highlights for a Fictitious Drug

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Indicon safely and effectively. See full prescribing information for Indicon.

INDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS
See full prescribing information for complete boxed warning.
Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Indicon immediately if any of the following occur:
- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

----------RECENT MAJOR CHANGES----------
Indications and Usage, Coronary Stenting (1.2) 2/200X
Dosage and Administration, Coronary Stenting (2.2) 2/200X

----------INDICATIONS AND USAGE----------
Indicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:
- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:
- For stroke, Indicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

----------DOSAGE AND ADMINISTRATION----------
- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 50 mg (3)

----------CONTRAINDICATIONS----------
- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

----------WARNINGS AND PRECAUTIONS----------
- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Anticoagulants: Discontinue prior to switching to Indicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X23

http://www.fda.gov/cder/learn/CDERLearn/prescriptionLabeling/default.htm

New Label Format – Additional Information

http://www.fda.gov/cder/learn/CDERLearn/prescriptionLabeling/default.htm

Black Box Warnings

"Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data."

Black Box Warnings

- Usually limited to the most serious warnings necessary to ensure the continued safe use of the product
- Applied to package inserts, PDR and any other material that describes the use of the drug by health care providers
- Requires FDA approval

Cases of life-threatening hepatic failure have been reported in patients treated with SERZONE.

The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 – 300,000 patient-years of SERZONE treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, 1 patient-year is equal to 2 patients each treated for 6 months, 3 patients each treated for 4 months, etc. (See WARNINGS).

Ordinarily, treatment with SERZONE should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that pre-existing liver disease increases the likelihood of developing liver failure, however baseline abnormalities can complicate patient monitoring.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRECAUTIONS: Information for Patients). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels ≥ 3 times the upper limit of NORMAL, while on SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reintroduced. Accordingly, such patients should not be considered for re-treatment.

Label Changes

- Based on safety information derived from postmarketing surveillance
- Can be initiated by FDA or pharmaceutical company
- Dear Dr letters/MedWatch

Additional Information

Drug labels may be accessed through the FDA website:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Black Box Warnings

- Website with complete list of drugs that have black box warnings:

  http://blackboxrx.com/

MedWatch Program

- Initiated in 1993
- Goals of program
  - Simplify reporting process
  - Clarify what is to be reported to FDA
  - Enhance awareness of serious side effects
  - Provide feedback to healthcare providers

MedWatch Program

- Not necessary to show direct causal relationship in the individual report
- Information needed
  - Patient
  - Drug
  - Adverse event
- Reporting is simplified
  - 1-800-FDA-1088
  - Prepaid mail form (FDA 3500)
  - Fax: 1-800-FDA-0178
  - Internet: www.fda.gov/medwatch

MEDWATCH FORM


MEDWATCH
For VOLUNTARY reporting by health professionals of adverse events and product problems
A. Patient information
B. Adverse event or product problem
C. Suspect medication(s)
D. Suspect medical device
E. Reporter (see confidentiality section on back)

Off-Label Use

- Use of a drug product in doses, patient populations, indications, or administration routes not included in FDA approved labeling
- Prescriber can use a drug off-label if use is reasonable under the auspices of the professional's practice
- Many drugs used in adolescents are off-label

Direct-to-Consumer Advertising

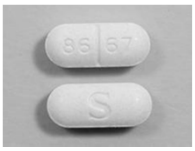
- **Ads are designed to sell not necessarily educate**
- Problems with DTC
  - Unproven claims of efficacy
  - Deceptive ads run for short periods of time
  - Subtle crafting which de-emphasizes adverse effects
    - Side effects presented quickly, during distractions, and/or in small print

Direct-to-Consumer Advertising

- Patients put pressure on prescriber based on DTC ads for inappropriate therapy
- Can encourage doctor shopping
  - European Economic Community banned DTC for this reason
- Drugs for more complicated diseases may be less advertised

Identification of Medications

- NDC (National Drug Code) – unique identifier
- http://www.rxlist.com/pill-identification-tool/article.htm



Risks for Adverse Drug Reactions

- Addition/removal of drug
- Change in dose
- Change in pathology
- Change from brand to generic or vice versa

Special Problems with Psychotropic Drugs

- Many drugs used off-label
- Special populations
- Co-morbid psychological diseases and other diseases
- Delayed therapeutic response
- Blood levels may not correlate to therapeutic response

78

Special Problems with Psychotropic Drugs

- Proper diagnosis (depression vs bipolar)
- Drug side effects can mimic disease
- Patient compliance

79

STAY INFORMED

By subscribing to the following link, you can be informed of safety updates as they become available:

https://service.govdelivery.com/service/user.html?code=USFD

80