Therapeutic Categories

Grouping drugs under the aspect of their pharmacological and therapeutic application results in about 200 categories:

ACE Inhibitor
Adrenocortical Suppressant
Adrenocorticotropic Hormones
Aldose Reductase Inhibitors
Aldosterone Antagonists
α-adrenergic Agonists
α-adrenergic Blockers
α-Glucosidase Inhibitors
Anabolic Steroids
Analgesic, Dental
Analgesic, Narcotic
Analgesic, Non-narcotic
Androgens
Anesthetics, Inhaled
Anesthetics, Intravenous
Anesthetics, Local
Angiotensin II Antagonists
Anorexics

...c.f. The Merck Index 13th ed.

In most cases it is not obvious to conclude from a therapeutic class the treated disease. (At least for non-medical persons)
Typical diseases

The search for pharmaceutical drugs used to be rather straightforward until recent times:

A wealth of information about the disease, its causes, and the clinical symptoms were readily available. Thus the starting point for the pharmacological therapy was known.

Example: inhibition of an enzyme

Thus the target was fixed. Frequently, experience with existing medications was available. Therefore a valid target or at least a drugable target was present.

→ The target undergoes a change of its activity caused by the drug
Flow of information in a drug discovery pipeline

Valid target

DNA sequences and maps
- Genomics/Proteomics
  - Gene expression analysis
  - Target genes
  - Protein data
  - Protein structure prediction and analysis
  - Disease model

Empirical medicine
- Animal disease models
- Physiology database
- Medical research database

Disease biology

Disease characterization

Drug Discovery Today
Fractional content of marketed drugs according to their biochemical targets

Enzymatic targets

Distribution within the class of enzymes
contribution to the human genome and marketed drugs about 500 enzymes have been used as targets 100,000 estimated potential targets in the genome
GPCRs and other targets

- ion channel
- ligand
- adenyl cyclase
- G-protein complex
- ATP to cAMP
- transcription factors
- gene expression regulation
- nucleus
- protein kinase A
- inactive enzymes
- active enzymes
How do drugs interact with targets?

enzymes: substrate analoges, reversible and irreversible inhibitors
receptors: antagonists and agonists
ion channels: openers and blockers (inhibitors)
transporters: (re-)uptake inhibitors
DNA: intercalate, binding to the specific DNA-bases, groves, etc.
Drugs: mode of action (I)

Normal enzymatic turn-over

allosteric binding

Induced fit

conformational change

reaction
Drugs: mode of action (II)

- **competitive inhibitor:** higher affinity than natural substrate, directly acting

- **allosteric inhibitor/effector:** prevents binding by modifying the conformation

- **Irreversible binding:** chemical reaction leads to inactivation of the enzyme
  - e.g. acetyl-salicylic acid acetylates Ser530 of COX

- **Anti-metabolite:** Competitive alternate („wrong“) substrate
  - e.g. methotrexate instead of dihydrofolate, antiviral nucleoside analogues
Drugs: mode of action (III)

Ion channels: Mode of action by ligand binding, indirectly through receptors, or voltage gated
Drugs: mode of action (IV)

Agonist: ligand that causes an intrinsic effect (response of the receptor)

Partial agonist: weakly working agonist with high binding affinity, thus also working as antagonist
antagonist: ligand that prevents binding of the agonist, either directly (competitive binding) or indirectly (allosteric, prevents adoption of the reactive conformation)

inverse agonist: ligand stabilizing the inactive conformation

functional antagonist: prevents receptor response by a different mode of action
Why do drugs have funny names?

Examples for such faults in naming products exist!
Naming of drugs (I)

The trade name of a drug is usually chosen very carefully. Associative and speech-psychological aspects are considered.

Example within the german language:
The more x and y are appearing in the name, the more toxic.

Acetylsalicylsäure → Aspirin®

Problems will occur, if a product should get the same name throughout all countries. Examples:

Twix® (earlier: Raider)
Naming of drugs (II)

Furthermore, legal aspects have to be considered: existing words and words that imply a direct connection or target a specific consumer group cannot be protected.

Example: „Schülerschokolade“ is not possible in Germany

Thus a lot of inspiration is required to find a pleasant sounding name. Frequently syllables and foreign words (Latin, Greek, Spanish) are used that bear associations.

c.f. names for cars

® this name is approved and protected.

™ the producer indicates his intention to have this name protected.
Naming of drugs (III)

For the naming of the actual chemical substances there are also some (loose and empirical) guidelines.

Such names are adopted as „International Nonproprietary Name“ (INN) or „United States Adopted Name“ (USAN) at the lastest upon patent application.

Most of the time, the therapeutic class can be identified solely by the name. (similar names for substances with similar function.)

Prefixes and suffixes reflect chemical modification of the root compound.

Examples: ibufenac, clofenac, diclofenac, oxidanac
compound data bases

present substance libraries

ACD >100,000 chemicals
World Drug Index 58,000 compounds
USAN <10,000 in clinical trial
virtual library 100,000 compounds

investment per new chemical entity: >500,000 $
new chemical entities per year: ca. 15

Commercial

company in house

NCBI

Pubchem > 3,000,000 compounds
towards the drug (I)

symptoms           disease model           available medications

Increasing knowledge

usable hypothesis of mechanism  therapeutic target

enzyme model  cell model  animal model  transgenic animals  sequenced genomes

effort & expenses
evolution of disease symptoms with time

1800 1900 2000

Disease causing agents environmental genetic
lack of hygiene influence disposition
germs, bacteria carcinogens life style susceptibility
viruses

bioethic component

accepted legal definition of diseases

legal regulation for drug marketing (e.g. FDA)
The preclinical phase

- Therapeutic Target
- Lead Discovery
- Lead Optimization
- Clinical Candidate
- Commercial Drug

drug design
towards the drug (II)

Example: arterial hypertension

Arterial hypertension ("Arterielle Hypertonie") is a frequently observed disease (about 10 - 25% of all adults are affected). Persistent hypertension can lead to damage of blood vessels, the eyes, and the kidneys. → symptoms

category | systolic | diastolic
---------|---------|---------
optimum  | <120    | <80     
normal   | <130    | <85     
normal-high | 130 - 139 | 85 - 89 |
mild HD  | 140 - 159 | 90 - 99 |
moderate HD | 160 - 179 | 100 - 109 |
strong HD | >180 | or | >110 | mm (Hg)

Regulation of the blood pressure (simplyfied)

blood pressure = blood volume \times peripheral resistance

- sympaticus $\uparrow$
- parasympathicus $\downarrow$
- hormones
- blood volume
- heart (pumping) capacity
- peripheral resistance
- salt deposits $\text{Na}^+$, $\text{K}^+$, $\text{Ca}^{2+}$
diuretica and saluertica

Ions in the blood and in other salt deposits bind water. By elimination these ions the volume of the blood can be reduced.

This effect is caused by diuretica and saluertica:

Examples: hydrochlorothiazide, furosemide

Therapeutic administration of thiazides since 1960

Disadvantages / side effects:

deficiency of potassium
increased level of uric acid (Harnsäure)
increased level of fatty acids in the serum
not suitable with diabetes
α and β-blocker

Act relaxing via the peripheral nervous system and reduce the pumping capacity of the heart.

Examples: prasozin, tetrazosin, doxazosin, propanolol, atenolol, labetalol, pindolol

Simultaneously, the hormonal control is affected, whereby the peripheral resistance is diminished.

Therapeutic administration since 1970

Disadvantages and side effects:

withdrawal symptoms
reduced capacity of the heart (Herzinsuffizienz)
increased levels of fatty acids in the serum
effects on the central nervous system
vasodilators and calcium antagonists

Act relaxing on the smooth muscles of the arteries and thereby reduce the resistance.

Bind to the $hAT_2$-receptor or inhibit the calcium pump

Examples: hydralazine, minoxidil, diazoxide, verapamil, diltiazem, nifedipine

Therapeutic administration since 1980

Disadvantages and side effects:

Predominately on the function of the heart
Angiotensin Converting Enzyme Inhibitors

The endogenous oligopeptide Angiotensin II is one of the strongest vasoconstrictors. By inhibiting the angiotensin converting enzyme (ACE) the synthesis of Angiotensin II is disabled.

Examples: captopril, fosinopril, quinapril

Therapeutic administration since 1990

disadvantages:

fetotoxic (pregnancy)

Picture source: M. Gurrath

Angiotensin-II antagonists

competitive binding of non-peptidic compounds to the $hAT_1$-receptor (GPCR), which is the binding site of Angiotensin II.

Examples: losartan, valsartan, irbesartan, candesartan, telmisartan
Furthermore in clinical testing: olmesartan, forartan

therapeutic administration since 1995

disadvantages:
same as for ACE-inhibitors

## Evolution of targets over time

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Increasing specificity