

**Gondolatok a gyógyszeres
kezelésről
Biztonságosság
Hibák
Különbségek
Evidenciák**

**Dr. Habon Tamás
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RATIONAL DRUG THERAPY*

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NEW YORK

The administration of drugs for remedial purposes should be based on a thorough knowledge of physiology, pathology and the principal physiologic actions, as well as the more important secondary actions of the drugs to be administered. The physician should always bear in mind that drugs do not cure. They may be made valuable adjuncts in our endeavor to restore normal function in an abnormally functioning organ.

In administering drugs, one should also bear in mind that the taking of medicine should not be made a punishment or a disagreeable task to the patient, and therefore it is the duty of the prescriber to administer the medicinal agent in as palatable a form as possible. Furthermore, it often happens that the desired physiologic reaction is not obtained from a given drug because of improper mode of administration, or because of failure to select from a given group of drugs the particular drug best indicated in a given case. To illustrate this, I shall take up a few groups of drugs and endeavor to show how selection may be made from the different drugs of the same group in given cases.

SOPORIFICS

In the group of soporifics we find in most textbooks chloral, its derivatives and compounds, the opium series (opium, morphin, codein, ethylmorphin hydrochlorid, heroin, etc.), and the bromids.

Let us now consider the principal action and principal secondary action of each.

The chloral group depresses the central nervous system and, eventually, completely paralyzes it. It has no specific effect on pain sensation, but it does depress the reflexes of the spinal cord, and affects last of all the medulla oblongata, and therefore practically does not depress the respiratory center to any extent. It becomes at once evident that its administration as a hypnotic in a case of insomnia due to pain would be contraindicated, while, on the other hand, it is eminently the remedy of choice in cases of insomnia due to nervous excitation, especially when such excitation is of spinal or reflex origin.

When we bear in mind, furthermore, that chloral is irritating to skin and mucous membranes, it follows logically that it should be administered in high dilution and preferably in combination with some bland substance, so that we would prescribe our chloral hydrate in combination with glycerin or mucilage of acacia and with plenty of water.

Opium and its derivatives, on the other hand, have a pronounced selective action on pain sensation and on respiration, markedly reducing both in doses too small to affect general consciousness. This is especially true of its principal alkaloid, morphin. Therefore, opium and its alkaloids are indicated as analgesics rather than as hypnotics, especially when the rate of respiration is above normal. The possibility of morphin addiction should, of course, be borne in mind.

Bromids act directly as depressants on the central nervous system, reduce the reflexes and impair the

passage of impulses from the sensory to the motor cells. Therefore, in a case of sleeplessness due to a moderate degree of excitation, bromids would be indicated. But we must remember that (1) a certain degree of concentration of bromids in the circulating blood and in the tissues is required; (2) bromids are fairly rapidly eliminated, especially in the presence of chlorids; (3) bromids, like all halogen derivatives, are irritating to mucous membranes in concentrated solution, and (4) last, but not least, they have a rather disagreeable taste. Therefore, the administration of the bromids should begin some time before the desired effect is to be obtained, and frequent small doses will bring about greater physiologic response than a single large dose. When a concentration of bromids is to be maintained in the blood and tissues for some time, as in the treatment of epilepsy, the patient should be kept on a practically salt-free diet. The bromids should be administered in high dilution to prevent gastric irritation, and the taste may be corrected by the addition of acid fruit syrups or by a combination of a small amount of citric acid with simple syrup.

STIMULANTS

Turning our attention to the stimulants, we find again a number of drugs or group of drugs, each of which has its special indication. For instance, nuxvomica and especially its principal alkaloid, strychnin, has selective action on the spinal cord, and its application is therefore indicated in conditions in which the ordinary normal stimuli fail to bring about the corresponding muscular response, whether of striped or unstriped muscles, generally referred to as lack of tonus.

The caffein group of stimulants must be divided into two subdivisions: caffein and its salts acting on the central nervous system as well as on the kidneys, while theobromin has but little effect on the central nervous system. Caffein produces restlessness to the point of insomnia and mental confusion, has but little effect on the circulation, and quickens the rate of respiration while at the same time decreasing its amplitude. It becomes at once apparent that in such cases as we saw in the recent epidemic of influenza, associated with or followed by lobar and lobular pneumonia, with increased rate of pulse and respiration, together with mental excitation to the point of delirium, caffein was distinctly contraindicated. If it was given with a view of aiding renal excretion, because of the oliguria found in these cases, it seems to me that the drug of choice should have been theobromin sodium salicylate, or better still, one of the many saline diuretics, such as the citrates and acetates of ammonium, sodium or potassium. On the other hand, caffein would be indicated in cases of mental or psychic depression, and particularly in cases of depression incident to poisoning.

For a similar reason, that is, its accelerating effect on the respiratory rate, atropin was contraindicated in these cases, excepting when it was desired to check secretions, as in impending edema; but its influence on secretion to the extent of lessening perspiration would also have to be considered, and for this reason morphin would probably be preferable because of its selective action in lessening all secretions except those of the sweat glands. Neither would camphor be indicated in the above mentioned cases, because in physiologic doses its effect on heart and respiration is relatively small and in larger doses may cause an acceleration,

* Read before the Bronx County Medical Society, Nov. 20, 1918.

RATIONAL DRUG THERAPY *

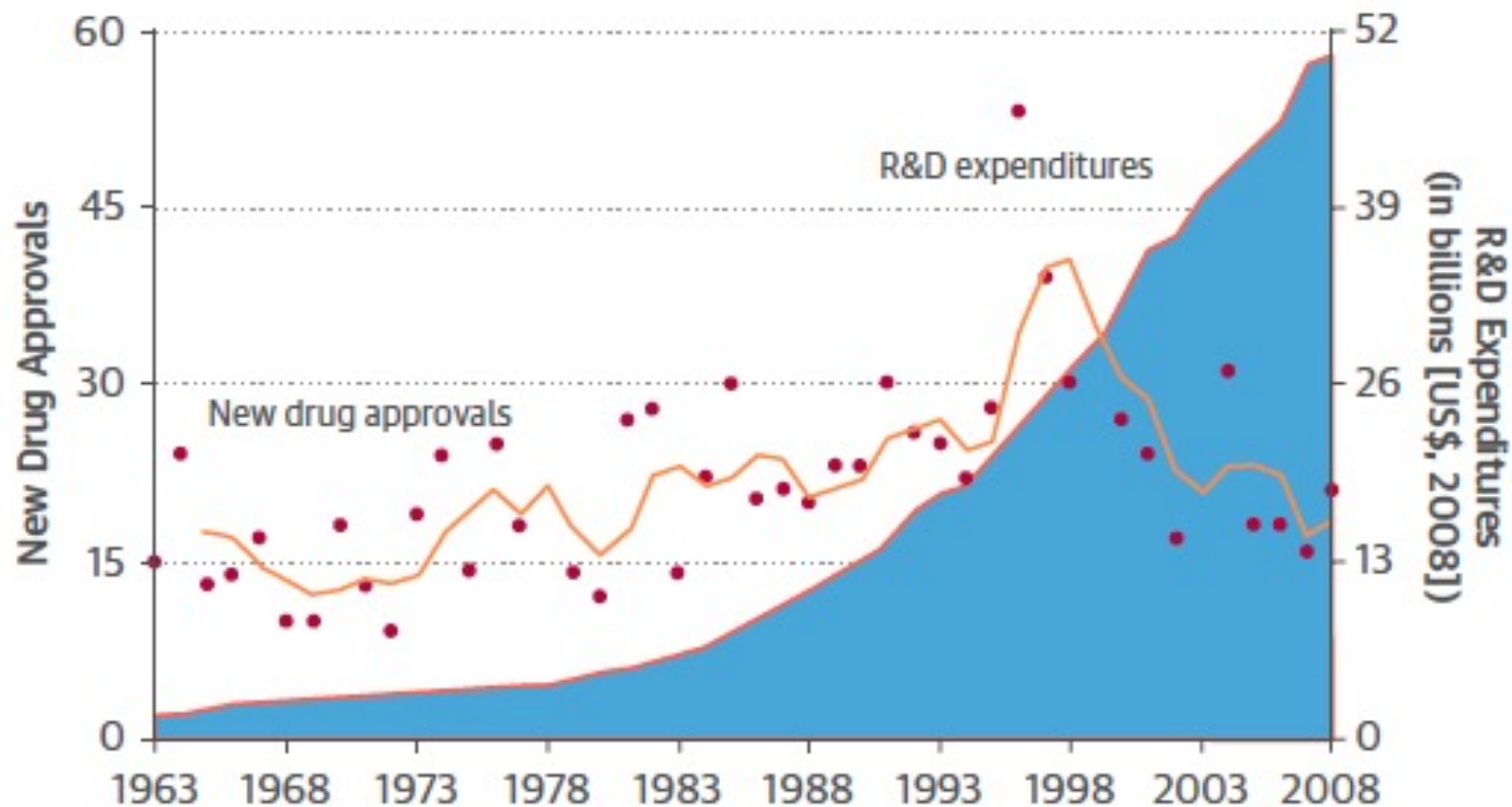
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FIGURE 4 New Drug Approvals and Pharmaceutical R&D Expenditures in the United States From 1963 to 2008



A node-link graph showing significant correlations between assigned terms in the “ontology of termination.”

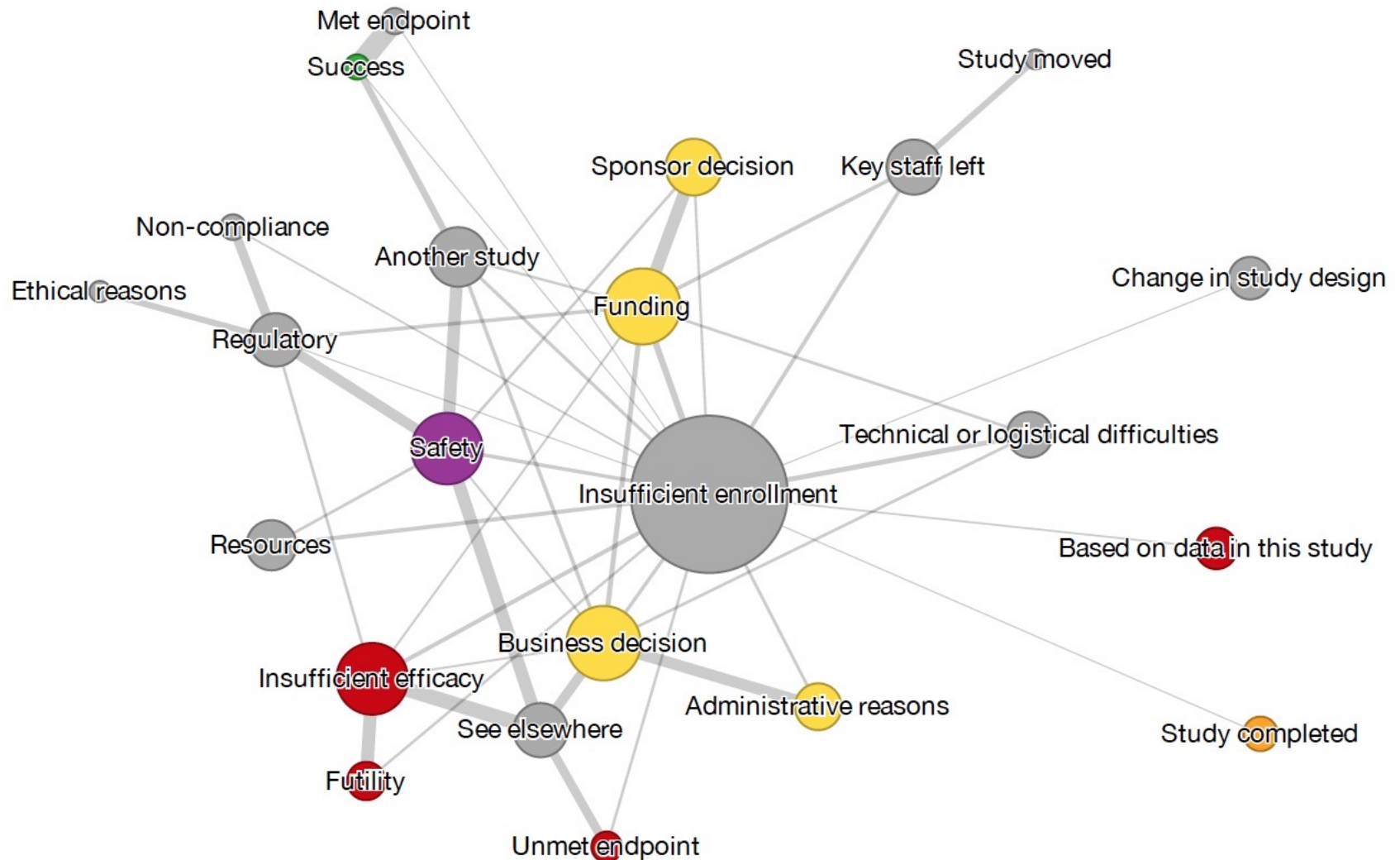
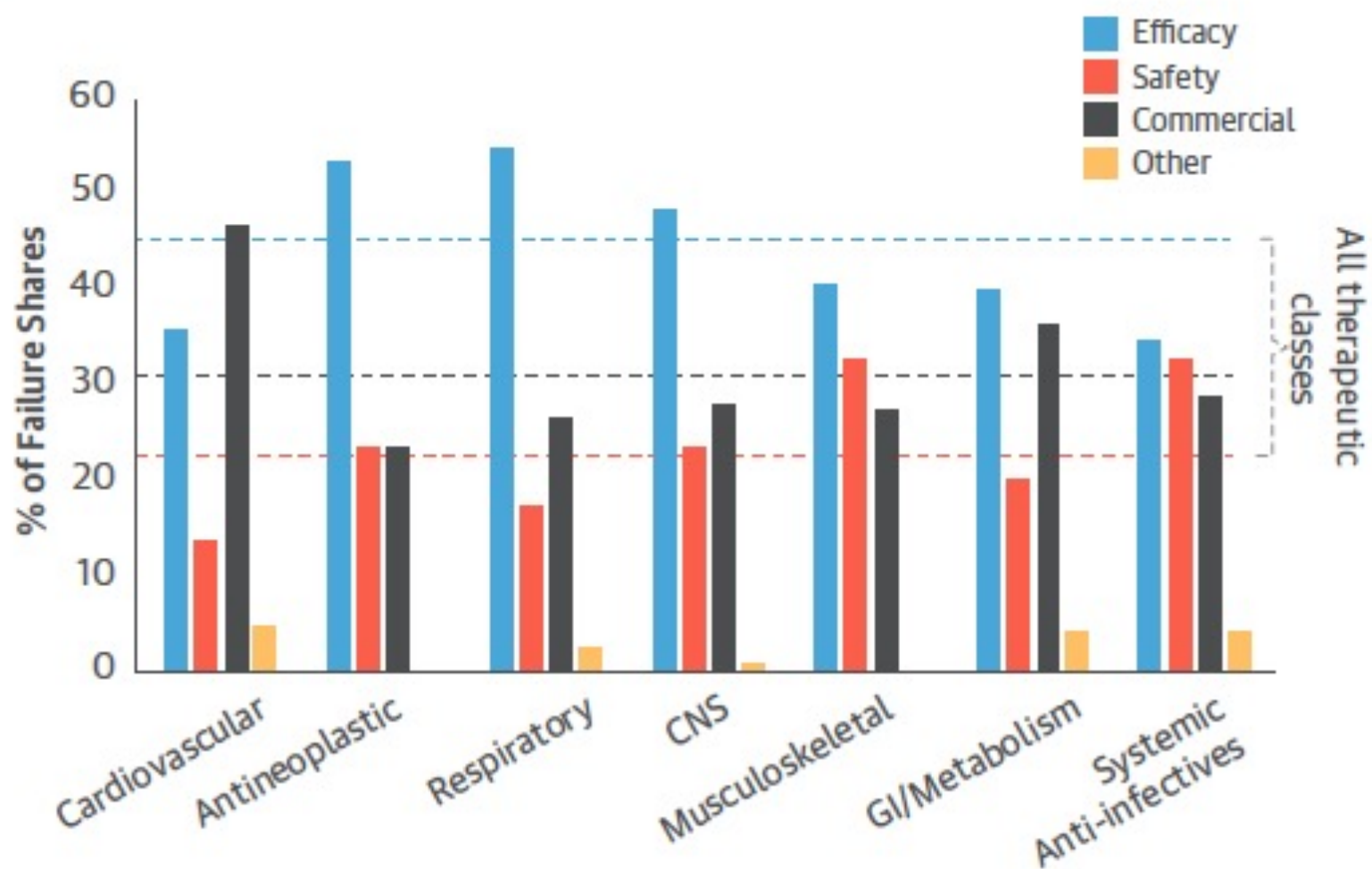


FIGURE 5 Drug Failures by Therapeutic Class, 2000 to 2009



RATIONAL DRUG THERAPY

Drug selection while treatment must be based on the following.

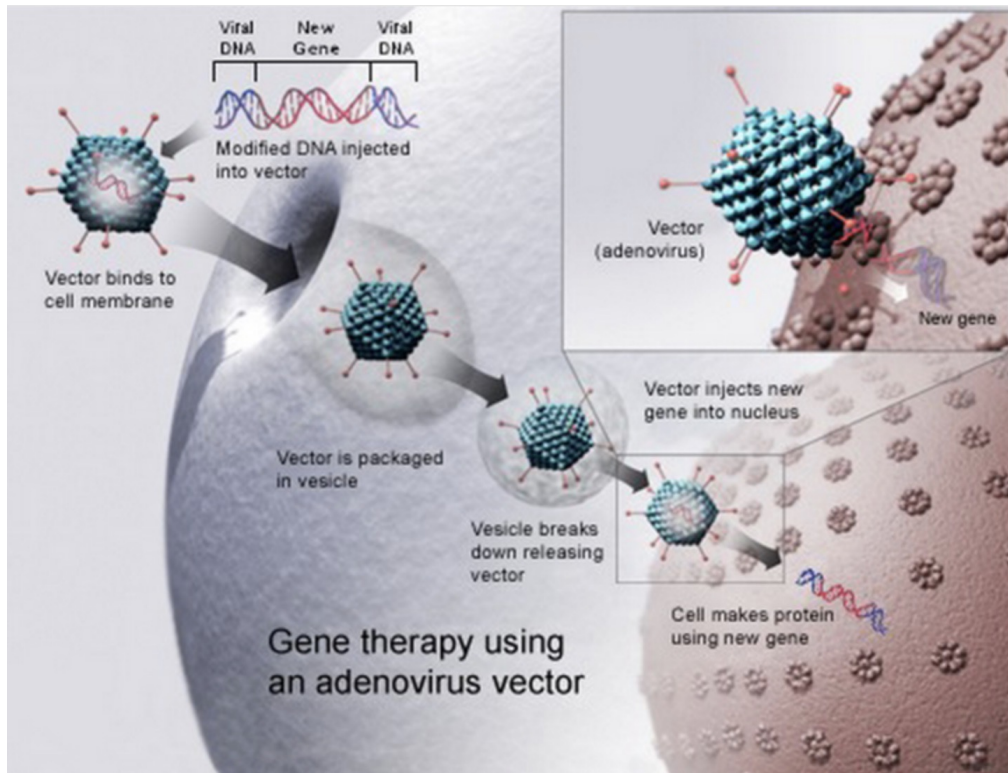
1. Relevance to disease - Indicated in the treatment of prevalent diseases.
2. Efficacy and safety - Based on the objective results from adequate pharmacological studies including at least expanded phase (II). clinical trials and / or additional phase (III). studies.
3. Quality.
4. Cost-of treatment regime (not just the unit cost).
5. Appropriateness to the capability of medical personnel at different levels of health care. The level of expertise required to prescribe, administer and monitor safety and adverse effects of single drug or group of drugs in the therapeutic category must be considered. Consideration should be given to the to the competence of local personnel in making the correct diagnosis.

The million-dollar drug

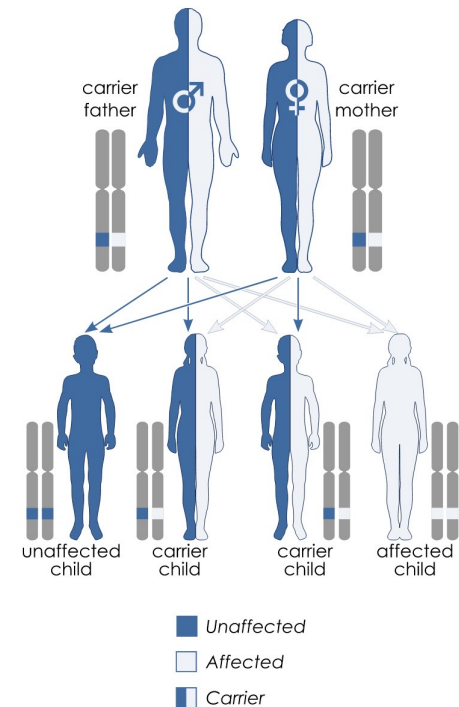
How a Canadian medical breakthrough that was 30 years in the making became the world's most expensive drug – and then quickly disappeared



Lipoprotein lipase deficiency



Autosomal recessive inheritance






Zolgensma is a gene therapy approved for children with the most severe form of SMA. Credit: Shutterstock.

The US Food and Drug Administration (FDA) has issued a statement regarding data accuracy issues related with Novartis' biologic license application (BLA) for gene therapy Zolgensma (onasemnogene abeparvovec-xioi).

[Zolgensma was approved in the US in May](#) this year for children under two years old with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 gene; this is the most severe form of SMA.

ZOLGENSMA FOR SPINAL MUSCULAR ATROPHY



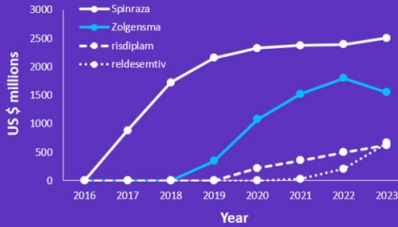
SMA is most often **LETHAL** in childhood

90% rate of death or permanent ventilation at two years of age in children with type 1 SMA

➔

ALL of the children were **ALIVE** at two years in the pivotal trial of Zolgensma

Price: \$425,000 annually for five years = \$2.125 million




Year	Spinraza	Zolgensma	Risdiplam	Reldesemtiv
2016	0	0	0	0
2017	1000	0	0	0
2018	1800	0	0	0
2019	2200	500	0	0
2020	2400	1200	100	0
2021	2450	1600	200	0
2022	2500	1800	300	0
2023	2550	1600	400	0

Spinraza: The first ever drug for SMA, but dosed every four months intrathecally

Risdiplam & reldesemtiv: two potential competitors currently in phase II/III trials

Zolgensma: the second SMA market entrant, but the first ever SMA gene therapy. Only requires a single intravenous dose



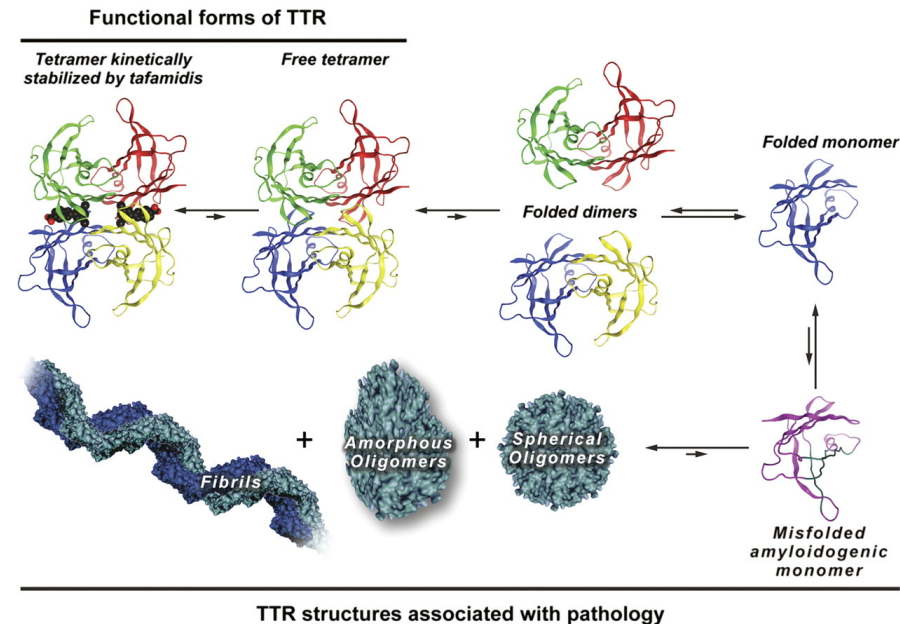


Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., et al., for the ATTR-ACT Study Investigators*

Endpoint	Tafamidis	Placebo	Hazard Ratio (95% Confidence Interval)
All-cause mortality, n (%)	78/264 (29.5)	76/177 (42.9)	0.70 (0.51 - 0.96)
Cardiovascular hospitalization (number per year)	0.48	0.70	0.68 (0.56 - 0.81)

Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils in the myocardium. The deposition occurs when wild-type or variant transthyretin becomes unstable and misfolds. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis.



Myosin modulation in HF: a personalized approach?

GALACTIC-HF
Results expected at AHA 2020

HCM

HFpEF

HFrEF

← Myosin inactivation
(Mavacamten)

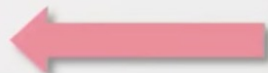
Hypertrophic
Cardiomyopathy

Myosin activation →
(Omecamtiv mecarbil)

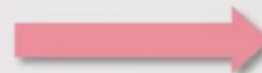
Dilated
Cardiomyopathy



Concentric
Hypertrophy



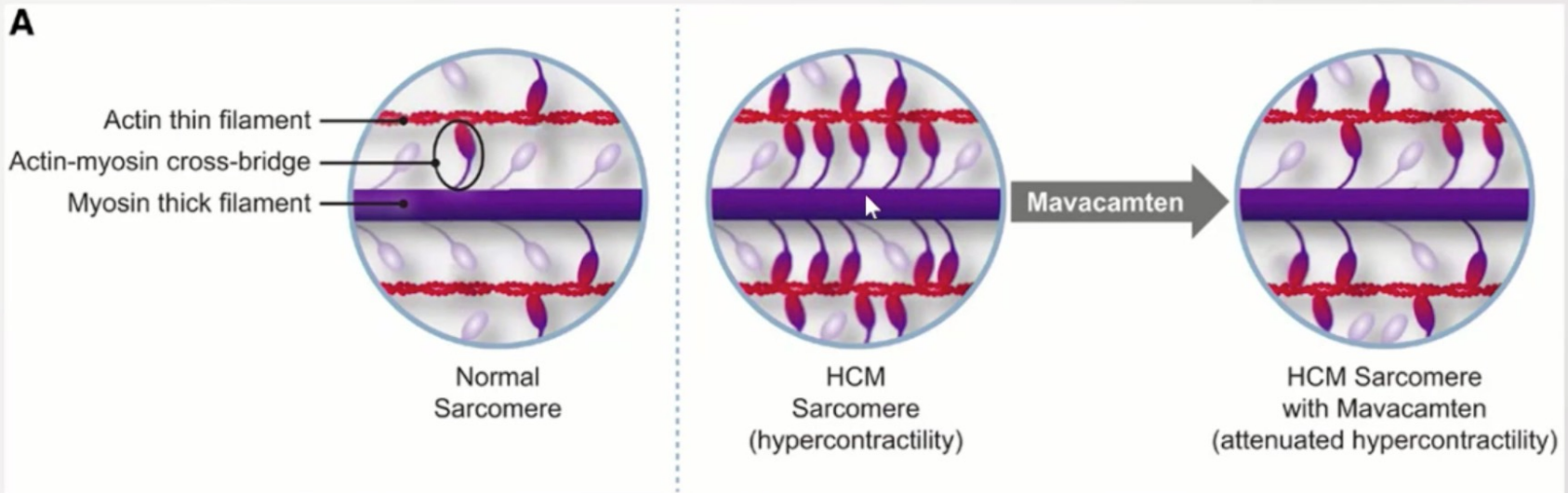
LV dilation



Myosin modulator Mavacamten in patients with HOCM

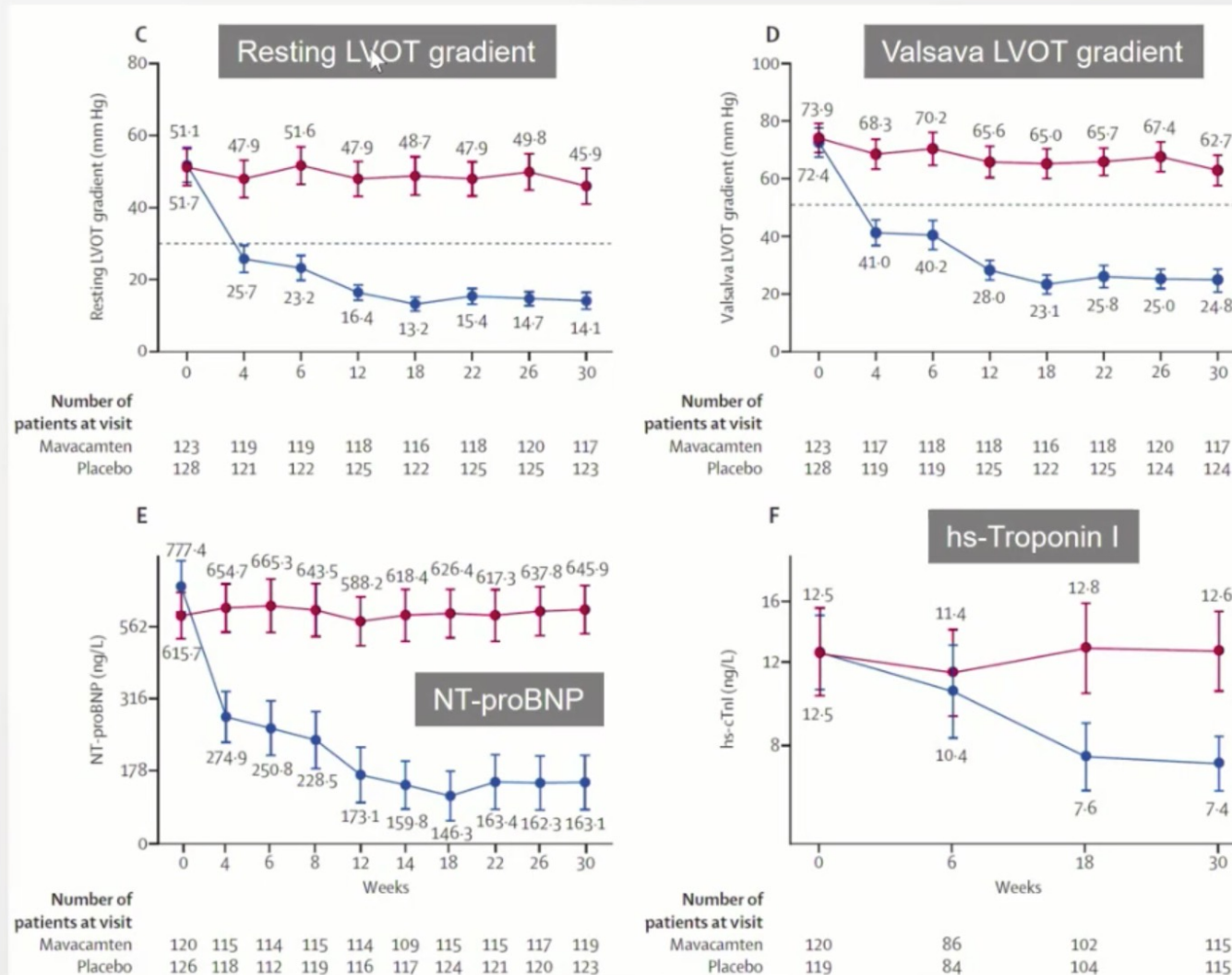
EXPLORER-HCM

Mode of action



Myosin modulator Mavacamten in patients with HOCM

EXPLORER-HCM





RATIONAL DRUG THERAPY

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3. Quality.

4. Cost-of treatment regime (not just the unit cost).

5. Appropriateness to the capability of medical personnel at different levels of health care. The level of expertise required to prescribe, administer and monitor safety and adverse effects of single drug or group of drugs in the therapeutic category must be considered. Consideration should be given to the competence of local personnel in making the correct diagnosis.

Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study

Anton Pottegård,¹ Kasper Bruun Kristensen,¹ Martin Thomsen Ernst,¹ Nanna Borup Johansen,² Pierre Quartarolo,³ Jesper Hallas¹

Zhejiang Huahai Pharmaceutical Co., Ltd.
SHA: 600521

[+ Követés](#)

11,06 CNY **-0,21 (1,86%)** ↓

dec. 28. 15:00 GMT+8 · Nyilatkozat

1 nap 5 nap 1 hónap **6 hónap** YTD 1 év 5 év Max.





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 September 2018
EMA/585263/2018

Update on review of valsartan medicines

Risk from NDMA remains low, a related substance NDEA also being investigated

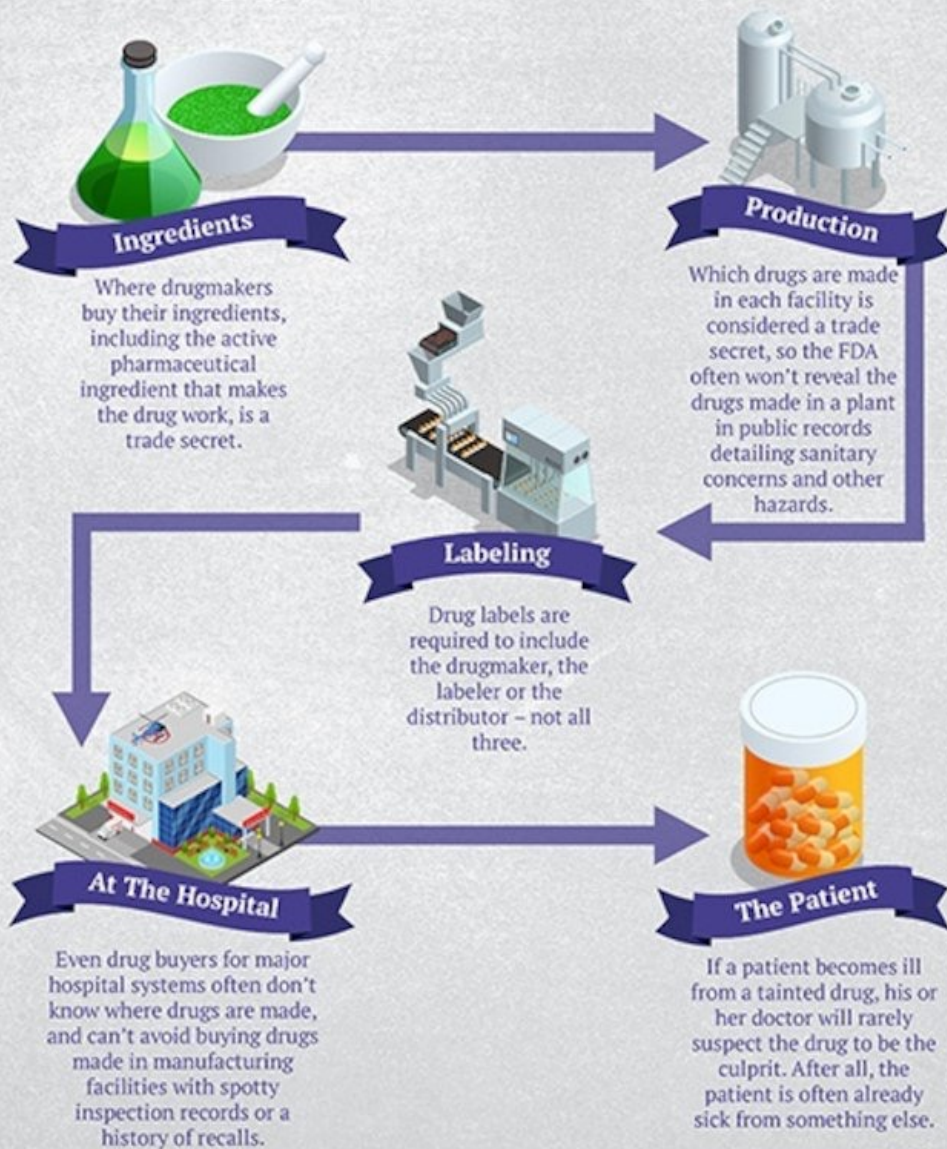
The European Medicines Agency (EMA) has updated its calculation of the risk from valsartan medicines containing N-nitrosodimethylamine (NDMA), taking into account results from latest tests on the active substance from Zhejiang Huahai.

In line with EMA's previous assessment, the life-time risk of cancer is considered low and is estimated to be in the order of 1 in 5,000 for an adult patient who had taken an affected valsartan medicine at the highest dose (320 mg) every day from July 2012 to July 2018.

EMA's risk assessment is based on the average levels of NDMA in the active substance produced by Zhejiang Huahai since 2012 (when the company changed its manufacturing process) and on the assumption that all the NDMA is transferred to the final product.

Why Is Tracking Bad Drugs So Difficult?

Our drug supply is shrouded in mystery, every step of the way.



Credit: Lydia Zuraw and Sydney Lapkin/Kaiser Health News; Getty Images

6. Local health problems. The influence of concomitant, locally prevalent diseases or conditions on pharmacokinetic and pharmacodynamic parameters modifying therapeutic response have to be considered in making the selection eg. malnutrition, liver disease.

7. Benefits / Risk ratio - when several comparable drugs are available for the same therapeutic indication it is necessary to select the one which provides the most favorable benefit/risk ratio.

8. Preferential factors for evaluating therapeutically equivalent drugs - when two or more drugs are therapeutically equivalent preference should be given to :-

(A) The drug most thoroughly investigated and therefore the best understood with respect to its beneficial properties and limitations.

(B) The drug which is clinically appropriate for more than one disease.

(C) The drug with the most favorable pharmacokinetic properties eg., to improve the compliance to minimize risk.

(D) The drug that are in a dosage form that is easy for the health staff to dispense easily and safely administer to the patient.

(E) The drugs that are easy for the patient to take or with the broadest acceptability.

(F) The drugs, pharmaceutical products and dosage forms with favorable stability under anticipated local conditions for which storage facilities exist.

(G) The drugs for which reliable local manufacturing facilities exist.

9. In the majority of cases the drugs should be formulated as single compounds. Fixed-ratio combination are only acceptable when-

(A) The clinical value of simultaneous use of more than one dose is documented.

(B) The therapeutic benefit of the combination is greater than the sum of each of the individual components.

(C) The combination is safer than the use of an individual drug.

(D) The cost of the combination product is less than or equal to the total cost of the individual products.

(E) The compliance is improved.

(F) The combination must be such that sufficient quantities to meet the needs of the majority of the population can be maintained.

10. Periodic review of druglist - Yearly or whenever necessary to incorporate significant new therapeutic advances and selected drugs.

(A) Generally new drugs should be introduced only if they offer distinct advantages over previously selected drugs.

(B) If on the basis of new information, drug already on the list are found to no longer posses a favorable benefit / risk ratio, they should be replaced by drugs with the higher benefit/risk ratio.

11. International Non-proprietary names (INN ; generic names) should be used for drugs.

COUNTERTHINK

WHAT THE DRUG COMPANIES REALLY WANT



Process of rational prescribing

- Establish a diagnosis
- Define therapeutic goals
- Select the class of drugs capable of achieving each goal
- Identify a drug from the class
- Decide the route, dose, duration of treatment
- Provide proper information to patient
- Monitor compliance, achievement of goal and ADR
- Modify therapy

CONCLUSION

- Drug use is the end of therapeutic consultation.
- Health professionals have a responsibility to ensure that the right drug is prescribed , dispensed and taken.
- Improving drug use improves the quality of care and frequently lowers cost.



VARIABILITY IN DOSE-RESPONSE



Sir William Osler
(1849-1919)

“If it were not for the great variability among individuals, medicine might as well be a science and not an art”

GYÓGYSZERES KEZELÉS PROBLÉMÁI...

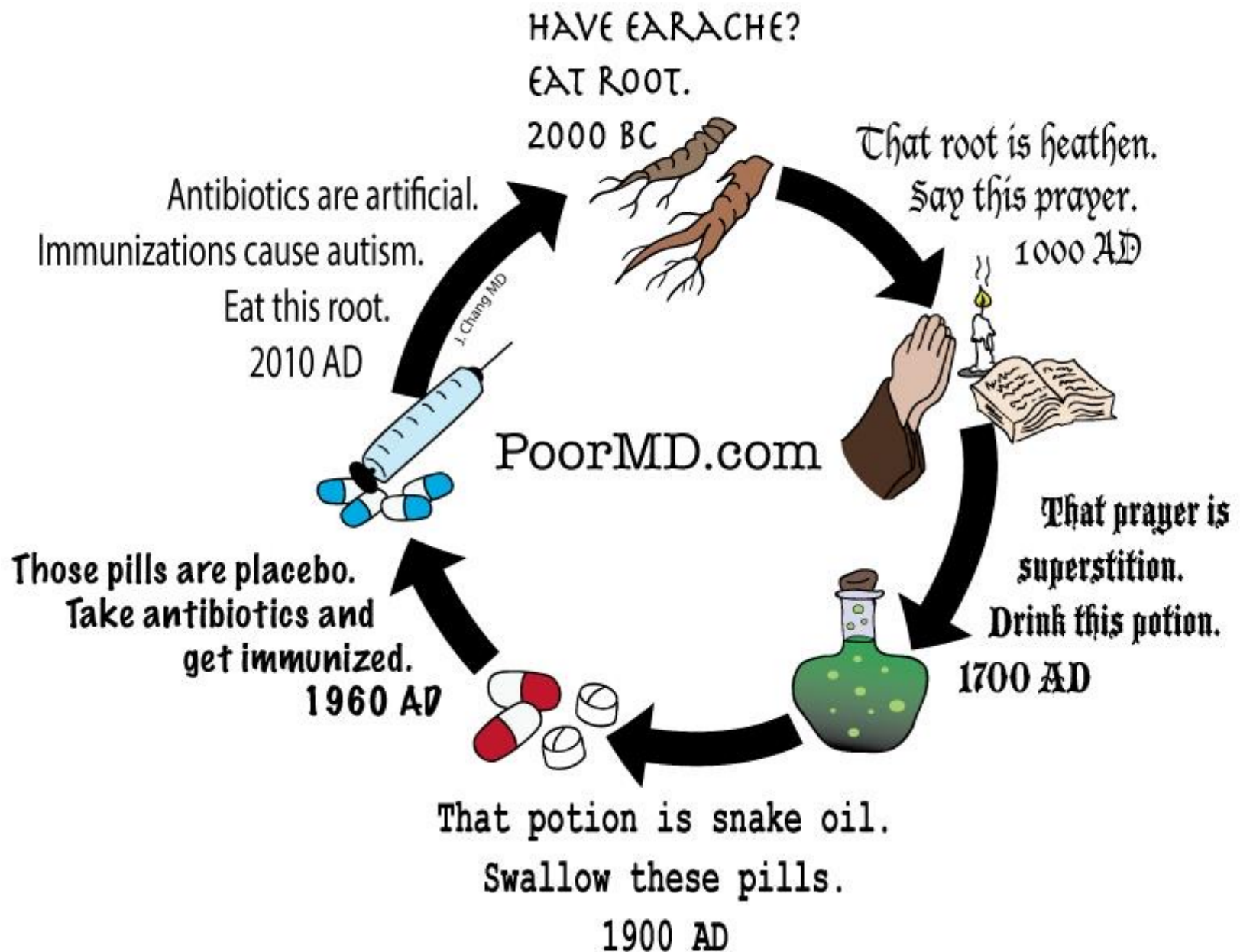
-

- Sok beteg – még a jól működő terápiák esetében is – nem reagál a kezelésre...

- Még a jól vezetett terápiák esetében is vannak nem kívánt mellékhatások...

-

The History of Medicine





Hogyan keletkezhetek a következő adatok?



- A kórházi felvételek **5** %-a gyógyszer-mellékhatások miatt következik be
- A kórházi betegek **5** %-nál kórházi kezelésük során mellékhatás lép fel
- Az **5**.. leggyakoribb kórházi halálok az EU-ban
- Évente kb. **197 000** halált gyógyszer-mellékhatással hoznak összefüggésbe az EU-ban
- **79**.. milliárd Euro/ év többletköltséget jelent

forrás: COMMISSION STAFF WORKING DOCUMENT Accompanying document to the Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

Prediszponáló tényezők

többféle gyógyszer egyidejű szedése

életkor – idős

újszülött

betegség

nem

genetikai polimorfizmus

Increased incidence of ADRs in elderly

These may be due to the following factors:

- A. Changes in pharmacokinetics
- B. Changes in pharmacodynamics
- C. Drug interactions
- D. Inappropriate prescribing in elderly
- E. Co-morbidities



Alapfogalmak

■ Adverse event – Nemkívánatos esemény (AE)

- A vizsgálati készítménnyel kezelt beteg vagy a vizsgálati alany egészségi állapotában bekövetkező kedvezőtlen változás, amely **nem áll szükségszerűen** oki összefüggésben az alkalmazott kezeléssel

■ Adverse reaction – mellékhatás (ADR)

- A vizsgálati készítmény bármely adagjának alkalmazása mellett bekövetkező minden kedvezőtlen és nem kívánt reakció, **amely összefüggésben** áll a vizsgálati készítménnyel

■ Unexpected adverse reaction – nem várt mellékhatás (uADR)

- Olyan mellékhatás, amely **jellegét** vagy **súlyosságát** tekintve eltér a megfelelő termékismertetőben található mellékhatástól, így vizsgálati készítmény esetén a vizsgáló részére összeállított ismertetőtől, illetve gyógyszer esetén az alkalmazási előírástól

■ Serious adverse event or serious adverse drug reaction - súlyos nemkívánatos esemény vagy súlyos mellékhatás (SAE/ SADR)

- a mellékhatás, illetve a nemkívánatos esemény akkor súlyos, ha a vizsgálati készítmény bármilyen adagjának alkalmazását a vizsgálati alany **halála**, **életveszélybe kerülése**, **kórházi kezelése**, folyamatban lévő kórházi ellátásának **meghosszabbodása**, **maradandó** vagy **jelentős egészségkárosodása**, fogyatékosága követi, illetve **veleszületett rendellenesség**, születési hiba fordul elő



Még néhány tisztázandó kérdés

■ Seriousness --- severity

- Súlyosság (**severity**): a súlyos (severe) kifejezést gyakran alkalmazzák valamely esemény mértékének jelzésére. Nem tévesztendő össze a súlyosság azon fogalmával (**seriousness**), amely a beteg állapotára/eseményre vonatkozó kimenetel alapján irányadóul szolgál adott intézkedések megtételére.

■ Életveszélyes állapot --- life threatening

- A súlyos (serious) nemkívánatos eseményre, vagy mellékhatásra vonatkozó életveszélyes" minősítés arra utal, hogy az esemény idején a vizsgálati alany halálos veszélyben volt; a minősítés nem olyan eseményre utal, amely ha súlyosbodik, feltételezhetően halálhoz vezethetett volna.

■ Ok-okozati összefüggés

- Lehetősége mindazon esetekben fennáll, amikor az összefüggés nem zárható ki teljesen
 - gyógyszeradás az AE megjelenése előtt történt?
 - van-e elváltozás az alkalmazás helyén?
 - az AE közvetlenül a gyógyszeradás után alakult ki?
 - dechallenge, rechallenge pozitív?
 - egyéb gyógyszer elhagyása befolyásolja-e az AE-t?
 - korábban jelentkeztek-e ezek a tünetek az adott gyógyszertől?
 - az AE a gyógyszer ismert mellékhatásai közé tartozik?
 - a gyógyszeradás és a AE közti idő összeegyeztethető-e az esemény jellegével?

ADR - etiología

Dose-related ADRs are particularly a concern when drugs have a narrow therapeutic index (eg, hemorrhage with oral anticoagulants). ADRs may result from decreased drug clearance in patients with impaired renal or hepatic function or from drug-drug interactions.

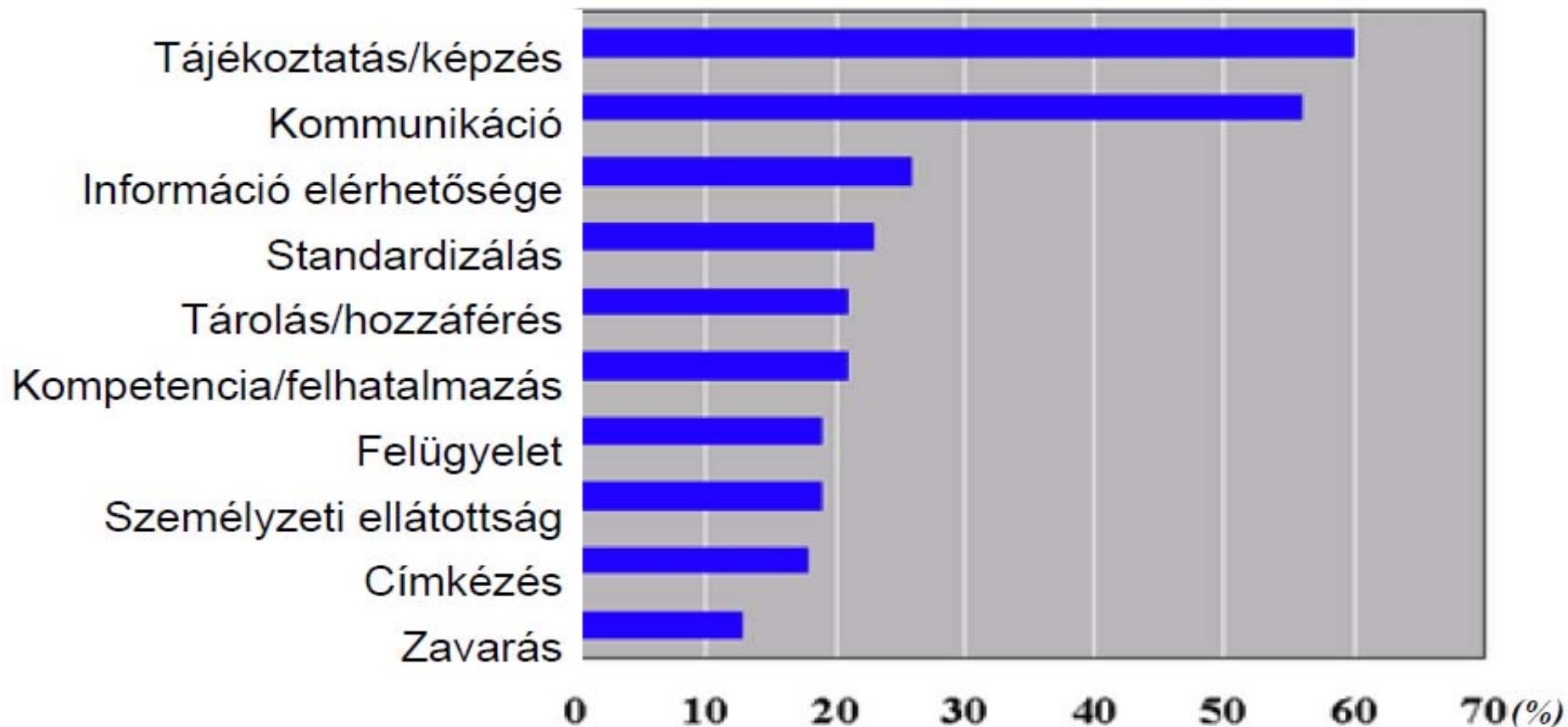
Allergic ADRs are not dose-related and require prior exposure. Allergies develop when a drug acts as an antigen or allergen. After a patient is sensitized, subsequent exposure to the drug produces one of several different types of allergic reaction /

Idiosyncrasy is an imprecise term used to classify unexpected ADRs that are not dose-related or allergic. They occur in a small percentage of patients given a drug. Idiosyncrasy has been defined as a genetically determined abnormal response to a drug, but not all idiosyncratic reactions have a pharmacogenetic cause. The term may become obsolete as specific mechanisms of ADRs become known.

ADR – osztályozás - súlyosság

Mild	No antidote or treatment is required; hospitalization is not prolonged
Moderate	A change in treatment (eg, modified dosage, addition of a drug), but not necessarily discontinuation of the drug, is required; hospitalization may be prolonged or specific treatment may be required
Severe	An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR
Lethal	An ADR directly or indirectly contributes to a patient's death

Gyógyszerezési hibák kiváltó okai



forrás: www.jcaho.org/sentinel_events

Where Do Errors Occur?

Prescribing	39%
Transcribing	11%
Dispensing	12%
Administering	38%

Drug error

- The wrong choice of a drug or a prescription for the wrong dose, frequency, or duration
- An error in reading the prescription by the pharmacist so that the wrong drug or dose is dispensed
- An error in reading the label of the drug container by the care provider giving the drug so that the wrong drug or dose is given
- Incorrect instructions to the patient
- Incorrect administration by a clinician, care provider, or patient
- Incorrect storage of a drug by the pharmacist or patient, altering the drug's potency
- Use of outdated drug, altering the drug's potency
- Confusion of the patient so that the drug is taken incorrectly

MEDICAL CENTER HOSPITAL

100-890 W. 4TH STREET

ODESSA, TEXAS

PH. 333-7771

FOR Varguez, Ramon

AGE _____

ADDRESS 11111 1st St

DATE 6/23/95

NO REFILLS ☐

REFILLS

LABEL ☐

Zenit 20mg # 120 -

20mg P.O. Q6hr

Fennos sulfate 300mg # 100

300mg P.O. TID E meals

Humulin N

30 units SQ BID

PRODUCT SELECTION PERMITTED

DISPENSE AS WRITTEN

✓ Under 20g

@ 30

50 1/4 1/2 50

Look-alike And Sound-alike Drug Names

Accupril®	Accutane®
Alprazolam	Lorazepam
Cardene®	Cardura®
Flomax®	Fosamax®
Lamisil®	Lomotil®
Nizoral®	Neoral®
Plendil®	Prilosec®
Zantac®	Zyrtec®

Tege + the 4R Day PDpd.

Arundin 4 m p.d. 5R



Mit gondolnak a mellékhatás bejelentésekről az egészségügyi szakemberek?

- Adminisztrációs teher (~80%)
- Önként vállalt társadalmi munka (~40%)
- Nincs törvényi előírás (40%)
 - De van!!! (Isd Gyógyszertörvény, EüM rendelet)
- A betegek tájékoztatása a gyógyszer alkalmazásával járó kockázatokról
 - Felesleges – betegtájékoztatóban szerepel minden (68%)
 - Túlzott (hamis) válaszreakciót eredményez (10%)
 - Rontja a beteg együttműködési készségét (15%)
- A forgalmazó nem igényli, sőt ellenérdekelt (20%)
- Nem tudományos tevékenység (45%)



ÖSSZEHASONLÍTÁSKÉPPEN.....

■ WHO által ideálisnak tartott
bejelentési szám:

200-250 / 1 millió lakos / év

■ Magyarország: **70-80**

Tények és tévhitek

[heartwire]

THROMBOSIS

Dabigatran fatal bleeding less than in clinical trials

MAY 25, 2012 Sue Hughes

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3

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26

g +1

1

in Share

7

1 Comments

Read later



🖨 Print

📧 Send

Font size

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ingelheim)
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Az interakció kialakulásának mechanizmusa

Farmakokinetikai

a gyógyszer koncentrációja változik meg a támadáspont helyén

a gyógyszernek kicsi a terápiás szélessége

a gyógyszer dózis-hatás görbéje meredek

Farmakodinámiás

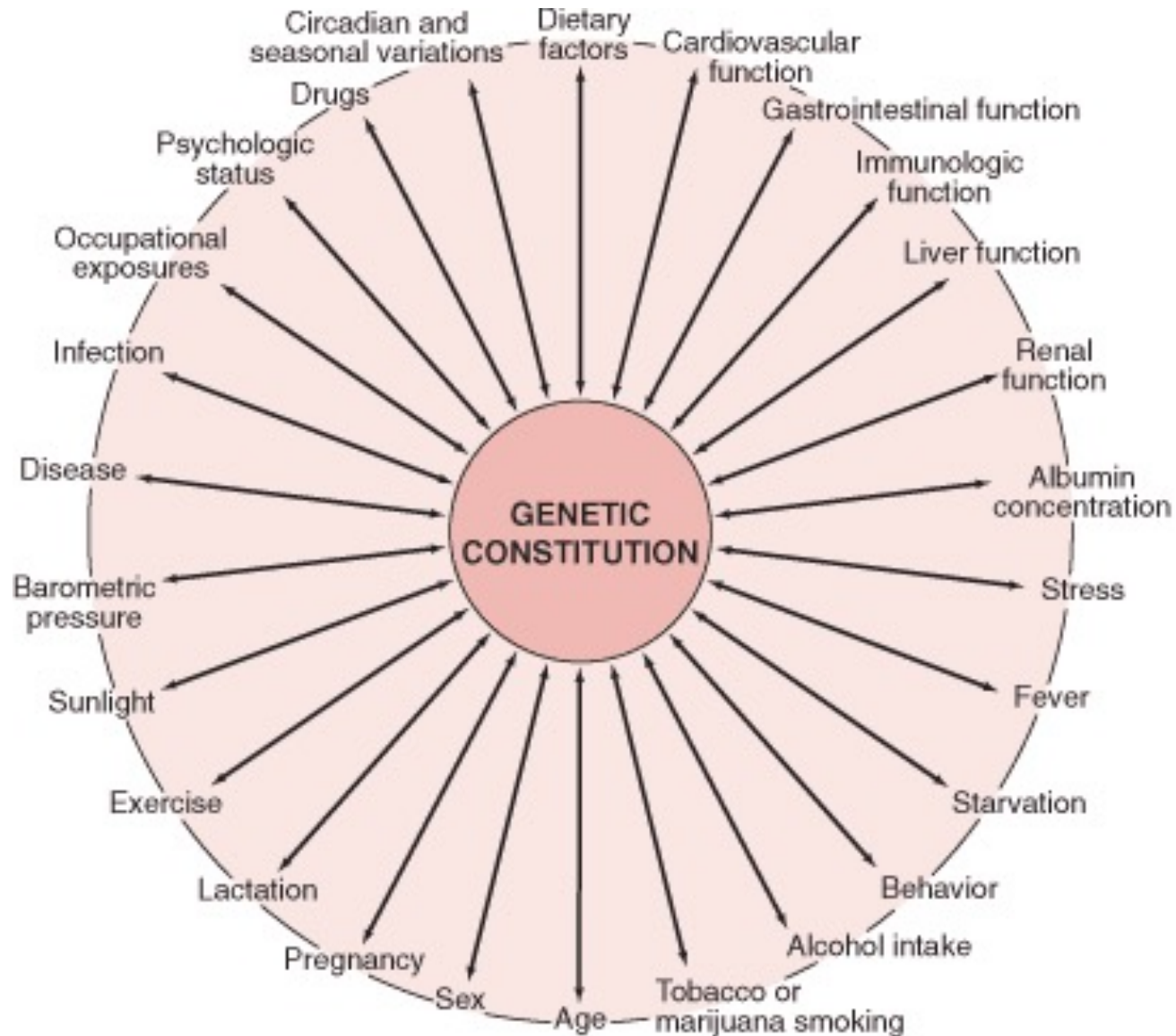
a farmakológiai hatás változik meg anélkül, hogy a gyógyszer koncentrációja változna

a gyógyszernek kicsi a terápiás szélessége

Farmakokinetika

Category	Parameter	Formula
Absorption	Absorption rate constant	Rate of drug absorption ÷ Amount of drug remaining to be absorbed
	Bioavailability	Amount of drug absorbed ÷ Drug dose
Distribution	Apparent volume of distribution	Amount of drug in body ÷ Plasma drug concentration
	Unbound fraction	Plasma concentration of unbound drug ÷ Plasma drug concentration
Elimination	Rate of elimination	Renal excretion + Extrarenal (usually metabolic) elimination
	Clearance	Rate of drug elimination ÷ Plasma drug concentration
	Renal clearance	Rate of renal excretion of drug ÷ Plasma drug concentration
	Metabolic clearance	Rate of drug metabolism ÷ Plasma drug concentration
	Fraction excreted unchanged	Rate of renal excretion of drug ÷ Rate of drug elimination
	Elimination rate constant	Rate of drug elimination ÷ Amount of drug in body
		Clearance ÷ Volume of distribution
	Biologic half-life	$0.693 \div \text{Elimination rate constant}$

Farmakogenetika



Variation	Incidence	Effects
Acetylation, fast	—	Need for higher or more frequent doses of drugs that are acetylated (eg, isoniazid) to produce the desired therapeutic response
Acetylation, slow (drug inactivation by hepatic <i>N</i> -acetyltransferase)	About 50% of the US population	Increased susceptibility to adverse effects of drugs that are acetylated (eg, with isoniazid , peripheral neuritis; with hydralazine or procainamide , lupus)
Aldehyde dehydrogenase-2 deficiency	About 50% of Japanese, Chinese, and other Asian populations	With alcohol ingestion, marked elevations of blood acetaldehyde, causing facial flushing, increased heart rate, diaphoresis, muscle weakness, and sometimes catecholamine-mediated vasodilation with euphoria
<i>CYP2C19</i> genetic polymorphisms	30% in one study Common among East Asians	Reduced enzymatic activation of clopidogrel , resulting in reduced antiplatelet effect and high risk of thrombosis in high-risk patients
G6PD deficiency	10% of black males High prevalence in people of Mediterranean descent	With use of oxidant drugs, such as certain antimalarials (eg, chloroquine , primaquine), increased risk of developing hemolytic anemia
Genetic polymorphisms of <i>CYP2C9</i> and vitamin K epoxide reductase complex subunit 1 (<i>VKORC1</i>)	—	Increased action of warfarin ,* increasing risk of bleeding events
HLA-B*1502	1 to 6/10,000 in countries with mainly white populations In some Asian countries, about 10 times higher	Increased risk of adverse reactions to carbamazepine , including serious dermatologic reactions (eg, Stevens-Johnson syndrome)
Plasma pseudocholinesterase deficiency	About 1/1500 people	Decreased succinylcholine inactivation

PPI and thienopyridines

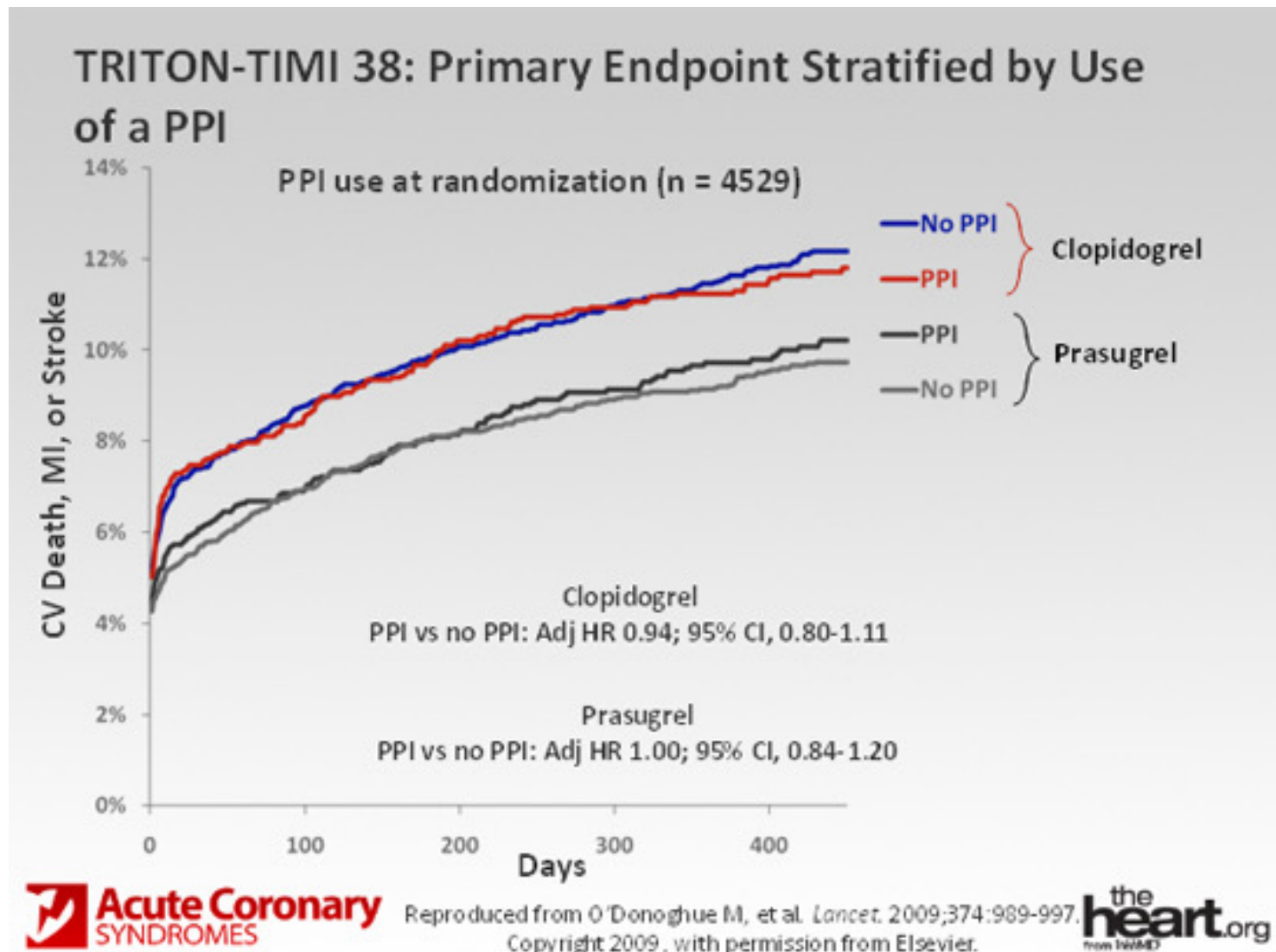
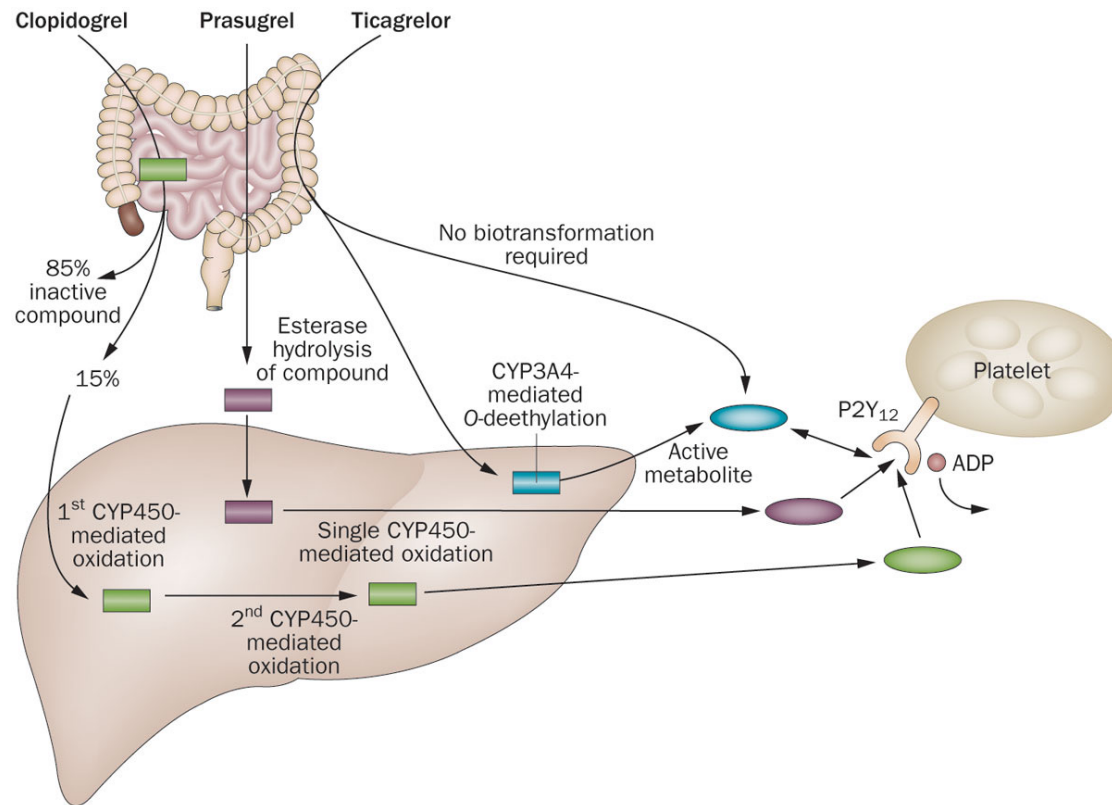
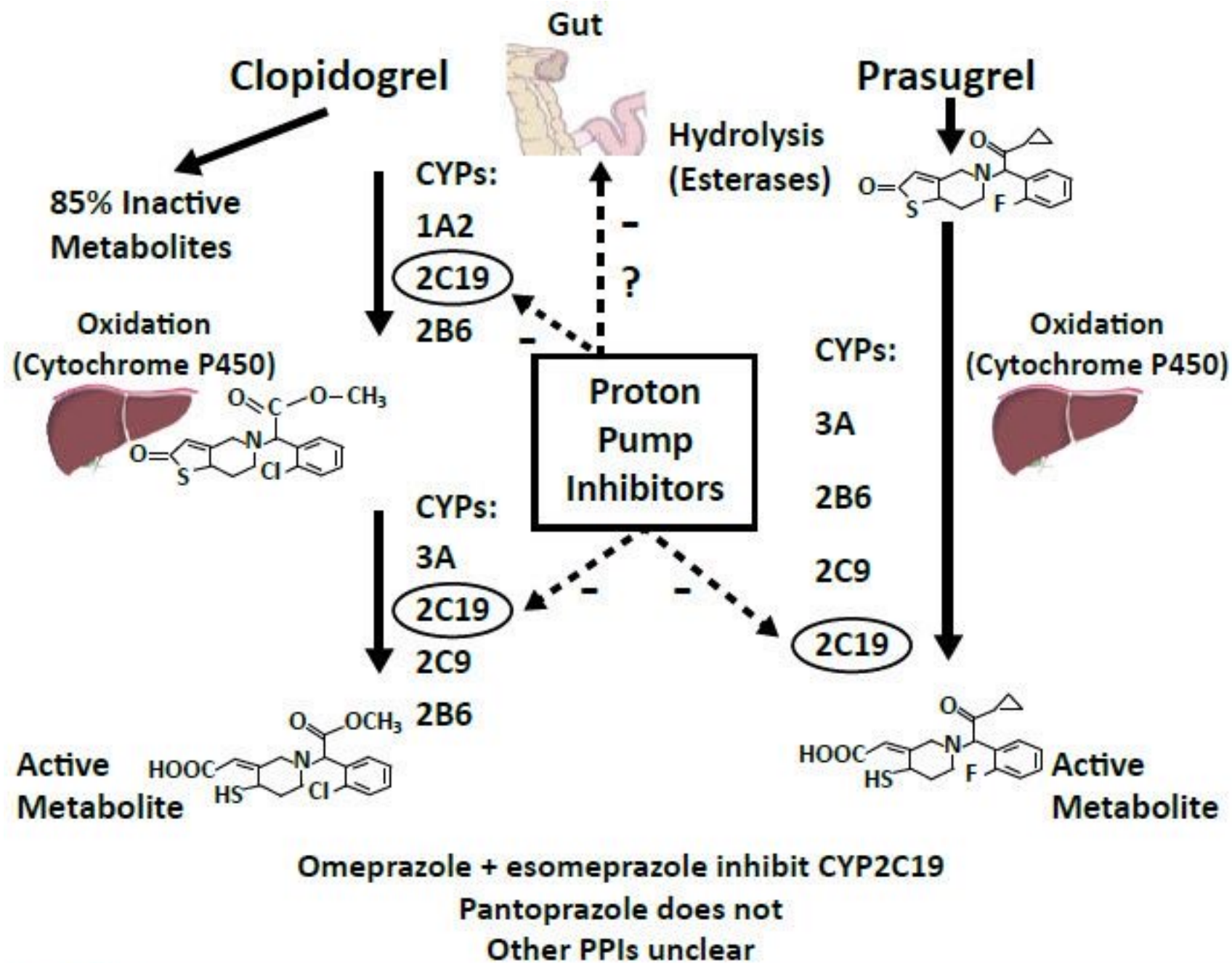


Figure 1 Prasugrel and ticagrelor are more-potent and faster-acting antiplatelet agents than clopidogrel

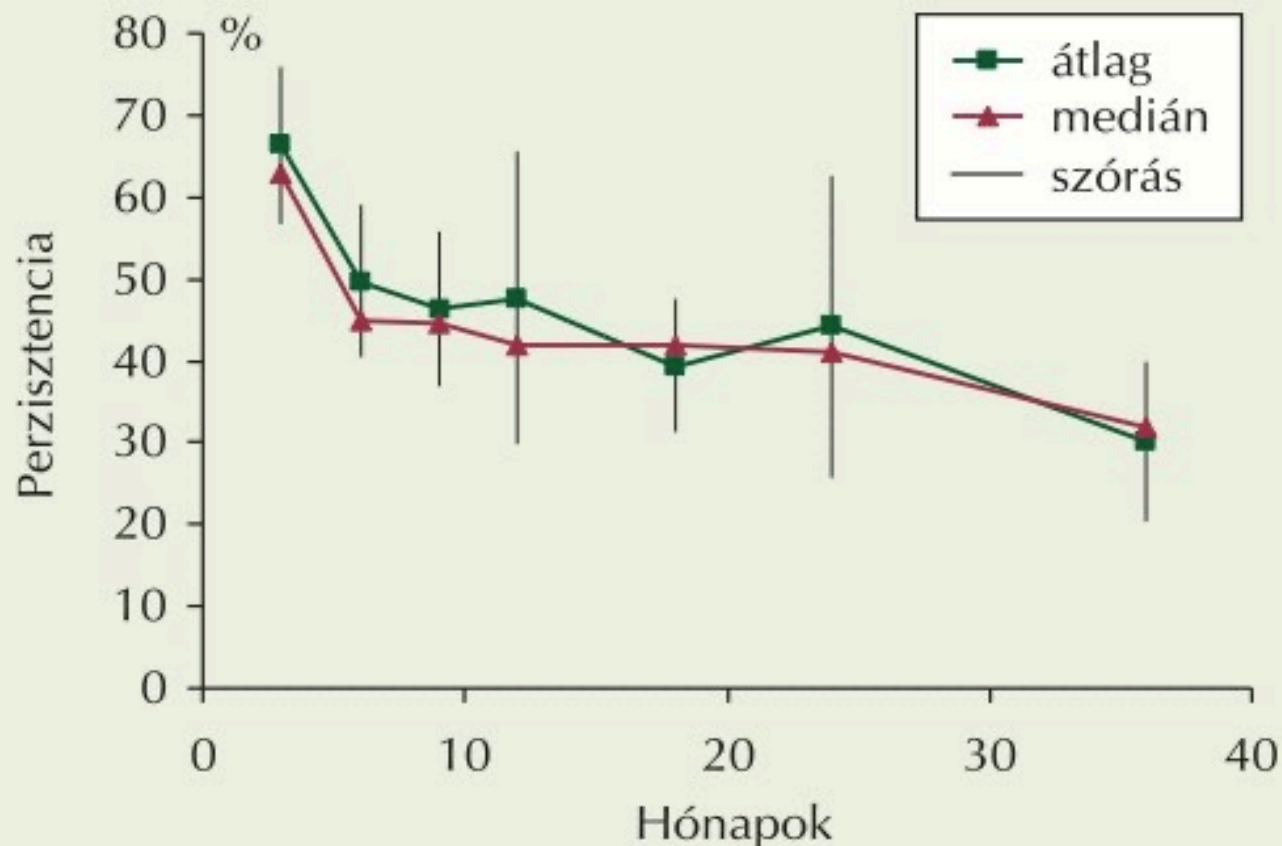


Permission obtained from Nature Publishing Group © Yousuf, O. & Bhatt, D. L. *Nat. Rev. Cardiol.* **8**, 547– 559 (2011)

Agrawal, K. & Bhatt, D. L. (2013) Does prasugrel or ticagrelor suffice in patients with STEMI?
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2012.199

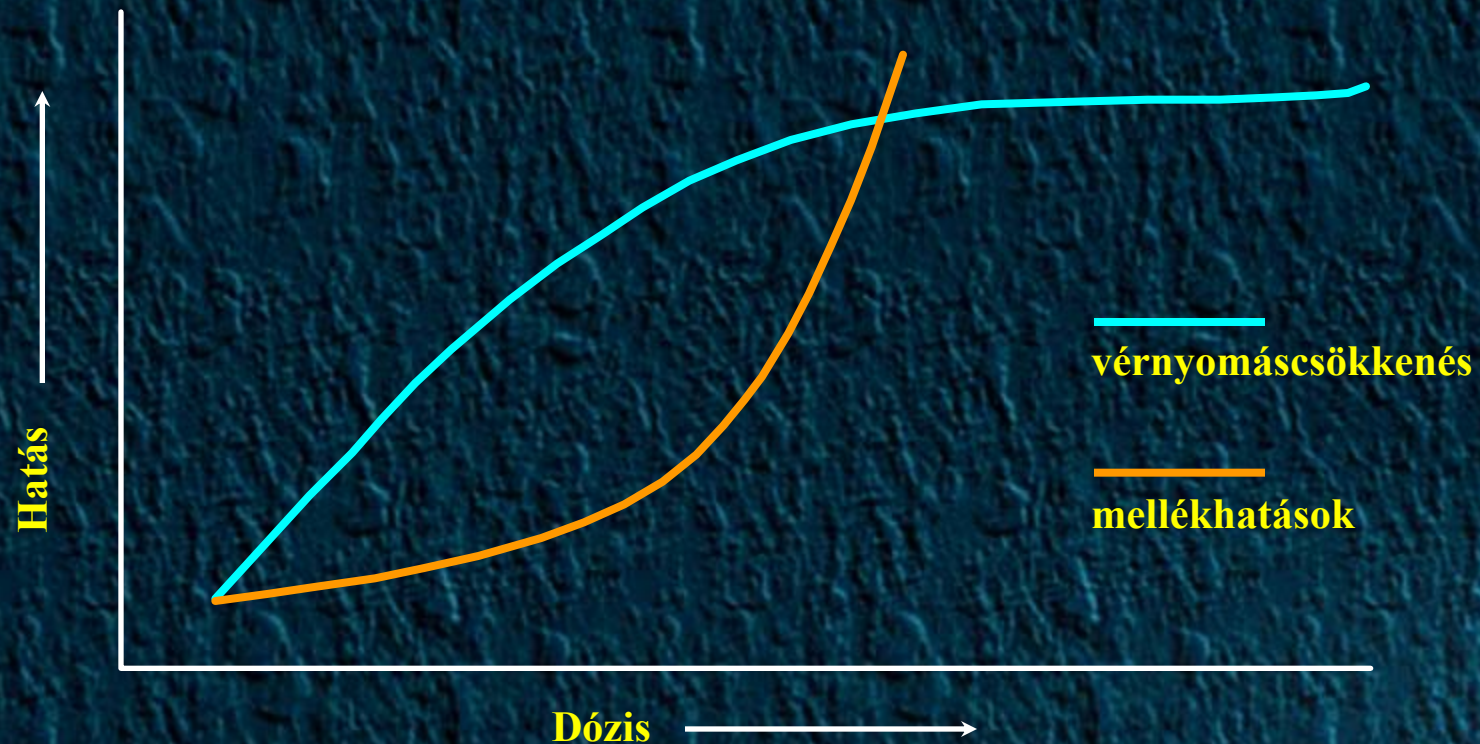


Perzisztencia és statinkezelés. Kilenc, nagy rizikójú betegek végzett vizsgálat összesítése



LAM 2007;17(6-7):403-410. Nagy: A gyógyszereszedési attitűd jelentősége a lipidszintcsökkentő kezelésben

A vérnyomáscsökkentők dózis-hatás és dózis-mellékhatás görbéje



Non-adherencia okai

Apathy

Concern about taking drugs (eg, adverse effects, addiction)

Denial of the disorder or its significance

Financial concerns

Forgetfulness

Misunderstanding of prescribing instructions

No faith in the drug's efficacy

Physical difficulties (eg, with swallowing tablets or capsules, opening bottles, or obtaining prescriptions)

Reduction, fluctuation, or disappearance of symptoms

Adverse effects (real or imagined)

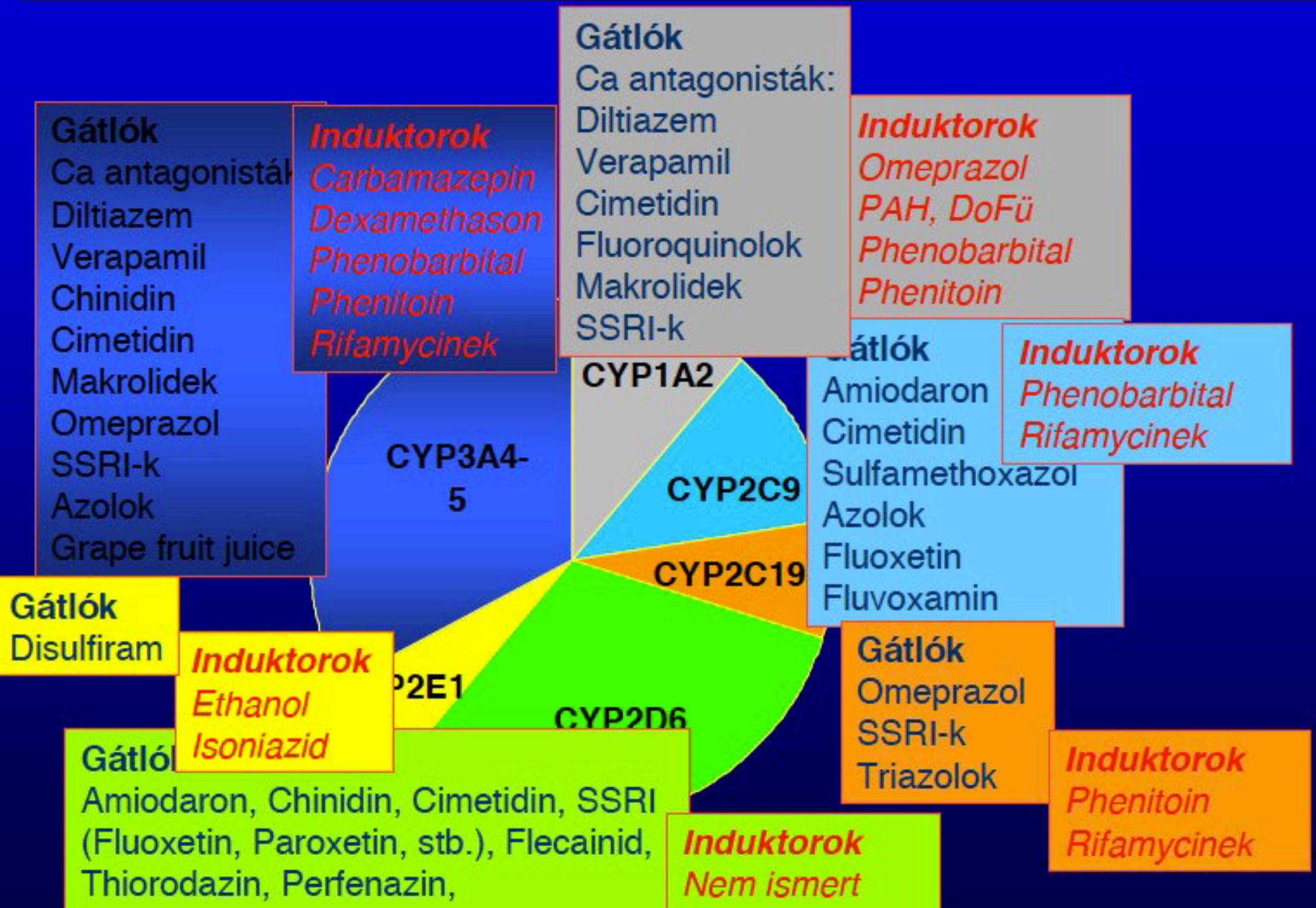
Complex regimen (eg, frequent dosing, many drugs)

Inconvenient or restrictive precautions (eg, no alcohol or cheese)

Similar appearance of drugs

Unpleasant taste or smell

POLIMORFIZMUS, SZUBSZTRÁTOKKAL KÖNNYEN TELITHETŐK, INDUKÁLHATÓK ÉS GÁTOLHATÓK



Néhány CYP enziminduktor gyógyszer

Induktor szerek

Metabolizmusa indukált

rifampicin

orális fogamzásgátlók

phenobarbital

kortikoszteroidok

carbamazepine

orális antikoagulánsok

phenytoin

theophyllin

Hypericum perforatum

DHP Ca-antagonisták

alkohol (krónikus)

simvastatin

dohányzás

verapamil

midazolam

Néhány CYP enzimgátló

ketoconazole, itraconazole

grépfrút

CYP3A4

ciclosporin

HIV proteáz-gátlók

erythromycin, clarithromycin

SSRI (fluoxetin, paroxetin, fluvoxamin, sertralin)

cimetidine

amiodarone

ciprofloxacin, norfloxacin

CYP1A2

alkohol (akut)

Grapefruit interakciók



Sliced pink grapefruit

Drug class	Major Interactions	Minor interactions
Calcium channel antagonists		Plendil Cardene (<i>Nicardipine</i>) Procardia (<i>Nifedipine</i>) Nimotop Sular DynaCirc
Antiarrhythmics	Cordarone Multaq	
Statins (HMG-CoA reductase inhibitors)	Mevacor (<i>Lovastatin</i>)	Lipitor Baycol (off the market)
Immunosuppressants		Sandimmune (<i>Cyclosporine</i>) Prograf Rapamune Mercaptopurine
Dissociatives	Dextromethorphan	
Sedatives, hypnotics, and anxiolytics	Buspar	Halcion Versed Valium (<i>Diazepam</i>) Sonata (<i>Zaleplon</i>) Alprazolam
Other psychotropics		Tegretol (<i>Carbamazepine</i>) Desyrel Serzone Seroquel Fluvoxamine
Antihistamines	Seldane (off the market) Hismanal (off the market)	Claritin (<i>Loratadine</i>)
HIV protease inhibitors		Invirase Norvir Viracept Agenerase
Hormones		Ortho-Cept (<i>Ethinyl estradiol</i>) Depo-Medrol (<i>Methylprednisolone</i>)
Other drugs		Viagra Propulsid ^[17]

CYP enzimgátlók által befolyásolt gyógyszerek

TCA

antipszichotikumok

Ca-antagonisták

daganatellenes szerek

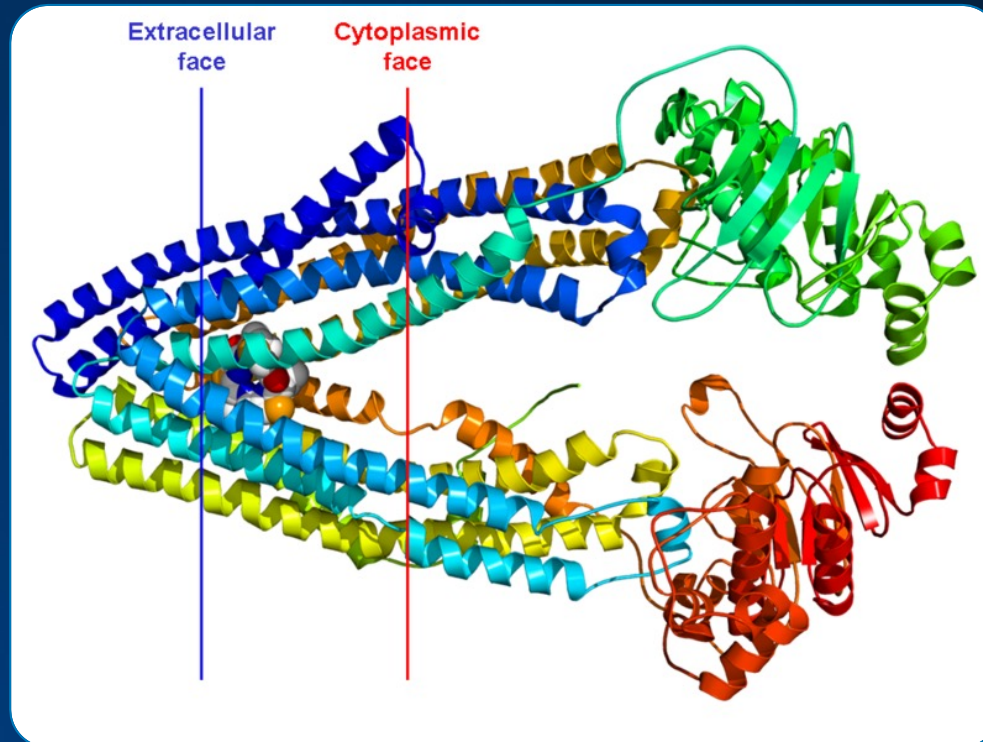
orális antikoagulánsok

statinok

antidiabetikumok

theophyllin

Gyógyszerkölsönhatások és kontraindikációk



P-glikoprotein 1

(permeabilitási glikoprotein, rövidítve P-gp vagy Pgp)

Gyógyszerkölsönhatások és kontraindikációk

Gyógyszer	Hatás	Javallat
Verapamil	↑ 20–150%	Használjon alacsonyabb dózist (110 mg BID)
Kinidin	↑ 50%	Alkalmazza körültekintően és értékelje a vérzéses kockázatot
Amiodaron	↑ 60%	Alkalmazza körültekintően és értékelje a vérzéses kockázatot
Clarithromycin	↑ 19%	Alkalmazza körültekintően és értékelje a vérzéses kockázatot
Dronederon	↑ 100%	Nem javasolt
Rifampicin	↓ 67%	Nem javasolt
Carbamazepin	↓ %-t nem jelentettek	Nem javasolt
Proteáz inhibitorok	Expozíciót nem jelentettek	Nem javasolt

A dabigatran alkalmazása kontraindikált szisztémás ketoconazolt, itraconazolt, tacrolimust és cyclosporint szedő betegeknél

A kumarin kezelés korlátai

Kiszámíthatatlan
válasz

Gyakori dózis
módosítás

Szűk terápiás ablak
(INR range 2-3)

A kumarin
kezelés
nehézségei a
klinikai rutin
során

Számos gyógyszer-
táplálék interakció

Rendszeres labor
ellenőrzés

Számos gyógyszer-
gyógyszer interakció

Lassú hatás/hatás
vesztés

Warfarin rezisztencia

Vonakodás a VKA felírástól

Főként idős betegek esetén, mert a vérzéses szövődmények
rizikóját magasnak tartják a lehetséges haszonhoz képest

K-vitamin antagonisták: gyógyszer interakciók

Fokozott INR válasz

Specific Drugs Reported

acetaminophen	fenofibrate	oxymetholone
alcohol†	fenoprofen	pantoprazole
allopurinol	fluconazole	paroxetine
aminosalicylic acid	fluorouracil	penicillin G, intravenous
amiodarone HCl	fluoxetine	pentoxifylline
argatroban	flutamide	phenylbutazone
aspirin	fluvastatin	phenytoin†
atenolol	fluvoxamine	piperacillin
atorvastatin†	gefitinib	piroxicam
azithromycin	gemfibrozil	pravastatin†
bivalirudin	glucagon	prednisone†
capecitabine	halothane	propafenone
cefamandole	heparin	propoxyphene
cefazolin	ibuprofen	propranolol
cefoperazone	ifosfamide	propylthiouracil†
cefotetan	indomethacin	quinidine
cefoxitin	influenza virus vaccine	quinine
ceftriaxone	itraconazole	rabeprazole
celecoxib	ketoprofen	ranitidine†
cerivastatin	ketorolac	rofecoxib
chenodiol	lansoprazole	sertraline
chloramphenicol	lepirudin	simvastatin
chloral hydrate†	levamisole	stanazolol
chlorpropamide	levofloxacin	streptokinase
cholestyramine†	levothyroxine	sulfamethizole
cimetidine	liothyronine	sulfamethoxazole
ciprofloxacin	lovastatin	sulfinpyrazone
cisapride	mefenamic acid	sulfisoxazole
clarithromycin	methimazole†	sulindac
clofibrate	methylidopa	tamoxifen
COUMADIN overdose	methylphenidate	tetracycline
cyclophosphamide†	methylsalicylate ointment (topical)	thyroid
danazol	metronidazole	ticarcillin
dextran	miconazole (intravaginal, oral, systemic)	ticlopidine
dextrothyroxine	moricyzine hydrochloride†	tissue plasminogen activator (t-PA)
diazoxide	nalidixic acid	tolbutamide
diclofenac	naproxen	tramadol
dicumarol	neomycin	trimethoprim/sulfamethoxazole
diflunisal	norfloxacin	urokinase
disulfiram	ofloxacin	valdecoxib
doxycycline	olsalazine	valproate
erythromycin	omeprazole	vitamin E
esomeprazole	oxandrolone	zafirlukast
ethacrynic acid	oxaprozin	zileuton
ezetimibe		

Csökkent INR válasz

Specific Drugs Reported

alcohol†	COUMADIN underdosage	phenytoin†
aminoglutethimide	cyclophosphamide†	pravastatin†
amobarbital	dicloxacillin	prednisone†
atorvastatin†	ethchlorvynol	primidone
azathioprine	glutethimide	propylthiouracil†
butabarbital	griseofulvin	raloxifene
butalbital	haloperidol	ranitidine†
carbamazepine	meprobamate	rifampin
chloral hydrate†	6-mercaptopurine	secobarbital
chlorthalidone	methimazole†	spironolactone
cholestyramine†	moricyzine hydrochloride†	sucralfate
clozapine	nafcillin	trazodone
corticotropin	paraldehyde	vitamin C (high dose)
cortisone	pentobarbital	vitamin K
	phenobarbital	

also: diet high in vitamin K
unreliable PT/INR determinations

INR Elevation

Amiodarone (2C9)

Ciprofloxacin (1A2/3A4)

TMP/SMX (2C9)

Metronidazole (2C9/3A4)

Fluconazole (2C9/3A4)

Fluvastatin (2C9)

Fluvoxamine (2C9)

Isoniazid (2C9)

Lovastatin (2C9)

Phenylbutazone (2C9)

Sertraline (2C9)

Gemfibrozil (2C9)

Ethanol (1A2)

Clarithromycin (3A4)

Erythromycin (3A4)

Voriconazole (3A4)

*INR Depression

Rifampin (2C9)

Secobarbital (2C9)

Carbamazepine (2C9)

Phenytoin (2C9)

Phenobarbital (2C9)

Primidone (2C9)

St John's wort (2C9)

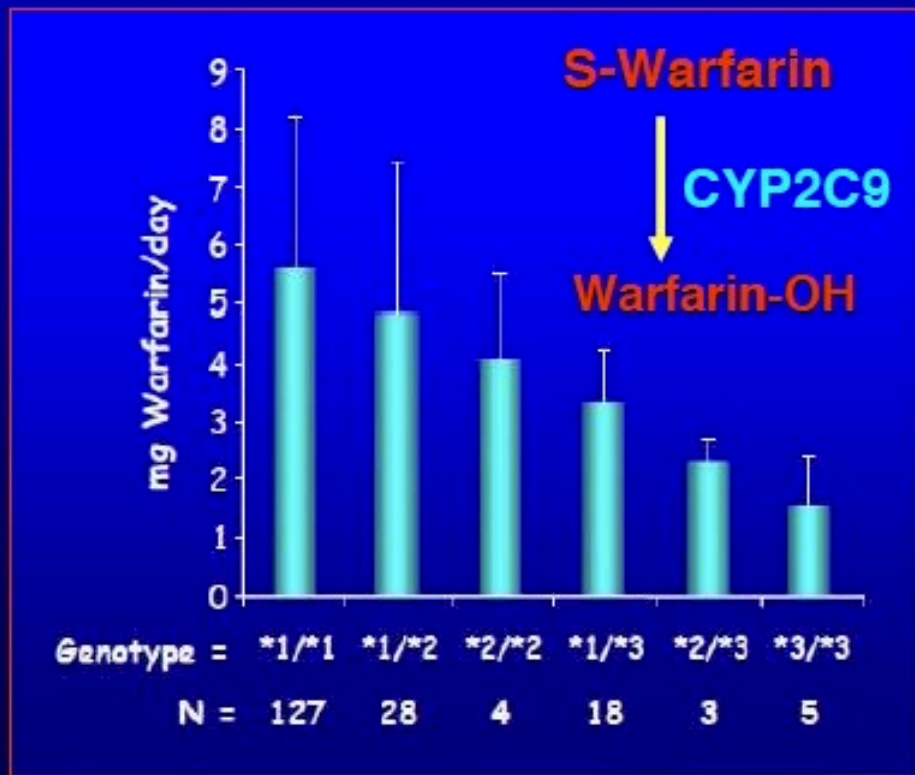
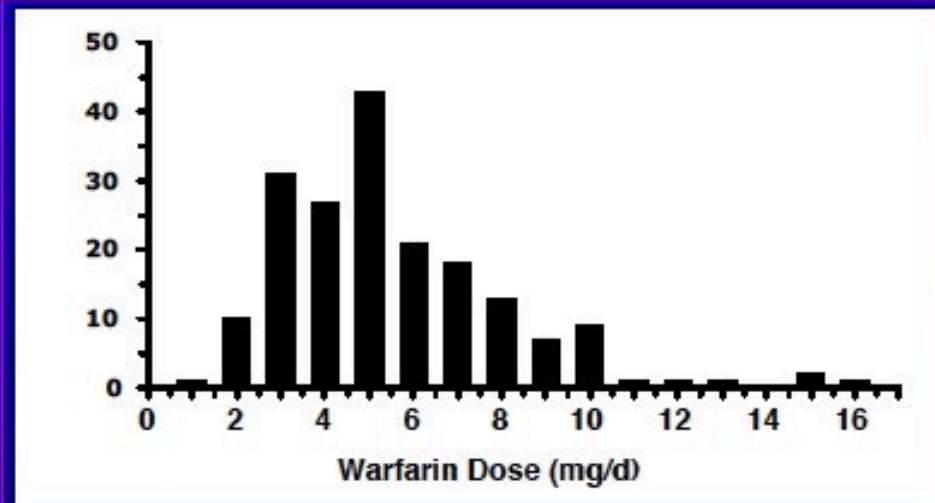
Cigarette smoking (1A2)

Charbroiled food (1A2)

Warfarin interakciók

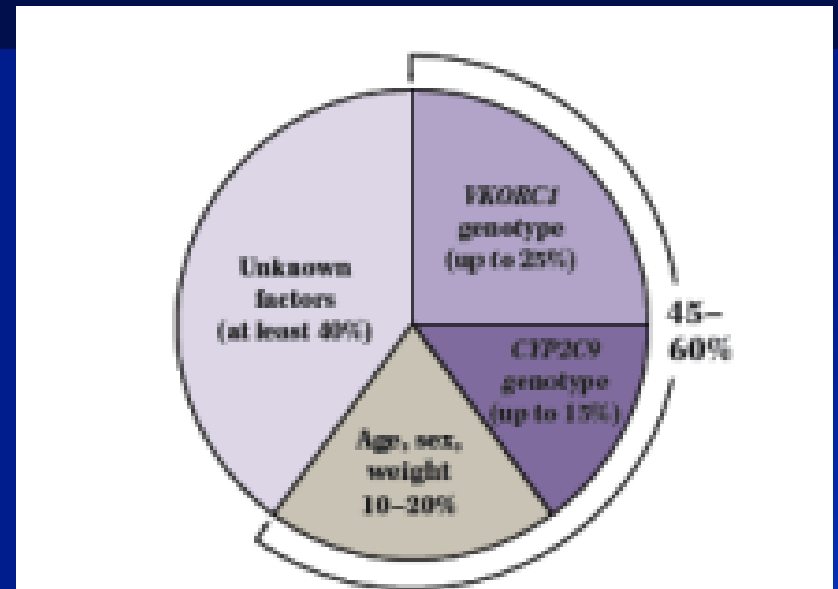
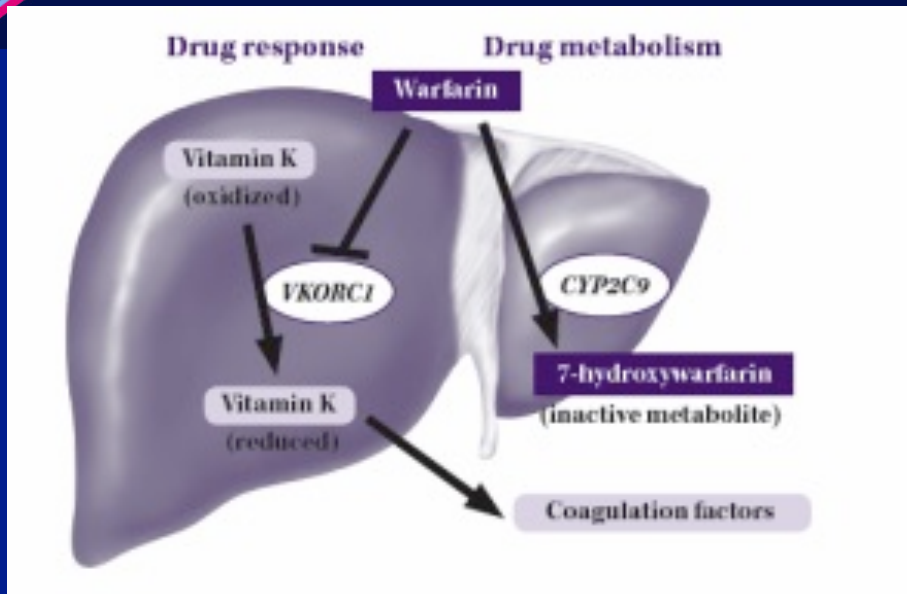
CYP2C9 - WARFARIN

- Szűk terápiás tartomány
- Nagy inter-individuális variabilitás - prothrombin idő (INR) = 2.0 - 3.0
- 30 x dózis variabilitás



- *CYP2C9* SNPs warfarin
 CYP2C9*1 (WT) - normál
 CYP2C9*2 (Arg144Cys) - alacsony/intermediér
 CYP2C9*3 (Ile359Leu) - alacsony
- *CYP2C9* allél előfordulás:
 Európai: *2 - 10.7% *3 - 8.5 %
 Ázsiai: *2 - 0% *3 - 1-2%
 Afro-Amerikai: *2 - 2.9% *3 - 0.8%

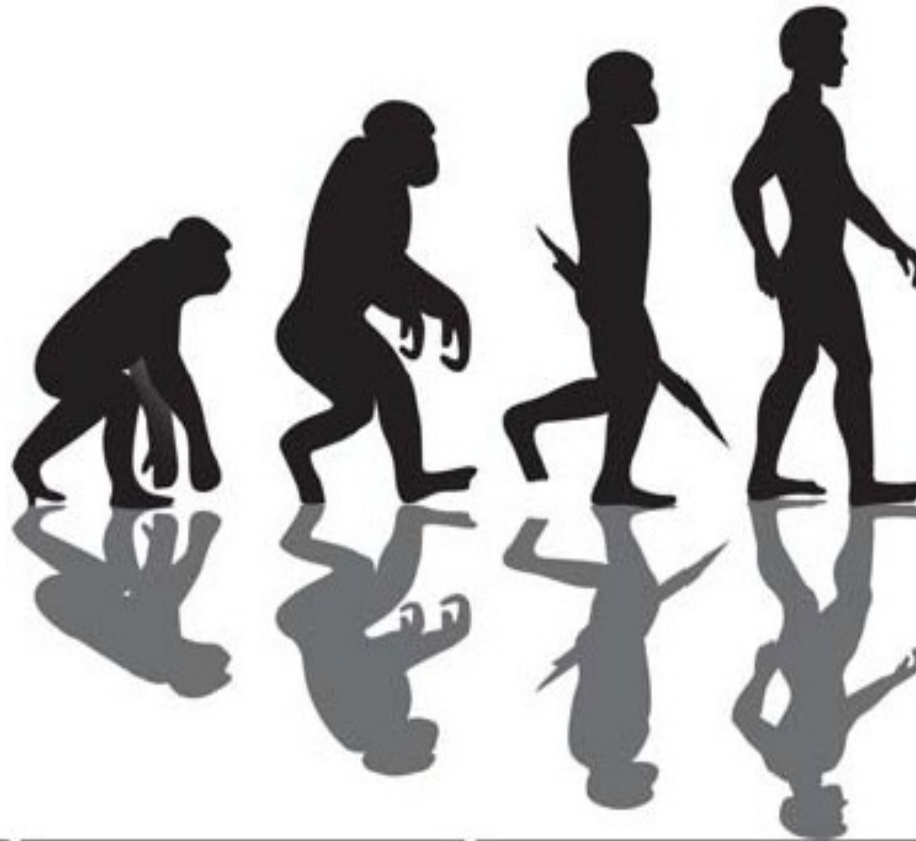
Warfarin genetika



CYP2C9 (warfarin metabolizmust befolyásolja) és VKORC1 (warfarin sensitivitásra van hatással)

Clarification of Optimal Anticoagulation through Genetics (COAG) trial

"Personalized, predictive medicine offers great promise, but we need to carefully examine benefits and understand the cost-effectiveness of such strategies before we spend a lot of money on very expensive tests"



Genetics

'One-size-fits-all'

Guideline recommendations based on ejection fraction, NYHA class, and QRS width.

BNP / NT-proBNP

B-type natriuretic peptides to prevent therapeutic complacency and encourage efforts to maximize treatment.

Interaction with treatment benefit

Use of biomarkers to optimise benefit of established therapies in patient subgroups.

New therapy & companion biomarker ?

New therapies based on enhanced understanding of pathophysiology provided by biomarkers.

Degrees of Tailoring

???

Mi is az az „Evidence-Based Medicine”?

A **mindenkori legjobb bizonyítékok** lelkiismeretes, tudatos és megfontolt alkalmazása az **egyes betegek** ellátásával kapcsolatos döntések meghozatalánál. (CEBM definíció)

1/ **mindenkori legjobb**

Amikor a tények megváltoznak, megváltoztatom a véleményemet. Ön mit tesz?

Michael F. Oliver, European Heart Journal, 1997

Understanding the Need for Evidence in Practice

Systematic Approach to Evaluating New Therapies

Half of what you learn in
your medical apprenticeship
(about therapy) will be correct...
you just don't know which half.

*Joe Greenfield, MD
Former Chair, Medicine
Duke University Medical Center*

Mi is az az „Evidence-Based Medicine”?

A **mindenkori legjobb bizonyítékok** lelkiismeretes, tudatos és megfontolt alkalmazása az **egyes betegek** ellátásával kapcsolatos döntések meghozatalánál. (CEBM definíció)

2/ **bizonyítékok**

Evidence - tény? A tény abszolút fogalom, a tény megdönthetetlen bizonyíték.

Evidence - bizonyíték? A bizonyíték meggyőző ereje széles skálán mozog, a gyengétől, az elsőprő erejűig (lásd jog).

Evidence - érv? Az érv nem feltétlenül megalapozott állítás, lehet subjectív, függ az érvelőtől, lehet magánvélemény.

EBM, BAO, TAO?

HUMBUG! by Jef



*I owe my
robust state of
health to this
wonderful,
magic crystal*

A true believer ignores the evidence.

Mi is az az „Evidence-Based Medicine”?

A **mindenkori legjobb bizonyítékok** lelkiismeretes, tudatos és **megfontolt** alkalmazása az **egyes betegek** ellátásával kapcsolatos döntések meghozatalánál. (CEBM definíció)

3/ lelkiismeretes, tudatos és megfontolt - hippokratészi eskü!

Vizsgálati eredmények adaptálása, szakirodalom ismerete
(naponta 19 cikk elolvasása!)

Mesterség ismerete! A jó döntés csakis a legjobb lehet!

Közgazdász: elszalasztott haszon = veszteség!

Orvos: akkori is árt, ha nem javít, amikor lenne rá mód!

Mi is az az „Evidence-Based Medicine”?

A **mindenkori legjobb bizonyítékok** lelkiismeretes, tudatos és **megfontolt** alkalmazása az egyes **betegek** ellátásával kapcsolatos **döntések** meghozatalánál. (CEBM definíció)

4/ **betegek, döntések** - az EBM nem egyenlő a vizsgálati eredmények összességével (bizonyítékok): azokon alapul, és az orvos megítélésével épül fel az egyes betegekre szabottan.

Orvostudomány - tudomány, bizonyítékok.

Orvostudomány - művészet

orvos intuíció + klinikai tapasztalat. „Ars longa vita brevis”

Hangsúlyeltolódás a tudomány felé.

EBM - alapja a bizonyíték, felépítménye az adott orvos az adott betegre szabott műve.



Evidence-based Medicine

Combining quantitative evidence about medical practice with expert judgment in an effort to ensure the provision of medical care with reproducible high quality

Adapted from D Sackett

Az „Evidence-Based Medicine” története

ORIATRIKE

O R,

Phylick Refined.

The common ERRORS therein

R E F U T E D,

And the whole ART

Reformed & Rectified:

BEING

A New Rise and Progreſs of PHILOSOPHY
and MEDICINE, for the Deſtruction of
Diſeaſes and Prolongation of Life.

Written

By that moſt Learned, Famous, Profound, and Acute Phyloſo-
pher, and Chymical Phyſitian,

John Baptiſta Van Helmont,

Toparch or Governor, in Morede, Royenborch, Oorſchoot, Pellines, &c.
And now faithfully rendred into *Engliſh*, in tendency to a common good, and
the increaſe of true Science; By

J. C. Sometime of M. H. Oxon.

Job 32. 8. *There is a Spirit in Man, and the inſpiration of the Almighty giveth
underſtanding.*

Pro. 8. 12. *Wiſdom dwell with Prudence, and find out knowledge of witty Inventions.
Æternarum rerum ſeria contemplatio eo uſq; animun noſtrum ſubveſcit, ut Divina
loquuti videamur de rebus Naturæ ſubjectis, quæ tantò perfectiores ſunt, quanto
propiores Æternis, &c.*

L O N D O N,

Printed for Lodowick Loyd, and are to be ſold at his Shop next the Caſtle in
Cornhill. 1 6 6 2.

THE DRUG TREATMENT OF ANGINA PECTORIS DUE TO CORONARY ARTERY DISEASE.

By ARTHUR M. MASTER, M.D.,

ASSOCIATE IN MEDICINE AND CHIEF OF THE CARDIOGRAPHIC LABORATORY, MT. SINAI
HOSPITAL; ASSOCIATE IN MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS,
COLUMBIA UNIVERSITY,

HARRY L. JAFFE, M.D.,

RESEARCH ASSISTANT, CARDIOGRAPHIC LABORATORY, MT. SINAI HOSPITAL,

AND

SIMON DACK, M.D.,

RESEARCH ASSISTANT, CARDIOGRAPHIC LABORATORY, MT. SINAI HOSPITAL,
NEW YORK CITY.

(From the Cardiac Clinic, Outpatient Department, and the Cardiographic Labora-
tory, The Mount Sinai Hospital.)

Four years ago a clinic for patients with precordial pain was

opened for one or more attacks of coronary occlusion.

The following routine of medication was employed in the clinic. When first seen, the patient was given a placebo, 1 grain of milk sugar 3 or 4 times daily, unless he was very ill. This was continued 2 to 4 weeks, until its effect on the precordial pain was determined. The patient was then given another drug for a similar trial period. In this way, the drugs listed in Table 1 were administered successively, the average number of drugs received by each patient being 7. When a drug was associated with improvement it was usually replaced by a placebo, and then repeated one or more times. Thus the effect of each drug, as compared to that of the placebo, was studied several times in the same patient. When a new drug was given the patient was usually aware of the fact, for very little attempt was made to disguise the different preparations. However, the drugs in tablet form, such as milk sugar, phenobarbital, codeine, aminophyllin, had a similar size and shape. As a rule, the maximum clinical dose of each drug was given during some period of its trial. Thus theobromine was given in 7.5 to 10-grain doses, and aminophyllin in 3-grain doses, 4 to 6 times daily; digitalis was pushed to full therapeutic dose, and then a maintenance dose continued.

The effect of a drug was judged by the statement of the patient concerning

Az „Evidence-Based Medicine” története

**Pierre Charles Alexandre Luise
1828-35: venasectio hatásosságáról
Kemény végpont: halál
bekövetkezte és az érvágás.
„Az érvágásnak a pneumonitis
lefolyására aligha van bárminemű
befolyása”**

**Semmelweis I. 1861: Medikusok
bonctermi gyakorlat után
(vizsgálati cs.) Bábák (kontroll cs.)
Klórmész (vizsgált módszer)
Statisztikailag szignifikáns
különbség utólagos számítások
szerint!**

Die Aetiologie, der Begriff
und
die Prophylaxis
des
Kindbettfiebers.

Von

Ignaz Philipp Semmelweis,

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etc. etc.

Pest, Wien und Leipzig.

C. A. Hartleben's Verlags-Expedition.

1861.

EVIDENCE-BASED MEDICINE (ÉRVEKKEL BIZONYÍTOTT MEDICINA)

Támogató érvek rendszere (ACC/AHA)

- "A" szint: Több randomizált, nagy betegszámú klinikai vizsgálat támasztja alá.
- "B" szint: Kevés, kisebb betegszámú randomizált tanulmány támasztja alá.
- "C" szint: Szakértők konszenzusa, esettanulmányok, klinikai tapasztalatok támogatják.

Indikációk rendszere

- I. osztály: Egyértelműen indikált beavatkozás, kezelés.
- II. osztály: Nem egységes az álláspont.
 - a/ inkább javasolt
 - b/ inkább nem javasolt
- III. osztály: Egyértelműen nem indikált.

SIZE OF TREATMENT EFFECT



CLASS I

Benefit >>> Risk

Procedure/Treatment **SHOULD** be performed/administered

CLASS IIa

Benefit >> Risk

Additional studies with focused objectives needed

IT IS REASONABLE to perform procedure/administer treatment

CLASS IIb

Benefit ≥ Risk

Additional studies with broad objectives needed; additional registry data would be helpful

Procedure/Treatment **MAY BE CONSIDERED**

CLASS III

Risk ≥ Benefit

Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**

LEVEL A

Multiple populations evaluated*

Data derived from multiple randomized clinical trials or meta-analyses

- Recommendation that procedure or treatment is useful/effective
- Sufficient evidence from multiple randomized trials or meta-analyses

- Recommendation in favor of treatment or procedure being useful/effective
- Some conflicting evidence from multiple randomized trials or meta-analyses

- Recommendation's usefulness/efficacy less well established
- Greater conflicting evidence from multiple randomized trials or meta-analyses

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Sufficient evidence from multiple randomized trials or meta-analyses

LEVEL B

Limited populations evaluated*

Data derived from a single randomized trial or nonrandomized studies

- Recommendation that procedure or treatment is useful/effective
- Evidence from single randomized trial or nonrandomized studies

- Recommendation in favor of treatment or procedure being useful/effective
- Some conflicting evidence from single randomized trial or nonrandomized studies

- Recommendation's usefulness/efficacy less well established
- Greater conflicting evidence from single randomized trial or nonrandomized studies

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Evidence from single randomized trial or nonrandomized studies

LEVEL C

Very limited populations evaluated*

Only consensus opinion of experts, case studies, or standard of care

- Recommendation that procedure or treatment is useful/effective
- Only expert opinion, case studies, or standard of care

- Recommendation in favor of treatment or procedure being useful/effective
- Only diverging expert opinion, case studies, or standard of care

- Recommendation's usefulness/efficacy less well established
- Only diverging expert opinion, case studies, or standard of care

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Only expert opinion, case studies, or standard of care

Suggested phrases for writing recommendations[†]

should
is recommended
is indicated
is useful/effective/beneficial

is reasonable
can be useful/effective/beneficial
is probably recommended
or indicated

may/might be considered
may/might be reasonable
usefulness/effectiveness is unknown/unclear/uncertain or not well established

is not recommended
is not indicated
should not
is not useful/effective/beneficial
may be harmful

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

Using Evidence for Clinical Decision-making: Role of the Randomized Clinical Trial

“Statistical methods may be no substitute for common sense but they are often a powerful aid to it.”

*D. D. Reid, commenting on the work of
Austin Bradford Hill, father of the
randomized clinical trial*

Randomization

- Eliminates assignment bias
- Ensures comparable study groups
- Allows for use of valid statistical tests
- Requires a predetermined ratio of allocation (usually equal allocation)
- *Day of week & visit number (e.g., even gets A and odd gets B) are NOT random assignments*

Blinding

Blinding is the masking of the treatment assignment among particular individuals.

This process helps to control the potential for bias because individuals tend to change their behaviors based on treatment information.

Unblinded

- Also known as open-label
- May be simpler to execute
- Better reflects actual clinical practice
- Introduces bias

Single Blind

Patient is blinded to treatment but investigator is not.

- Puts investigators at ease
- Easier to administer
- May introduce investigator bias

Double Blind

Patient and investigator are blinded to treatment.

- Reduces risk of bias
- Requires outside personnel to monitor safety and treatment allocation
- May be very difficult to accomplish in studies of some treatments

Triple Blind

Patient, investigator, and monitoring committee (and/or trial statistician) are blinded to treatment.

- Allows monitoring committee and/or statistician to remain objective
- May be difficult to make crucial decisions on trial conduct without information on the treatments
- Creates the need for an unblinded statistician for DSMB if the trial statistician is blinded

Phases of a Study

- **Phase 1: Initial safety study**

- Usually performed on a small number of patients to evaluate toxicity and drug pharmacodynamics

- **Phase 2: Dose finding study**

- Smaller study to determine the optimal dose for the efficacy study

Phases of a Study

- **Phase 3: Efficacy study**

- Large(r) study to establish superiority, equivalence, or noninferiority; usually performed for FDA drug indication

- **Phase 4: Marketing study**

- May not include any control arm

Superiority Trials

These trials test for statistically significant and clinically meaningful improvements (or *harm!*) from the use of the experimental treatment over the results obtained through the use of standard care.

Equivalence

- **Equivalence studies are designed to evaluate whether the difference in outcomes for the new treatment compared to those obtained with standard care falls within the boundaries of the minimally important difference (MID).**
- **MID is the largest difference one will accept between the outcomes of 2 groups and still consider them clinically similar.**

Noninferiority Trials

- The results will be evaluated assuming that the experimental treatment will not be worse than the standard of care by a clinically meaningful amount.
- Unlike equivalency studies, these studies do not look for small improvements from the experimental drug (one-sided as opposed to two-sided evaluations).

Data Safety Monitoring Boards in RCTs

Purpose

- To protect the welfare of patients in clinical trial human experiments, primarily by reviewing accumulating data and overall trial progress

EVIDENCE-BASED MEDICINE (ÉRVEKKEL BIZONYÍTOTT MEDICINA)

Multicentrikus, nemzetközi klinikai tanulmányok

- Randomizáltak
- Kontrolláltak
- Kettős vakok (egyes, hármás, PROBE stb...)

Problémák

- végpontok – kemény, surrogate, kombinált
- placebo – betegszám - megatrial
- study beteg
- statisztika – posthoc analysis, metaanalysis
- comperator – pofozógép
- negatív tanulmányok

Biometriai útvesztők

Megatrial paradoxon - minél nagyobb a tanulmány esetszáma, annál kisebb az individuális prognosztikus értéke

Study tervezés - végpontok

Study bevonás, kizárás - steril betegek

Levont következtetések:

ISIS-2: Aspirin - Mérleg és Irkek jegy v. gólya és születés

Kezelt betegek száma/megmentett betegek száma

Relatív rizikó/abszolút rizikó csökkenés

Statisztikailag szignifikáns/klinikailag releváns

Metaanalízisek – „publication bias”

epidemiológusok, statisztikusok – nem klinikusok



Minden nézőpont kérdése ?

