Introduction to Pharmacology for the Toxicologist

Amy Avila, Ph.D.
Pharmacologist/Toxicologist Reviewer
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products

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Disclaimer

The content of this presentation represents the opinions of the speaker and does not necessarily represent the official position of CDER and FDA.
Pharmacology:
The study of drug action

Pharmacology encompasses and contributes to many medical disciplines such as physiology, biochemistry, molecular/cell biology and others.

Pharmacology: The study of drug action

“Although pharmacology is a basic medical science in its own right, it borrows freely from and contributes generously to the subject matter and [techniques] of many medical disciplines, clinical as well as preclinical.”

Taken from the preface of the 1st edition of Goodman and Gilman
Pharmacology Definitions

**Pharmacology**
- The study of the interactions that occur between a living organism and exogenous chemicals that alter normal biochemical function.

**Pharmacotherapeutics**
- The use of drugs in the prevention and treatment of disease.

**Clinical Pharmacology**
- The study of drugs and their clinical use; from the discovery of new targets, to the effects of drugs in whole populations.

**Pharmacogenomics**
- The influence of genetic variation on drug response in patients by correlating gene expression with a drug’s efficacy or toxicity. “personalized medicine”
Small Molecules vs. Biologics

**Small Molecule**
- Low MW <1000 daltons
- Chemically synthesized
- Metabolism
- Generally active in multiple animal species
- Toxicity due to parent or metabolite

**Biologic**
- Large MW >500 daltons
  - IgG ~150 kd
- Derived from recombinant DNA technology
  - Bacteria, yeast, mammalian cells, plants
- Toxicity due to exaggerated pharmacology
- Responsive and non-responsive animal species
Pharmacology Definitions

Pharmacodynamics: *what the drug does to the body*
- The study of the biochemical and physiological effects of drugs and their mechanisms of action.

Pharmacokinetics: *what the body does to the drug*
- Deals with the absorption, distribution, metabolism, and excretion of drugs (ADME).
Pharmacodynamics

**Primary**: Desired Activity
- Studies that investigate the mechanism of action and receptor binding in relation to its therapeutic target.

**Secondary**: Off-Target Effects
- Studies that investigate effects other than the desired effect of the drug at other sites.
Primary Pharmacodynamics
Desired Activity

Majority of drugs either:
- Mimic or inhibit normal physiological/biochemical processes or inhibit abnormal processes (cancer).
- Inhibit processes of microbial organisms, parasites and viruses.

Major drug actions include:
- Depression
- Stimulation
- Destroying cells (cytotoxicity)
- Irritation
- Replacing substances/drug interaction
Primary Pharmacodynamics

Desired Activity

Desired activity of a drug is mainly due to:

- Ligand binding to receptors (hormone, neurotransmitter, ion channels, immune)
- Interaction with enzyme proteins
- Interaction with structural proteins
- Interaction with carrier proteins
- Cellular membrane disruption
- Chemical reaction
Biochemical Classes of Drug Targets of Current Therapies

N = 483

- Receptors, 45%
- Enzymes, 28%
- Hormones & factors, 11%
- Ion channels, 5%
- Nuclear receptors, 2%
- DNA, 2%
- Unknown, 7%

Mechanism of Action
Therapeutic Drug Targets

Receptors:
Any cellular macromolecule to which a drug binds to initiate its effects. Many are cellular proteins whose normal functions are to act as receptors for endogenous regulatory ligands e.g. hormones, growth factors, neurotransmitters, and autacoids.

Many drugs bind to receptors and either mimic the effect of the endogenous ligand, producing a regulatory signal in the target cell, or inhibit the response of the endogenous ligand.
Ion channel
1
Agonist

G-protein coupled
2
Agonist

Tyrosine kinase
3
Agonist

Nuclear receptor
4
Agonist

Na

Activation of conductance

G-Protein Activation

Generation of Second Messenger

Phosphorylation of Tyrosines on Key Signaling Molecules

Activation of Cell Signaling

Transport to the Nucleus

Activation of transcription and translation
Mechanism of Action
Therapeutic Drug Targets (cont.)

Enzymes

- An enzyme inhibitor is a molecule that binds to enzymes and decreases their activity.
- Enzyme activators are molecules that bind to enzymes and increase their activity, and are often called coenzymes or cofactors.

Examples:

- Protease inhibitors to treat HIV.
- cGMP-specific phosphodiesterase type 5 inhibitor: Dildenafil (Viagra®)
Mechanism of Action
Therapeutic Drug Targets (cont.)

Interaction with DNA

- Alkylating agents
- Cross-link DNA
- Nucleoside analogues
- Oligonucleotides

Examples:
Cisplatin crosslinks DNA in several different ways, interfering with cell division. The damaged DNA elicits DNA repair mechanisms, which in turn activate apoptosis when repair proves impossible.
Mechanism of Action
Therapeutic Drug Targets (cont.)

Structural Proteins

- Colchicine inhibits microtubules polymerization by binding to tubulin.
  Treatment for Gout

Cellular membrane disruption

- Antibiotics disrupt the integrity of bacterial cell membranes.
Mechanism of Action
Therapeutic Drug Targets (cont.)

Extracellular sites of drug action

- Chemical Reactions: increasing gastric pH, free radical scavenging, cytotoxicity
- Chelation
- Replacement

Examples:
- Antacids
- Chelating agents
- Iron for iron deficiency
Drug Receptor Interactions
Occupancy Theory of Drug Action

(relationship between drug concentration and effect)

\[
\text{Drug(D)} + \text{Receptor(R)} \overset{k_1}{\underset{k_2}{\rightleftharpoons}} \text{DR} \rightarrow \text{Effect}
\]

The intensity of effect of a drug is proportional to the fraction of receptors occupied by the drug.

\[
\text{Effect} = \text{maximal effect} \times [D] \quad K_D = \frac{k_1}{k_2}
\]

\[
K_D + [D]
\]

This equation describes a simple rectangular hyperbola and is called a Dose-Response Curve.
Dose-Response Curve

% of Maximal Effect

Drug X (concentration)

EC$_{50}$
Types of Drug Receptor Interactions (Agonists)

**Full Agonist**: able to activate the receptor and result in a maximal biological response (most natural ligands).

**Partial Agonist**: does not result in complete activation of the receptor, causing a response which is partial compared to that of a full agonist.

**Inverse Agonist**: reduces the activity of a receptor by inhibiting its constitutive activity.

**Super Agonist**: is capable of producing a maximal response greater than the endogenous agonist, efficacy >100%.
Log Dose-Response Curves (Sigmoidal)

% Maximal Response

Efficacy

Full Agonist

Super Agonist

Partial Agonist

Inverse Agonist

Log [Agonist]

EC$_{50}$

Potency

Maximal Response
Types of Drug Receptor Interactions (Antagonists)

**Antagonist:**
Binds to a receptor, or components of the target site effector mechanism, to inhibit the action of an agonist, but does not illicit any effect itself.

**Competitive Antagonist:** (Reversible)
The inhibition can be overcome by increasing the concentration of the agonist, ultimately achieving the same maximal effect.

**Noncompetitive Antagonist:** (Irreversible)
Prevents the agonist, at any concentration, from producing a maximum effect on a given receptor.
Dose-Response Curves

- Agonist alone
- Agonist + Competitive Antagonist
- Agonist + Non-competitive Antagonist

% Maximal Response

Log [Agonist]

EC$_{50}$
Regulation of Receptors

Desensitization (Refractoriness or down regulation): can result after continued stimulation of cells with agonists resulting in producing a diminished effect.

- Mechanisms: covalent modification (e.g. phosphorylation) of the receptor, destruction of the receptor, or its relocalization within the cell.
Pharmacology Studies in Drug Development
Pharmacology Studies in Drug Development

There are legal, technical, as well as ethical reasons that limit pharmacological evaluation of drugs in humans. Evaluations are therefore done in part in animals.

Hence, knowledge of animal and comparative pharmacology is important in deciding to what extent animal data can be extrapolated to humans.
Pharmacology Studies in Drug Development

- Identify the effective/therapeutic dose as tested in animal models.
- Aid in selecting a **start dose** in humans with minimal adverse effects.
- Results of *in vitro* and *in vivo* pharmacology studies can be used to predict human efficacious doses.
Pharmacology Studies in Drug Development

Pharmacology studies aid in determining the **therapeutic index (ratio)** in both animals and humans. An indicator of how selective a drug is in producing its desired effects relative to its toxicity.

In animals: **Therapeutic ratio: \(LD_{50}/ED_{50}\)**

In humans: **Therapeutic ratio: \(TD_{50}/ED_{50}\)**

\(LD_{50}\) = dose that produces death in 50% of population  
\(TD_{50}\) = dose that produces a toxicity in 50% of population
Therapeutic Index

![Therapeutic Index Graph]

- **ED$_{50}$**: Dose at which 50% of the desired effect is achieved.
- **LD$_{50}$**: Dose at which 50% of the population experiences death.
- **TI** (Therapeutic Index): Ratio of ED$_{50}$ to LD$_{50}$.
Pharmacology Studies: Other uses

- Animal Rule:
  
  Evidence needed to demonstrate effectiveness of new drugs when human efficacy studies are not ethical or feasible.

  21 CFR 314.600-650

  Studies in animals (including pharmacology studies) are basis for determining the efficacy of a drug.

  (anthrax, nerve gases, smallpox, etc.)
Types of Pharmacology Studies
Primary Pharmacology Studies:

*In Vitro*

- Receptor binding: affinity and selectivity of the compound to the primary receptor(s)
  - Generate dose-response curves and Ki for receptor(s)
  - May include positive control for reference

- Functional activity: agonist/antagonist
  - Cell based assays to measure receptor activity:
    - increase/decrease in neurotransmitter levels, 2nd messengers, immune response, etc.
  - Calculate EC$_{50}$ or IC$_{50}$ values
  - May include positive control for reference
Structure Activity Relationship (SAR)

- The effect or the potency (activity) of a drug can be altered by modifying their chemical structure.
  - Assumption: similar molecules have similar activities.

- Compounds are often classified together because they have structural characteristics in common including shape, size, stereochemical arrangement, and distribution of functional groups.

- Use not only for predicting mechanism of action and toxicity profile of new compounds, but also in predicting potential toxicity of metabolites and impurities e.g. using quantitative SAR (QSAR computer modeling).
Structure Activity Relationship (SAR)

Pharmacology: All 3 drugs have a similar pharmacology. They are all opioid receptor agonists. They also all have similar toxicological profiles.
In vitro Primary Pharmacology Studies: examples

New Antipsychotic drug

- Receptor binding: HEK cells transfected with rat and human DA receptor subtypes
  - Drug binds with high affinity ($K_i = \text{low nM range } 0.1-1.2 \text{ nM}$) to rat and human D1 and D2 receptor subtype, but not D3 or D5.

- Functional activity: cellular assays
  - Drug acts as a partial agonist at D2 receptor
    - $EC_{50} = 100 \text{ nM}$. Found to be less potent than known marketed antipsychotics
Primary Pharmacology Studies: 

*In Vivo*

- Sometimes referred to as nonclinical efficacy studies.
Primary Pharmacology Studies:

*In vivo*: Animal Model Selection

- The selection of the most appropriate animal model is more important in toxicology than in pharmacology studies.

- In pharmacology studies the tendency has been to use small animals i.e. rodents, due to convenience, availability, low cost.

- When selecting animal models to use for MOA studies, should still consider species and strain, animal sensitivity to the disease and/or toxic effects of the drug, route of administration, and ADME similarities and differences to humans (will aid in making animal to human comparisons).
In vivo Animal Models

- There are animal models of many human diseases/disorders.
  - Monkey MPTP model for Parkinson's disease
  - PTZ, electroshock for anticonvulsive drugs
  - Obese mice
  - Nude mice for cancer and immune system drugs
  - Transgenic mouse models
- Animal models can be used to predict how well a new drug will be in treating the disease/disorder in humans.
- Can extrapolate data from animals to calculate probable efficacious doses in humans.
In vivo Animal Models: Behavioral Models

Models of anxiety and depression

Animals are placed in a potential or actual threatening situation/stressful condition and, a specific test is applied to measure the behavioral and physiological responses.
In vivo Primary Pharmacology Studies: examples

- Receptor occupancy studies in rat brain
  - High receptor occupancy in striatum for D2 receptor
- Efficacy for antipsychotic activity
- Found to be less efficacious than known marketed antipsychotic.
- Test for potential common side effects
  - Potential extra-pyramidal side effects were evaluated in a classical catalepsy test and showed a dose-dependent increase in catalepsy time.
- Computer simulations predict a human efficacious dose ~100 mg.
Secondary Pharmacology Studies

**In vitro receptor binding screens**

- Investigates the compounds affinity towards secondary receptor sites. Commercially available receptor binding screens incorporate large lists of receptors, channels, enzymes, transporters, etc.
<table>
<thead>
<tr>
<th>TARGET</th>
<th>% INHIBITION</th>
</tr>
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<tbody>
<tr>
<td>CYP450, 1A2</td>
<td>-7</td>
</tr>
<tr>
<td>CYP450, 2C9</td>
<td>3</td>
</tr>
<tr>
<td>CYP450, 2D6</td>
<td>-20</td>
</tr>
<tr>
<td>CYP450, 3A4</td>
<td>8</td>
</tr>
<tr>
<td>Adenosine A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-7</td>
</tr>
<tr>
<td>Adenosine A&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>12</td>
</tr>
<tr>
<td>Adenosine A&lt;sub&gt;2B&lt;/sub&gt;</td>
<td>10</td>
</tr>
<tr>
<td>Adrenergic α&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>14</td>
</tr>
<tr>
<td>Adrenergic α&lt;sub&gt;1B&lt;/sub&gt;</td>
<td>46</td>
</tr>
<tr>
<td>Adrenergic α&lt;sub&gt;1D&lt;/sub&gt;</td>
<td>39</td>
</tr>
<tr>
<td>Adrenergic α&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>46</td>
</tr>
<tr>
<td>Adrenergic β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>24</td>
</tr>
<tr>
<td>Adrenergic β&lt;sub&gt;2&lt;/sub&gt;</td>
<td>6</td>
</tr>
<tr>
<td>Bradykinin B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>10</td>
</tr>
<tr>
<td>Bradykinin B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>12</td>
</tr>
<tr>
<td>Calcium Channel L-Type, Benzothiadiazepine</td>
<td>13</td>
</tr>
<tr>
<td>Calcium Channel L-Type, Dihydropyridine</td>
<td>24</td>
</tr>
<tr>
<td>Calcium Channel N-Type</td>
<td>4</td>
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<tr>
<td>Dopamine D&lt;sub&gt;1&lt;/sub&gt;</td>
<td>37</td>
</tr>
<tr>
<td>Dopamine D&lt;sub&gt;2S&lt;/sub&gt;</td>
<td>36</td>
</tr>
<tr>
<td>Dopamine D&lt;sub&gt;3&lt;/sub&gt;</td>
<td>6</td>
</tr>
<tr>
<td>Dopamine D&lt;sub&gt;4&lt;/sub&gt;</td>
<td>16</td>
</tr>
<tr>
<td>Dopamine D&lt;sub&gt;A2&lt;/sub&gt;</td>
<td>14</td>
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<tr>
<td>Endothelin ET&lt;sub&gt;A&lt;/sub&gt;</td>
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<tr>
<td>Endothelin ET&lt;sub&gt;B&lt;/sub&gt;</td>
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<tr>
<td>Epidermal Growth Factor (EGF)</td>
<td>6</td>
</tr>
<tr>
<td>Estradiol ERα</td>
<td>4</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;, Agonist Site</td>
<td>14</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;B&lt;/sub&gt;, Benzodiazepine, Central</td>
<td>1</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;B1&lt;/sub&gt;</td>
<td>-18</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>0</td>
</tr>
</tbody>
</table>
Secondary Pharmacology Studies

Secondary pharmacology data to assess potential off-target activity of new drugs: a regulatory perspective

Thomas Papoian, Haw-Jyh Chiu, Ikram Elayan, Gowraganahalli Jagadeesh, Imran Khan, Adebayo A. Laniyouni, Cindy Xinquang Li, Muriel Saulnier, Natalie Simpson and Baichun Yang

Secondary Pharmacology Studies

Table 1 | Aspects of secondary pharmacology data considered useful for regulatory review

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Target panel**  | • For new molecular entities, a broad panel of G protein-coupled receptors, transporters, ion channels, nuclear receptors and enzymes, including various kinases  
                      • Safety or pharmacological rationale provided for selection of targets  
                      • Panel of targets not limited to the same drug class, putative mechanism of action or group of related chemical structures as the lead compound |
| **Methodology section** | • Detailed description of methodology used for all binding and functional assays  
                              • Rationale and/or criteria for a positive response (for example, ≥50% inhibition or stimulation at the maximum concentration tested) |
| **Results section** | • Data expressed in a readable tabular and/or graphical format  
                              • Percentage inhibition or activation  
                              • Effector concentration for half-maximum response ($EC_{50}$), half-maximal inhibitory concentration ($IC_{50}$) or inhibition constant ($K_i$) values versus internal reference value  
                              • Graphs displaying magnitude of change (percentage inhibition or stimulation)  
                              • $IC_{50}$ titration curves (percentage inhibition versus increasing concentration)  
                              • Criteria given for a positive response |
| **Discussion section** | • Biological significance of findings  
                             • How potency of off-target activity compares with that of the intended target  
                             • Relative in vitro potency for off-target activity versus potency for intended target (or targets)  
                             • $IC_{50}$ or $K_i$ values versus projected or observed plasma drug levels achieved at efficacious doses (animals or humans)  
                             • Correlation between in vitro findings and those observed in animals  
                             • Discussion of possible drug-related effects that should be monitored in humans |

Secondary Pharmacology Studies

Table 2 | Examples of regulatory actions based on positive off-target activity

<table>
<thead>
<tr>
<th>Case example</th>
<th>Drug effects</th>
<th>Possible regulatory action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disruptors</td>
<td>• Interference with some aspect of the endocrine system</td>
<td>• Use of receptor-binding and enzyme assays to screen for potential unintended effects, including interference with certain endocrine receptors</td>
</tr>
<tr>
<td></td>
<td>• Blocking of hormone receptors (membrane and nuclear)</td>
<td>• If in vitro results are positive, additional studies may be warranted: Developmental and reproductive toxicity, pre- and post-natal development, and juvenile animal toxicity studies to assess endocrine-related developmental effects</td>
</tr>
<tr>
<td></td>
<td>• Effects on synthesis, transport or excretion of hormones</td>
<td>Assessment of hormone levels in human clinical trials</td>
</tr>
<tr>
<td></td>
<td>• Sex hormones (oestrogens and androgens) most commonly affected</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can affect development and maturation</td>
<td></td>
</tr>
<tr>
<td>Peroxisome proliferator-activated receptor-γ-agonists (for example, thiazolidinediones)</td>
<td>Human target organs include heart (in the case of congestive heart failure), kidney (fluid retention), skeletal muscle (rhabdomyolysis), and liver, bone marrow and bladder (cancers)</td>
<td>• Significant off-target activity in vitro (for example, low effector concentration for half-maximum response (EC₅₀) in cell-based reporter gene assay) may result in: Additional monitoring to assess human risk at therapeutic drug concentrations Rodent carcinogenicity studies to support clinical studies of &gt;6 months duration</td>
</tr>
<tr>
<td>Cardiac (voltage-gated) ion channel protein antagonists</td>
<td>• Potassium voltage-gated channel subfamily H member 2 (hERG1), which mediates the repolarizing current Iᵦᵡ [AU:OK?]: Antagonists slow conduction and repolarization of action potential Associated with corrected QT prolongation and torsades de pointes</td>
<td>Positive results may prompt additional electrocardiography monitoring in patients</td>
</tr>
<tr>
<td></td>
<td>• Sodium channel protein type 5 subunit-α (Nav1.5): Antagonists prolong QRS interval and slow conduction</td>
<td></td>
</tr>
</tbody>
</table>

## Secondary Pharmacology Studies

| 5-HT\(_{2b}\) (serotonin) receptor agonists (for example, fenfluramine–phentermine, 3,4-methylenedioxymethamphetamine (MDMA; also known as ecstasy)) | Agonist activity to 5-HT\(_{2b}\) receptors on heart valve leaflets known to result in fibrotic cardiac valvulopathy | • In vitro agonist activity (for example, calcium flux assay) may result in:  
  - Request for focused histopathology of animal heart valves  
  - Additional cardiac monitoring (echocardiography) in humans if the safety margin is sufficient based on the animal no-observable adverse effect level  
  - If no safety margin, then possible clinical hold due to serious and irreversible nature of the effect |
| Ligand-gated ion channels: N-methyl-D-aspartate (NMDA) receptor antagonists (for example, dizocilpine (MK-801) and ketamine) | • Protect neurons against excess glutamate neurotoxicity  
  • Used to treat stroke, epilepsy, pain and Parkinson disease  
  • Can injure or destroy certain other neurons and induce psychotic symptoms and memory impairment  
  • Mechanism of toxicity is complex, involving cholinergic, glutamatergic, GABAergic, dopaminergic and/or noradrenergic systems | Positive in vitro results may prompt focused animal studies for possible neurotoxic effects on structure (expanded neurohistopathology) and function (neurobehavioural testing, including evaluation for effects on sensory, motor and cognitive functions) |
| Drugs with potential for abuse | Off-target activity affecting the neurotransmitter system, (for example, dopamine, noradrenaline, serotonin, GABA (\(\gamma\)-aminobutyric acid)), acetylcholine, opioid (for example, \(\mu\)-type), NMDA or cannabinoid receptors | • Positive results may prompt:  
  - Further animal and human behavioural studies for addictive or abuse liability  
  - Drug scheduling by the US Drug Enforcement Administration |

Pharmacology: Physiological System/Therapeutic Area
Pharmacology: Physiological System/Therapeutic Area

- Many pharmacology courses are taught by system/therapeutic area. Year long courses.

- First, understand the normal physiology of the system, then the pathophysiology of the disorder/disease state.

- Learn about the mechanism of action of each drug class used to treat specific diseases/disorders.

- Currently at FDA/CDER, within the Office of New Drugs, divisions are organized by therapeutic area.
Pharmacology: Therapeutic Area
Importance for Regulatory Toxicologists

- It is useful to know about the mechanisms of actions of established pharmacological classes to treat certain diseases/disorders.

- Become familiar with common side effects of these established drug classes.

- For a new drug: does it fall into an already established class? This helps to aid in predicting animal and human toxicity.

- Or does the drug belong to a new pharmacological class? Important to determine the toxicity profile for the new pharmacological class: does it share any of the toxicities of established classes, are there any new toxicities, is this new class “safer” or more “effective”? 
CNS/PNS

Adrenergic
GABA
Glutamate
Neuropeptides
CNS/PNS

**Benzodiazepines**: (stimulate GABA receptors) used for anxiety, seizure disorders and insomnia.

**Barbiturates**: CNS-depressant for seizure disorders and insomnia

**SSRIs and SNRIs**: (increase 5-HT, NE or both) used for depression and anxiety

**Antipsychotics**: typical and atypical: dopamine receptor antagonists used for schizophrenia

**Stimulants**: methylphenidate (Ritalin), mixed amphetamines used for ADHD

**Alzheimer’s drugs**: acetylcholinesterase inhibitors (donepezil), NMDA receptor antagonist (memantine)

**Parkinson’s**: levodopa, dopamine agonists, MAO-B inhibitors

**Analgesics**: NSAIDS, COX-2 inhibitors, opioids

**Anesthetics**: inhaled gases (isoflurane), i.v. barbiturates/ benzodiazepines, opioids, Na⁺ channel blockers (procaine)
Cardiovascular and Renal

**General:** $\beta$-adrenergic antagonists, $\text{Ca}^{2+}$ channel blockers, diuretics, cardiac glycosides, Antiarrhythmic drugs

**Antihypertensives:** ACE inhibitors, angiotensin receptor blockers, $\alpha$-blockers, $\text{Ca}^{2+}$ channel blockers

**Coagulation:** Anticoagulants, heparin, antiplatelet drugs, fibrinolytics, anti-hemophilic factors

**Atherosclerosis/cholesterol inhibitors:** hypolipidaemic agents, statins
Antihypertensive Drugs: Mechanisms of Action

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Organ</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>β blockers</td>
<td></td>
<td>Decrease in force and rate of cardiac contraction</td>
</tr>
<tr>
<td>Peripherally acting sympatholytics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td>Decrease in blood volume</td>
</tr>
<tr>
<td>Converting enzyme inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripherally acting sympatholytics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td>Relax vascular smooth muscle</td>
</tr>
<tr>
<td>Oral vasodilators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Converting enzyme inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrally acting sympatholytics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β blockers</td>
<td></td>
<td>Decreased sympathetic outflow</td>
</tr>
</tbody>
</table>

**FIGURE 13-2** Summary of sites and mechanisms by which antihypertensive drugs bring about a reduction in blood pressure. CO, Cardiac output; TPR, total peripheral resistance.

Taken from: Human Pharmacology: Molecular to Clinical Brody, Larner, Minneman and Neu 2nd Ed., 1994
Pulmonary and Allergy

**Antihistamines**: H$_1$ receptor antagonists  
(diphenhydramine, loratidine)

**Anti-inflammatory drugs**: Inhaled glucocorticoids: Prednisone, beclomethasone

**Bronchodilators**: $\beta_2$-selective adrenergic agonists: albuterol

**Phosphodiesterase inhibitor**: Theophylline
Gastroenterology

Upper digestive tract
- Antacids
- Reflux suppressants
- Antiflatulents
- Antidopaminergics
- Proton pump inhibitors
- H$_2$-receptor antagonists
- Cytoprotectants
- Prostaglandin analogues

Lower digestive tract
- Laxatives
- Antispasmodics
- Antidiarrheal
- Bile acid sequestrants
- Opioids
Metabolism and Endocrinology

**Diabetes**: sulfonylureas, biguanides/metformin, thiazolidinediones, insulin

**Obesity**: inhibit pancreatic lipase (orlistat)

**Endocrine disorders (various)**: androgens, antiandrogens, gonadotropin, corticosteroids, human growth hormone, insulin

**Thyroid hormones or anti-thyroid drugs**:
- synthetic thyroxine hormone (levothyroxine), goitrin
  (decreases thyroid hormones)
Oncology

- Alkylating agents
- Antimetabolites
- Anthracyclines
- Plant alkaloids
- Topoisomerase inhibitors
- Antitumor agents
- Monoclonal antibodies
- Tyrosine kinase inhibitors
Figure X–1. Summary of the mechanisms and sites of action of chemotherapeutic agents useful in neoplastic disease.

PALA = N-phosphonooxycetyl L-aspartate; TMP = thymidine monophosphate.
Antimicrobials  
(Antibiotics, antifungals, antiparasitics)

Inhibit bacterial cell wall synthesis: Cycloserine, ketoconazole

Act directly on the cell membrane of the microorganism: Amphotericin B, nystatin

Inhibit protein synthesis: Tetracyclines, aminoglycosides

Alter nucleic acid metabolism: Quinolones, rifampin

Antimetabolites block specific metabolic steps that are essential to microorganisms: Sulfonamides, trimethoprim
Antivirals

Specific antivirals are used to target different viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

- Can inhibit viral enzymes that are essential for DNA synthesis.
- Nucleic acid analogs result in arresting viral replication.
Other

- Dermatology drugs
- Reproductive disorder drugs
- Drugs for contraception, obstetrics and gynecology
- Drugs that act on the immune system
Pharmacology Section of Drug Applications
Pharmacology Section of Drug Applications

General Pharmacology
- Primary pharmacology
- Secondary pharmacology

Safety Pharmacology
- investigate the adverse effects of the compound on physiological function at exposures “generally” in the therapeutic range.

Pharmacokinetics

Drug-Drug Interactions
Regulations

Pharmacology and Drug Distribution

[21 CFR 312.23(a)(8)(i)]

This section should contain, if known:

- A description of the pharmacologic effects and mechanism(s) of actions of the drug in animals
- Information on the absorption, distribution, metabolism, and excretion of the drug.

“*To the extent that such studies may be important to address safety issues, or to assist in evaluations of toxicology data, they may be necessary; however, lack of this potential effectiveness information should not generally be a reason for a Phase 1 IND to be placed on clinical hold.*”
Regulations: Drug Labeling

Pharmacological Class

- 21CFR parts 201, 314, and 601: Requirements and Content and Format of Labeling for Human Prescription Drug and Biological Products.

- In January 2006, FDA published a final rule that amended the requirements for the content and format of approved labeling (prescribing information).

- The rule requires the following statement to appear under the Indications and Usage section of Highlights if a drug is a member of an established pharmacologic class:
  “(Drug) is a (established pharmacologic class) indicated for (indication(s)).”

There is list of pharmacologic class codes for active moieties for FDA approved human prescription drug products.
FANAPT™ (Iloperidone Tablets)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

The mechanism of action of FANAPT, as with other drugs having efficacy in schizophrenia, is unknown. However it is proposed that the efficacy of FANAPT is mediated through a combination of dopamine type 2 (D₂) and serotonin type 2 (5-HT₂) antagonisms.

12.2 Pharmacodynamics

FANAPT exhibits high (nM) affinity binding to serotonin 5-HT₂A and dopamine D₂ and D₃ receptors (Kᵢ values of 5.6, 6.3, 7.1 nM, respectively). FANAPT has moderate affinity for dopamine D₄, serotonin 5-HT₆ and 5-HT₇, and norepinephrine NEₐ₁ receptors (Kᵢ values of 25, 43, 22, and 36 nM respectively), and low affinity for the serotonin 5-HT₁₀, dopamine D₁, and histamine H₁ receptors (Kᵢ values of 168, 216 and 473 nM, respectively). FANAPT has no appreciable affinity (Kᵢ>1000 nM) for cholinergic muscarinic receptors. FANAPT functions as an antagonist at the dopamine D₂, D₃, serotonin 5-HT₁₀ and norepinephrine α₁/α₂C receptors. The affinity of the FANAPT metabolite P88 is generally equal or less than that of the parent compound. In contrast, the metabolite P95 only shows affinity for 5-HT₂A (Kᵢ value of 3.91) and the NEₐ₁A, NEₐ1B, NEₐ1D, and NEₐ2C receptors (Kᵢ values of 4.7, 2.7, 8.8 and 4.7 nM respectively).
VICTRELIS™ (boceprevir capsules)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VICTRELIS is a direct acting antiviral drug against the hepatitis C virus [see Microbiology (12.4)].

12.4 Microbiology

Mechanism of Action

Boceprevir is an inhibitor of the HCV NS3/4A protease that is necessary for the proteolytic cleavage of the HCV encoded polyprotein into mature forms of the NS4A, NS4B, NS5A and NS5B proteins. Boceprevir covalently, yet reversibly, binds to the NS3 protease active site serine (S139) through an (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells. In a biochemical assay, boceprevir inhibited the activity of recombinant HCV genotype 1a and 1b NS3/4A protease enzymes, with $K_i$ values of 14 nM for each subtype.

Activity in Cell Culture

The $EC_{50}$ and $EC_{90}$ values for boceprevir against an HCV replicon constructed from a single genotype 1b isolate were approximately 200 nM and 400 nM, respectively, in a 72-hour cell culture assay. Boceprevir cell culture anti-HCV activity was approximately 2-fold lower for an HCV replicon derived from a single genotype 1a isolate, relative to the 1b isolate-derived replicon. In replicon assays, boceprevir had approximately 2-fold reduced activity against a genotype 2a isolate relative to genotype 1a and 1b replicon isolates. In a biochemical assay, boceprevir had approximately 3- and 2-fold reduced activity against NS3/4A proteases derived from single isolates representative of HCV genotypes 2 and 3a, respectively, relative to a genotype 1b-derived NS3/4A protease. The presence of 50% human serum reduced the cell culture anti-HCV activity of boceprevir by approximately 3-fold.

Evaluation of varying combinations of boceprevir and interferon alfa-2b that produced 90% suppression of replicon RNA in cell culture showed additivity of effect without evidence of antagonism.
12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ruxolitinib, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. In a mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen and decreased circulating inflammatory cytokines (eg, TNF-α, IL-6).

12.2 Pharmacodynamics

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects and MF patients. Jakafi administration resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 10 hours in both healthy subjects and myelofibrosis patients.
Summary

Many adverse effects of drugs can be anticipated by understanding the mechanism of action of the drug, its pharmacokinetics, and its interactions with other drugs.
Summary

- Pharmacology studies are important in safety testing of a compound.

- Results can identify mechanism(s) and site(s) of action, adverse effects, and the efficacious dose in animal models.

- Results aid in selecting a start dose in humans.

- Animal models can be good predictors of the clinical disease therefore, comparative pharmacology can be used to assess drug safety.

- Under certain conditions, studies in animals (including pharmacology studies) may be accepted as proof of substantial evidence of effectiveness (Animal Rule).

- Secondary pharmacodynamic study results can identify binding to undesirable receptors therefore, predicting potential adverse effects.
References

- “The Pharmacological Basis of Therapeutics”, Goodman & Gilman
- Pharmacological Class Guidance and List
  - Labeling for Human Prescription Drug and Biological Products-
  Determining Established Pharmacologic Class for Use in the
  Highlights of Prescribing Information
- FDA ICH Guidances
  - M3R(2): Nonclinical Safety Studies for the Conduct of Human
    Clinical Trials and Marketing Authorization for Pharmaceuticals
  - S6: Preclinical Safety Evaluation of Biotechnology-Derived
    Pharmaceuticals
  - S7A: Safety Pharmacology Studies for Human Pharmaceuticals
  - S9: Nonclinical Evaluation for Anticancer Pharmaceuticals
- CDER Mapps
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