Royal Liverpool & Broadgreen University Hospitals NHS Trust

LIVERPOOL HEALTH PARTNERS

Important Drug Interactions

Richard FitzGerald

CRU Director, RLBUHT

Consultant Physician, CPT & GIM, RLBUHT

UNIVERSITY OF LIVERPOOL

THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

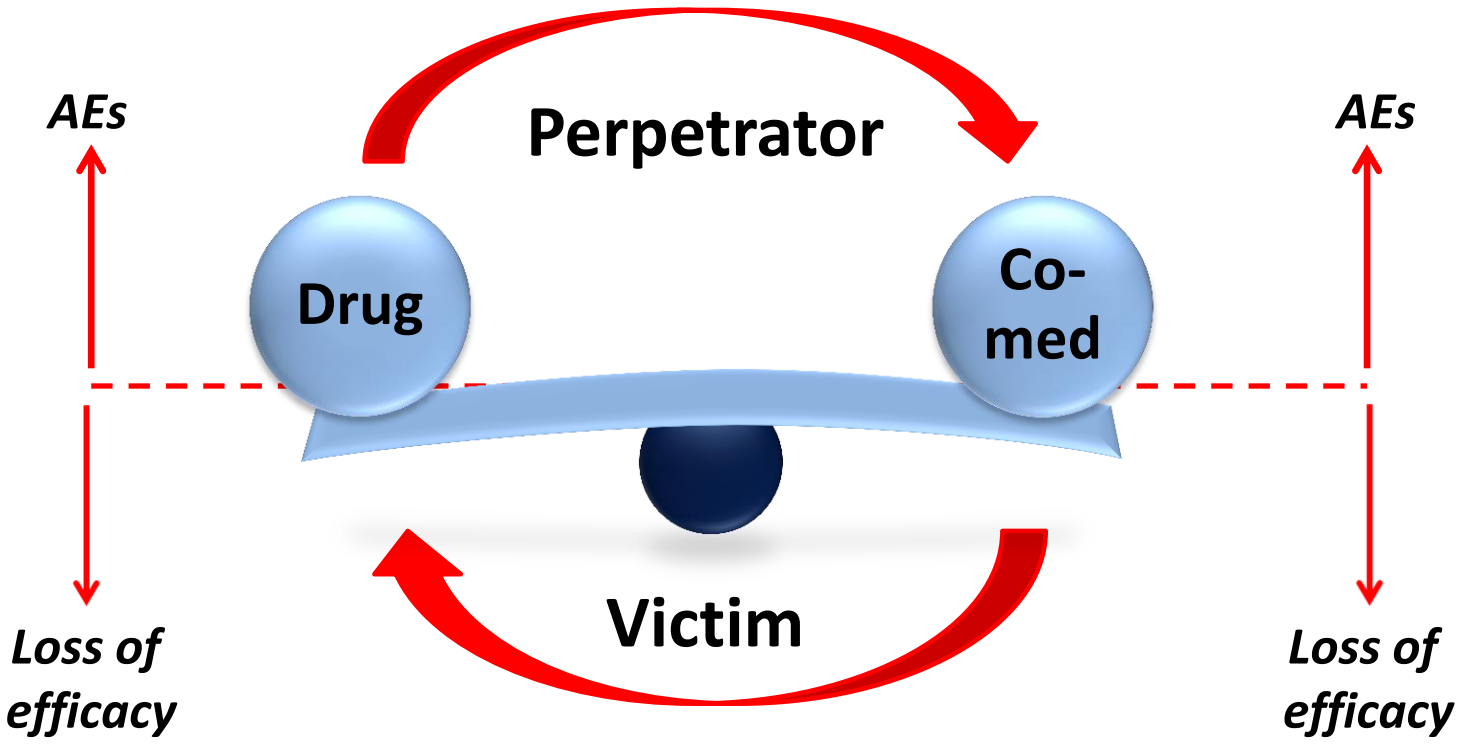
Outline

- Definitions
- Epidemiology
- Some examples and underlying science
- Information sources and prevention of drug interactions

Definitions

- **Drug-drug interactions**: the effects of one drug are changed by the presence of a concomitant drug
- **Drug-food interactions**: the effect of the drug is changed by food substances
- **Drug-herbal interactions**: the effect of a drug is changed by concomitant administration of a herbal medicine

Drug–Drug Interactions



Slide courtesy of Prof David Back

Potential drug-drug interactions and admissions due to drug-drug interactions in patients treated in medical departments

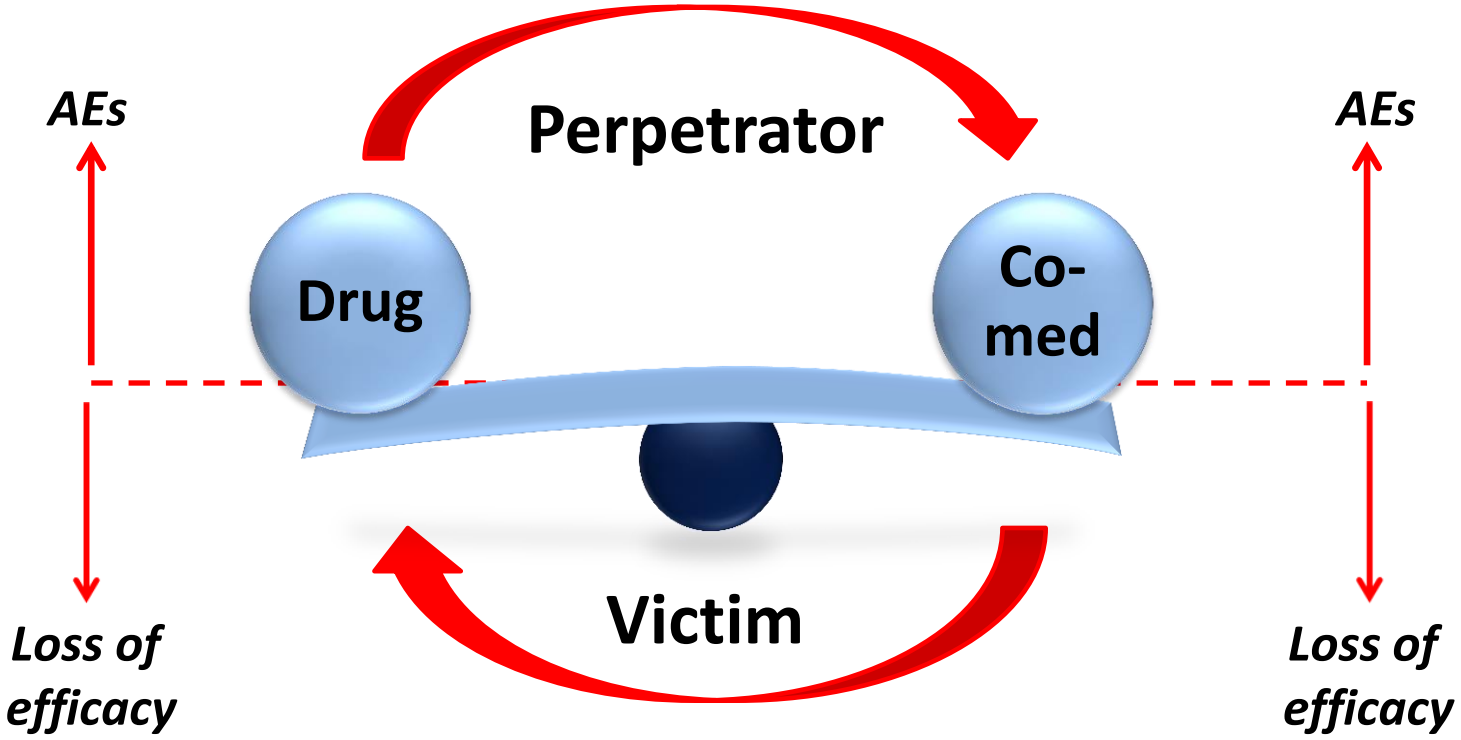
Nina Fokter[1], Martin Možina[2,3], Miran Brvar[2]

Wien Klin Wochenschr (2010) 122: 81–88

- A retrospective study of 520 patients in various medical wards
- Potential DDIs seen in
  - 51% of patients on admission (13% major)
  - 63% of patients on discharge (18% major)
- Drug interaction was the cause of hospital admission in 1.2% of cases

Potential DDIs far outnumber those which lead to clinically significant effects

Drug–Drug Interactions



Need to understand:

- The disposition or handling of each drug
- The therapeutic window of each drug
- Exposure – Response and Exposure – Adverse Response based on PK and PD relationships

Outline

- Definitions
- Epidemiology
- Some examples and underlying science
- Information sources and prevention of drug interactions

Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients

Munir Pirmohamed, Sally James, Shaun Meakin, Chris Green, Andrew K Scott, Thomas J Walley, Keith Farrar, B Kevin Park, Alasdair M Breckenridge

BMJ 2004;329:15–19

- Data from two hospitals
- 6.5% (n=1225) of admissions are due to ADRs
- 1.1% of all the ADRs that led to admission were due to DDI
  - Aspirin and warfarin
  - Aspirin and NSAIDs
  - Combinations of diuretics

Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes

Emma C. Davies[1,2], Christopher F. Green[3], Stephen Taylor[4], Paula R. Williamson[4], David R. Mottram[2], Munir Pirmohamed[5]*

1 The Royal Liverpool and Broadgreen University Hospitals Trust, Liverpool, United Kingdom, **2** School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, United Kingdom, **3** Countess of Chester NHS Foundation Trust, Pharmacy: Martindale House, Countess of Chester Health Park, Chester, United Kingdom, **4** Centre for Medical Statistics and Health Evaluation, University of Liverpool, Liverpool, United Kingdom, **5** Department of Pharmacology and Therapeutics, The University of Liverpool, Liverpool, United Kingdom

PLoS ONE. 2009;4(2):e4439. Epub 2009 Feb 11

- 14.7% of patients experienced one or more ADRs
- Highest risk in females, older and taking more than one medicine
- 8.7% of ADRs (1.3% overall) were due to DDIs (92% were PD, 5% were PK, 3% were mixed)

Deaths Caused by DDIs

L. Juntti-Patinen · P.J. Neuvonen

Drug-related deaths in a university central hospital

Eur J Clin Pharmacol, 2002; 58: 479-482)

- 5 deaths (0.035%) out of 1511 deaths were due to DDIs

Identifying Adverse Drug Reactions Associated with Drug-Drug Interactions

Data Mining of a Spontaneous Reporting Database in Italy

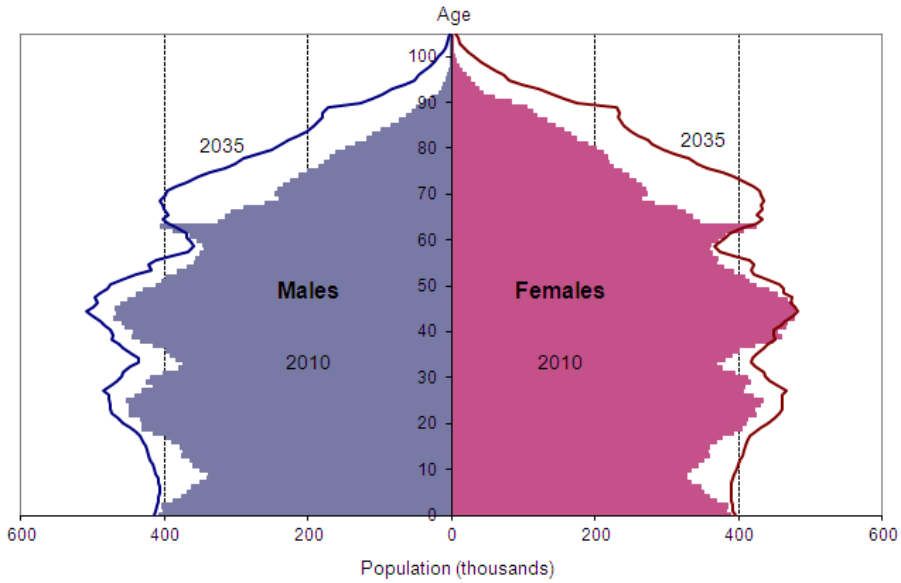
Roberto Leone,[1] *Lara Magro,*[1] *Ugo Moretti,*[1] *Paola Cutroneo,*[2] *Martina Moschini,*[3] *Domenico Motola,*[4] *Marco Tuccori*[5] and *Anita Conforti*[1]

Drug Saf 2010; 33 (8): 667-675

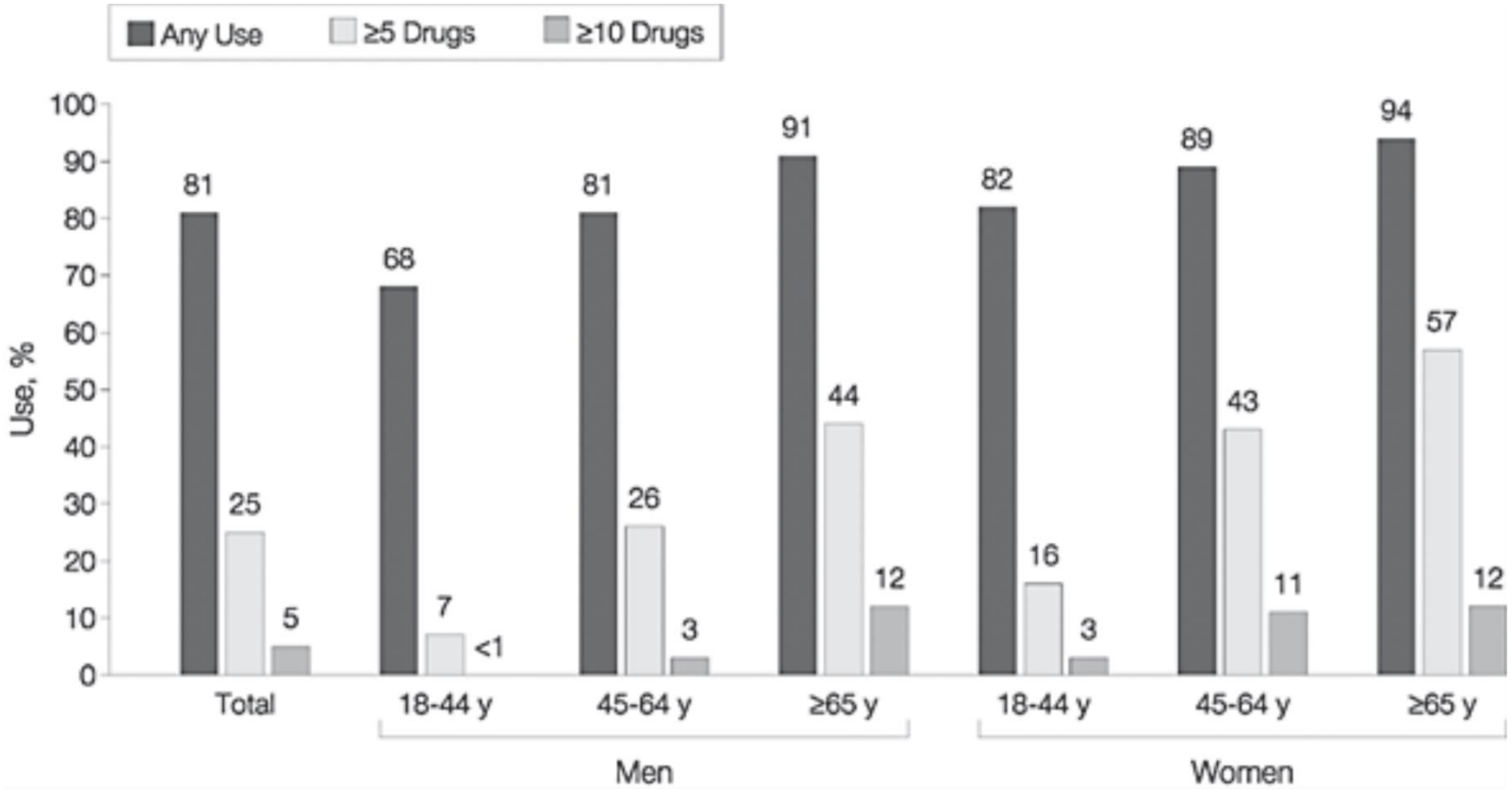
Fatal consequences of DDIs-related ADRs (4.2%) higher than for other ADRs (1.4%)

Polypharmacy

- Polypharmacy is becoming more common
- Ageing population with multiple co-morbidities
- Polypharmacy is sometimes necessary
- De-prescribing is uncommon



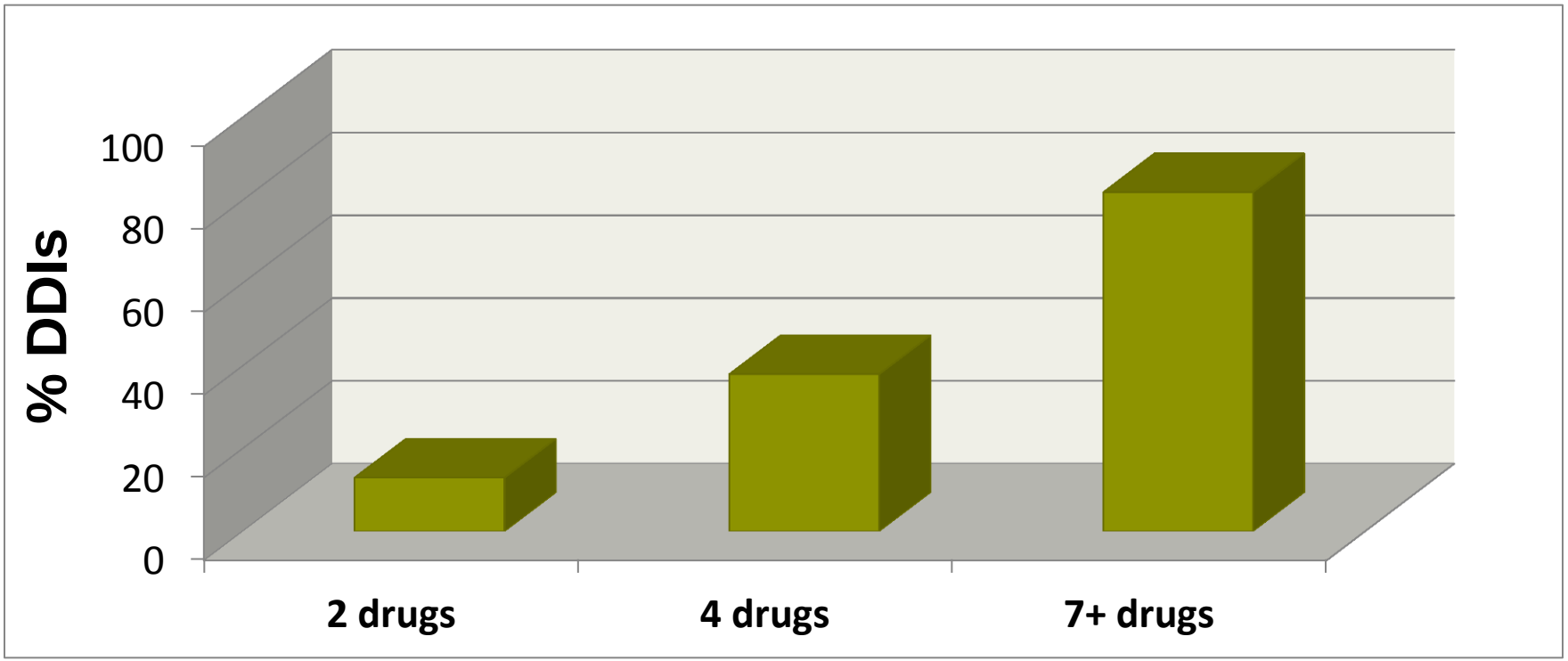
Polypharmacy: Use of Medicines in the Preceding Week (Kaufman et al, JAMA, 2002; 287: 337-44)



Drug-Drug and Drug-Disease Interactions in the ED: Analysis of a High-Risk Population

RICHARD M. GOLDBERG, MD, JOHN MABEE, PA-C, MS,
LINDA CHAN, PHD, SANDRA WONG, MA

AMERICAN JOURNAL OF EMERGENCY MEDICINE ■ Volume 14, Number 5 ■ September 1996



Outline

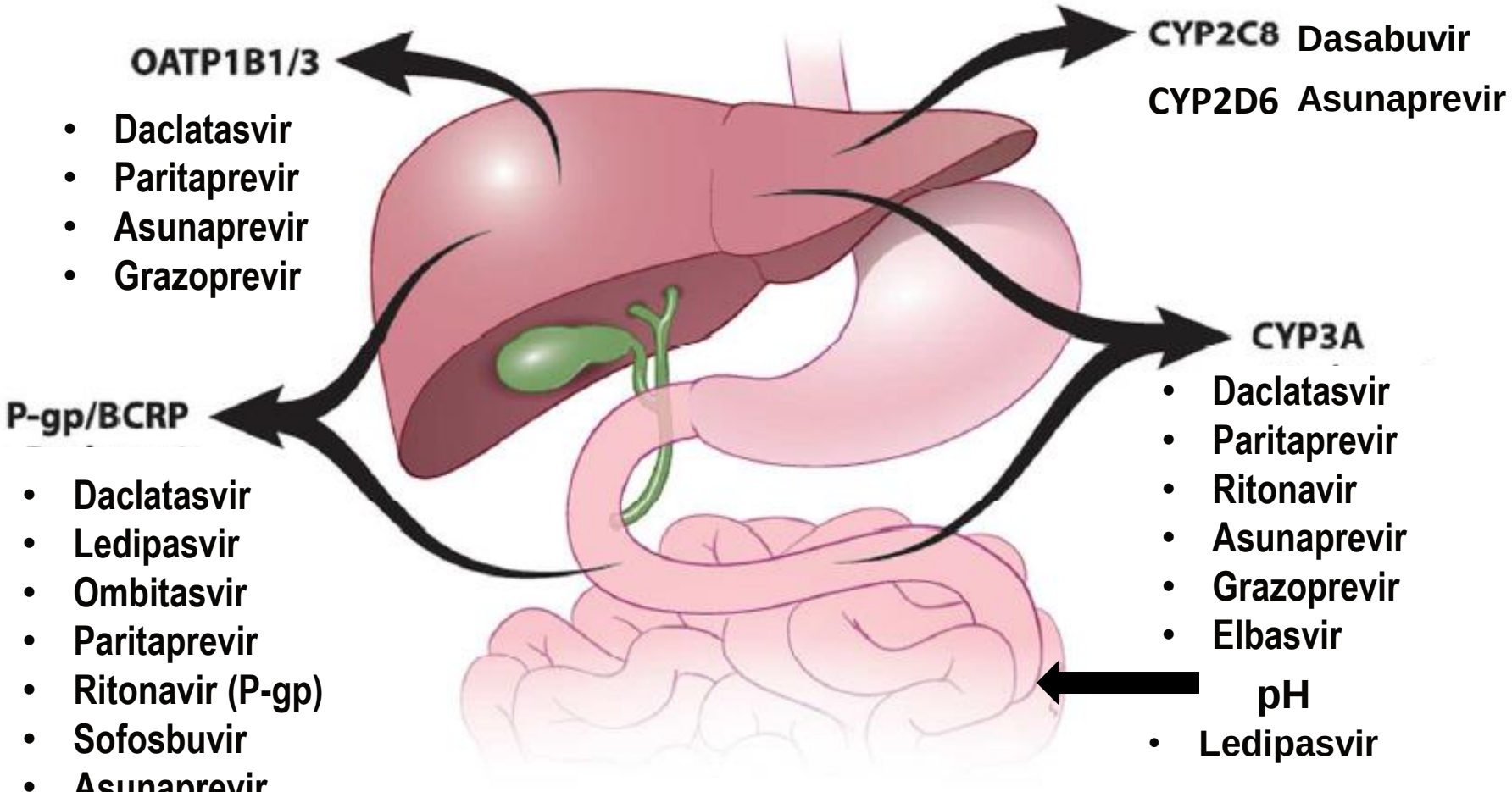
- Definitions
- Epidemiology
- Some examples and underlying science
- Information sources and prevention of drug interactions

Mechanisms of Drug Interactions With Warfarin

- Direct GI injury – e.g. NSAIDs
- Altered gut vitamin K synthesis – e.g. antibiotics
- Altered warfarin metabolism
  - Enzyme induction (e.g. carbamazepine)
  - Enzyme inhibition (e.g. amiodarone)
- Altered platelet function – e.g. aspirin
- Interference with vitamin K cycle – e.g. paracetamol

More than one mechanism may operate

Interactions with Hepatitis C Drugs

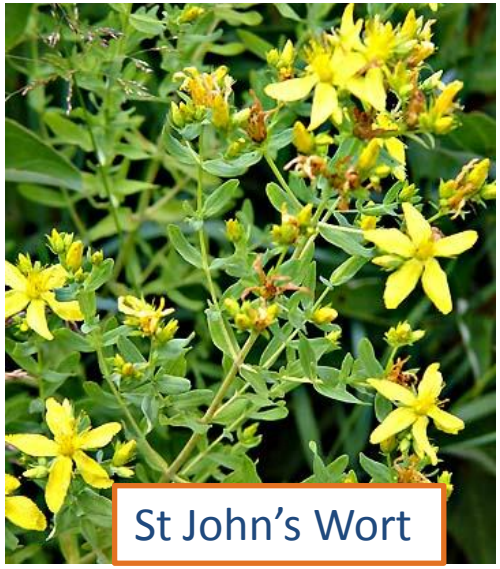


Also need to consider renal mechanisms

Adapted from Dick T et al Hepatology 2015 [Epub ahead of print]

Herbal Medicines: An Unrecognised Danger

- Known to cause interactions with prescribed drugs
- Recorded in notes occasionally – 4%
- Most notorious was St John's Wort
- Enzyme inducer

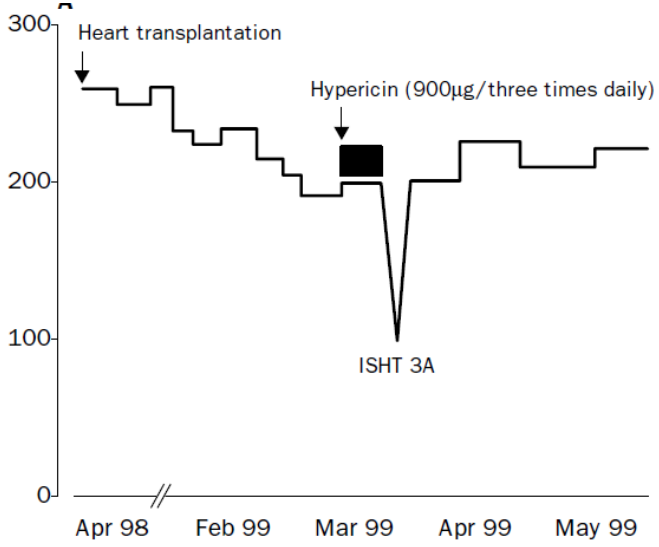


St John's Wort

Acute heart transplant rejection due to Saint John's wort

Frank Ruschitzka, Peter J Meier, Marko Turina, Thomas F Lüscher, Georg Noll

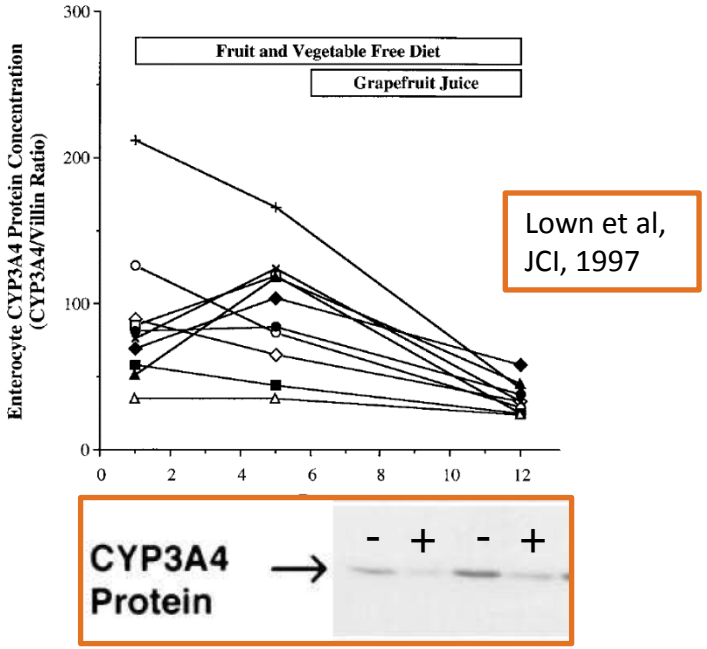
THE LANCET • Vol 355 • February 12, 2000



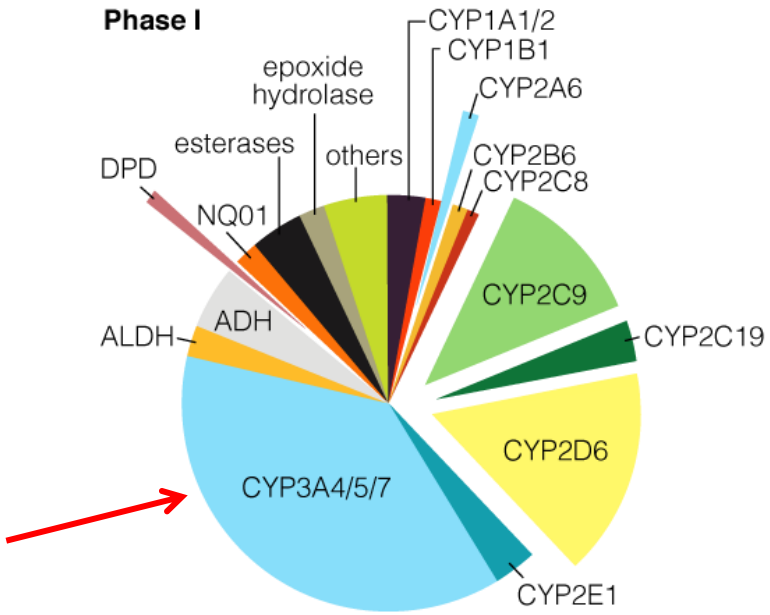
UNIVERSITY OF LIVERPOOL

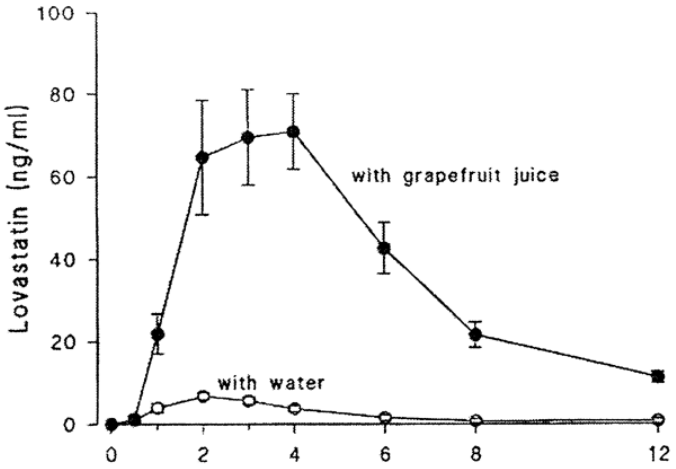
THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

Grapefruit Juice Interactions



Lown et al, JCI, 1997





UNIVERSITY OF LIVERPOOL

THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

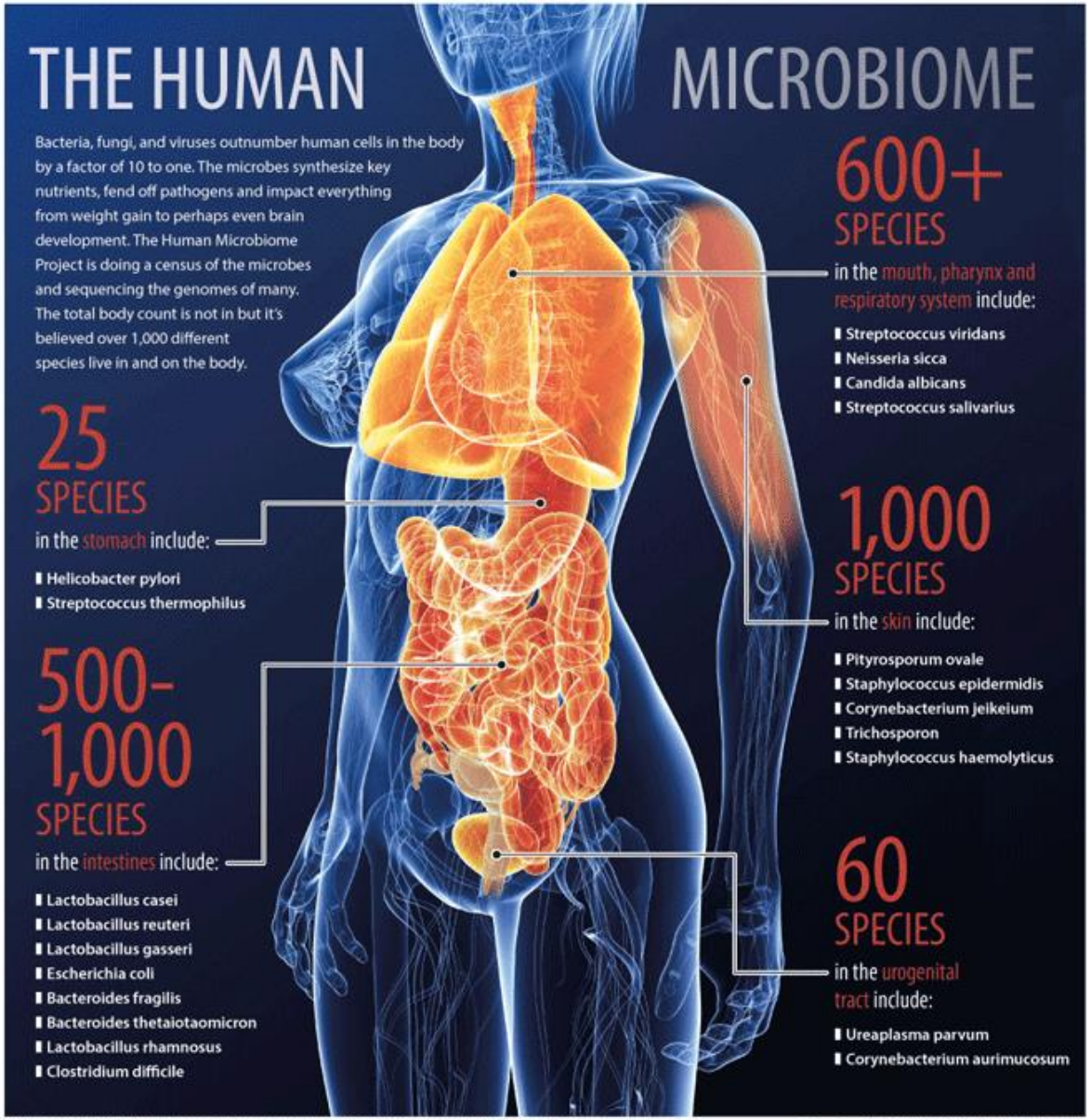
MRC Centre for Drug Safety Science

Grapefruit–medication interactions: Forbidden fruit or avoidable consequences?

David G. Bailey BScPhm PhD, George Dresser MD PhD, J. Malcolm O. Arnold MB BCh MD

Table 2: Case reports of serious adverse events related to grapefruit–drug interaction[18–26]

Serious adverse event	Drug	Amount of grapefruit consumed
Torsade de pointes	Amiodarone[18]	Juice, 1–1.5 L/d on a regular basis
	Quinine in tonic water[19]	Juice, high volume during preceding days
Complete heart block	Verapamil[20]	Juice, high volume during preceding days
Rhabdomyolysis	Atorvastatin[21,22]	Juice, 1–2 glasses/d for 5 d; juice from fresh grapefruit daily for 2 mo
	Simvastatin[23]	Whole fruit, 1 fruit/d for 2 wk
Nephrotoxicity	Tacrolimus[24]	Marmalade, 1.5 kg eaten during preceding 1 wk
Myelotoxicity	Colchicine[25]	Juice, 1 L/d for preceding 2 mo
Venous thrombosis	Ethinylestradiol[26]	Whole fruit, 1 fruit/d for breakfast for preceding 3 d


THE HUMAN MICROBIOME
Bacteria, fungi, and viruses outnumber human cells in the body by a factor of 10 to one. The microbes synthesize key nutrients, fend off pathogens and impact everything from weight gain to perhaps even brain development. The Human Microbiome Project is doing a census of the microbes and sequencing the genomes of many. The total body count is not in but it's believed over 1,000 different species live in and on the body.
600+ SPECIES in the mouth, pharynx and respiratory system include:
Streptococcus viridans
Neisseria sicca
Candida albicans
Streptococcus salivarius
25 SPECIES in the stomach include:
Helicobacter pylori
Streptococcus thermophilus
1,000 SPECIES in the skin include:
Pityrosporum ovale
Staphylococcus epidermidis
Corynebacterium jeikeium
Trichosporon
Staphylococcus haemolyticus
500–1,000 SPECIES in the intestines include:
Lactobacillus casei
Lactobacillus reuteri
Lactobacillus gasseri
Escherichia coli
Bacteroides fragilis
Bacteroides thetaiotaomicron
Lactobacillus rhamnosus
Clostridium difficile
60 SPECIES in the urogenital tract include:
Ureaplasma parvum
Corynebacterium aurimucosum
SOURCES: NATIONAL INSTITUTES OF HEALTH, SCIENTIFIC AMERICAN; HUMAN MICROBIOME PROJECT
Dean Tweed • POSTMEDIA NEWS / IMAGE: Fotolia

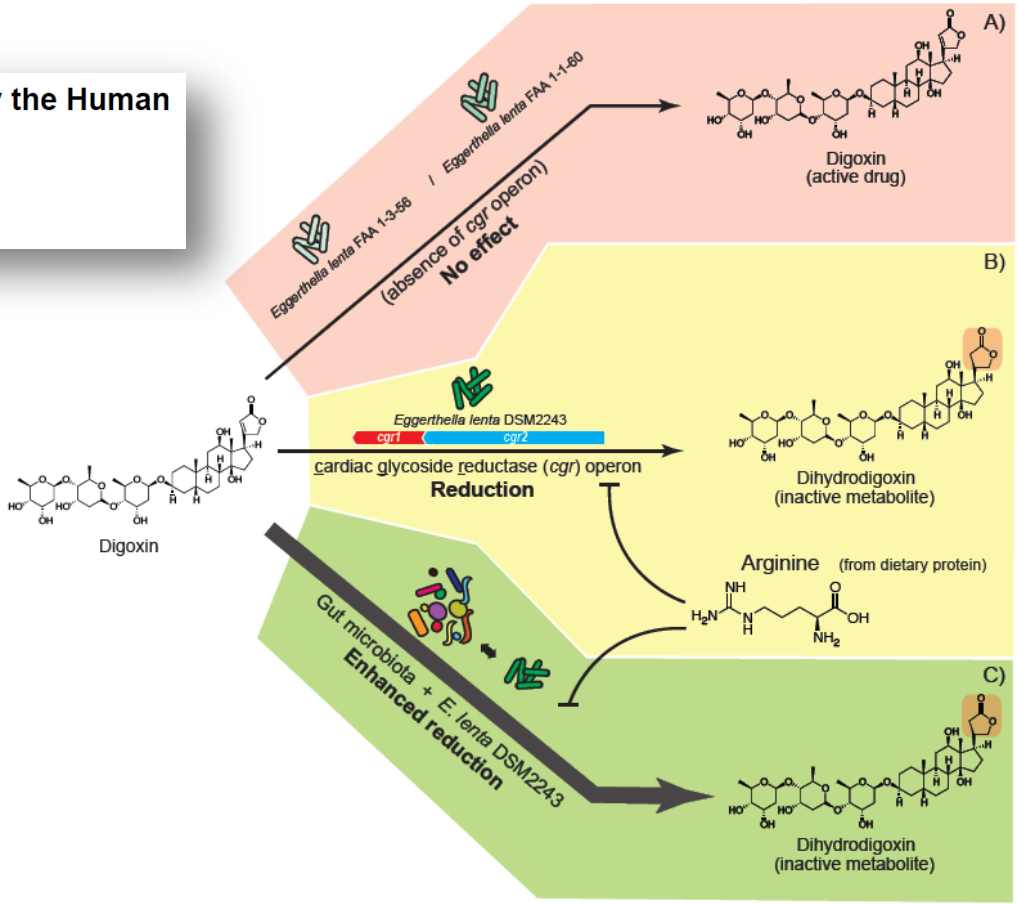
INACTIVATION OF DIGOXIN BY THE GUT FLORA: REVERSAL BY ANTIBIOTIC THERAPY

JOHN LINDENBAUM, M.D., DEBORAH G. RUND, M.D., VINCENT P. BUTLER, JR., M.D., DORIS TSE-ENG, B.S., AND JNAN RANJAN SAHA, M.Sc.

N Engl J Med. 1981; 305

In about 10% of patients, use of broad-spectrum antibiotics can double serum digoxin levels

Predicting and Manipulating Cardiac Drug Inactivation by the Human Gut Bacterium *Eggerthella lenta*
Henry J. Haiser *et al.*
Science **341**, 295 (2013);
DOI: 10.1126/science.1235872



UNIVERSITY OF LIVERPOOL | THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

Microbiome and Cancer Immunotherapy

CANCER IMMUNOTHERAPY

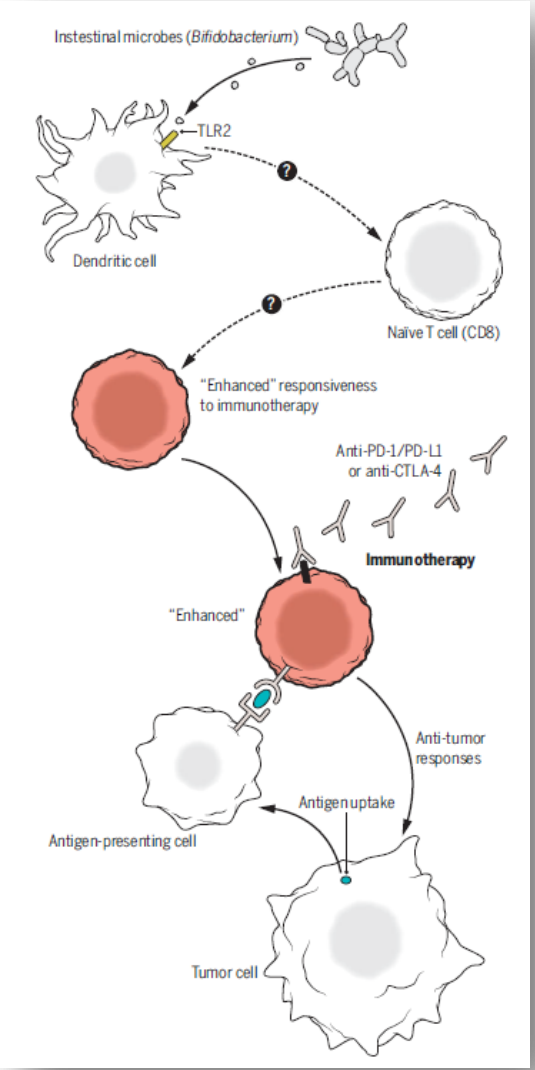
Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Marie Vétizou,[1,2,3] Jonathan M. Pitt,[1,2,3] Romain Daillère,[1,2,3] Patricia Lepage,[4] Nadine Waldschmitt,[5] Caroline Flament,[1,2,6] Sylvie Rusakiewicz,[1,2,6] Bertrand Routy,[1,2,3,6] Maria P. Roberti,[1,2,6] Connie P. M. Duong,[1,2,6] Vichnou Poirier-Colame,[1,2,6] Antoine Roux,[1,2,7] Sonia Becharef,[1,2,6] Silvia Formenti,[8] Encouse Golden,[8] Sascha Cording,[9] Gerard Eberl,[9] Andreas Schlitzer,[10] Florent Ginhoux,[10] Sridhar Mani,[11] Takahiro Yamazaki,[1,2,6] Nicolas Jacquelot,[1,2,3] David P. Enot,[1,7,12] Marion Bérard,[13] Jérôme Nigou,[14,15] Paule Opolon,[1] Alexander Eggermont,[1,2,16] Paul-Louis Woerther,[17] Elisabeth Chachaty,[17] Nathalie Chaput,[1,18] Caroline Robert,[1,16,19] Christina Mateus,[1,16] Guido Kroemer,[7,12,20,21,22] Didier Raoult,[23] Ivo Gomperts Boneca,[24,25]* Franck Carbonnel,[3,26]* Mathias Chamaillard,[5]* Laurence Zitvogel[1,2,3,6]†

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy

Ayelet Sivan,[1]* Leticia Corrales,[1]* Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2]†

Science, 27 Nov 2015



Snyder et al, Science, Nov 2015

UNIVERSITY OF LIVERPOOL | THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

Identifying Drug Interactions

- During drug development based on pharmacological properties
- *In silico* approaches – development of sophisticated modelling technologies
- Observational datasets (including case reports)
- Randomised controlled trials

- New approaches needed to accelerate identification

- Big data – mining of EHRs
- Social media – WEB-RADR
- Learning health systems – Connected Health Cities Program in NHSA

Outline

- Definitions
- Epidemiology
- Some examples and underlying science
- Information sources and prevention of drug interactions

Preventing DDIs

- Careful history of drugs, herbals, alcohol, cigarettes and foods
- Number, dosage and duration of drugs should be kept to the minimum
- Use of drugs should be reviewed regularly
- Patient education and information leaflets
- Education of prescribers
- Information on DDIs
- Electronic prescribing systems

Smartphone apps to support hospital prescribing and pharmacology education: a review of current provision

Faye Haffey,[1] Richard R. W. Brady[2] & Simon Maxwell[3]

[1]Department of Neonatal Medicine, Flinders Medical Centre, Adelaide, South Australia, Australia, [2]Department of Clinical Surgery, Royal Infirmary of Edinburgh, Edinburgh and [3]Clinical Pharmacology Unit, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK

BJCP, 2013; 77: 31-38

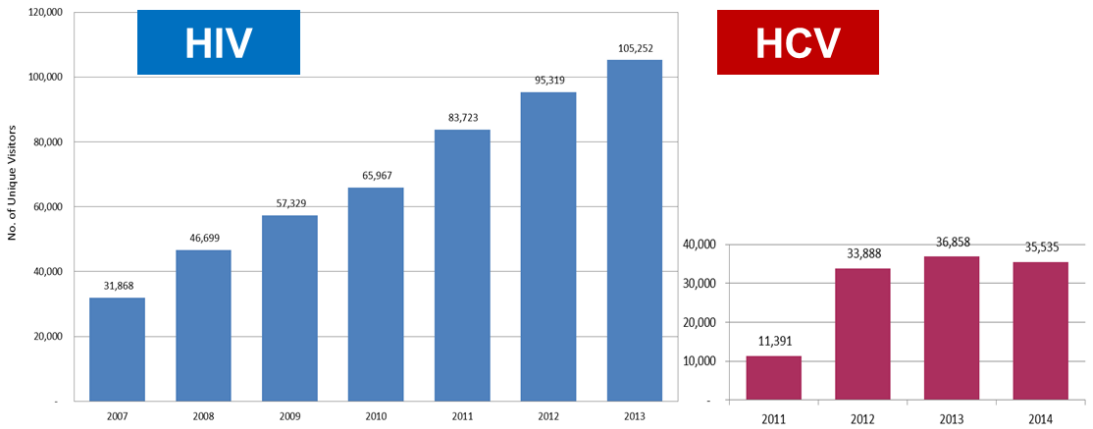
- 306 apps identified
- 34% for use within clinical environment
- Drug interactions covered by some, but likely quality variable
- Expertise of app developers

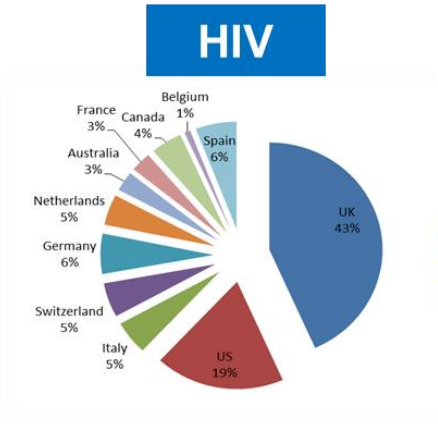
HIV and Hepatitis C Drug Interaction Websites (Courtesy Prof David Back)

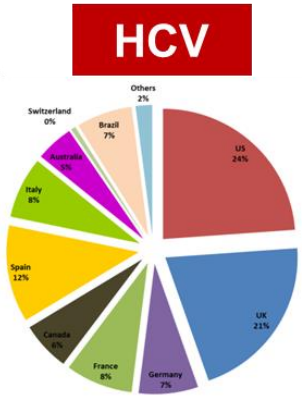
www.hiv-druginteractions.org

www.hep-druginteractions.org

- **Leading DDI resource**
  - used by Treatment Guidelines in > 16 countries/territories
  - UK Standards & BHIVA Guidelines require every GP letter to carry URL
  - partnered with major specialist societies in Europe and USA
- **Web metrics (Google analytics)**
  - Unique users/y – 105,000 (HIV) and 35,500 (Hep)- rising year-on-year
  - multiple territories
  - App downloads: >55,000 (HIV); >13,000 (Hep)







Comparative assessment of four drug interaction compendia

Vitry, BJCP. 2006; 63: 709-714

- 4 drug interaction compendia compared (BNF [UK], Vidal [France], Drug interaction facts [US], Micromedex [US]
- Major drug interactions in one compendia – 14-44% were not listed in other compendia
- ".. lack of consistency in the inclusion and grading of drug interactions of major significance for 50 drugs across the four drug compendia examined".

Electronic Prescribing Systems

- Although effective, operators receive too many alerts: generation ranges 7-35%, with acceptance ranging from 9-12%
- Lack of standardization of identification and severity rating systems
- Tiered alert systems ("traffic lights") may be more useful
- There is a need to improve computerised systems – improve coverage, assessment of likelihood of DDI, reduce alerts, tier alerts

Magro et al, *Expert Opin. Drug Saf*. 2012; 11: 83-94

Summary

- DDIs are common and likely to increase with the change in demographics
- Potential DDIs are more common that clinically relevant DDIs, but the latter still represent a significant clinical problem
- It is important not to forget over the counter medicines, herbal medicines and food as sources of interactions
- We need better systems for identifying interactions in real time
- Electronic sources of information are important and are likely to become more intelligent
- Multi-functional approaches needed in reducing the incidence of DDIs