EAHP Hamburg 2015

WS 1
Ethical and legal dilemmas: focus on the patient

Hans-Peter Lipp and Christoph Rehmann-Sutter

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Statement about conflicts of interests

Neither presenters have conflicts of interest with regard to the substances or products discussed in this Workshop.

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Self-assessment questionaire

1. Are you aware that ethical dilemmas play a role in daily pharmaceutical practice? (1....10)
2. Do you have knowledge how to deal with ethical dilemmas in pharmaceutical practice? (1....10)
3. Should a pharmacist fill any prescription and prepare extemporeanously any medicinal product despite of ethical concerns? (1....10)

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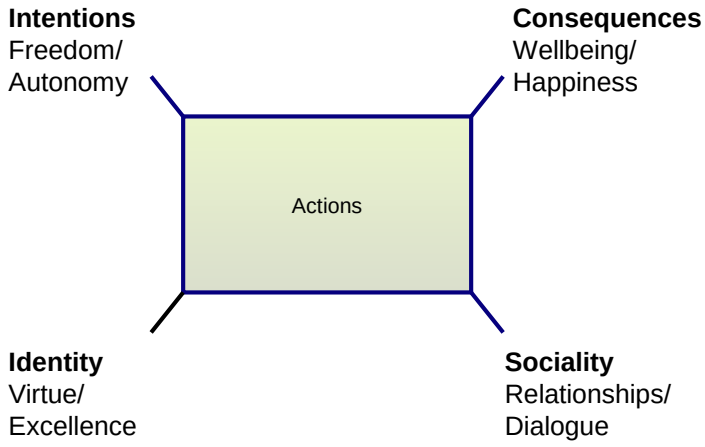
Ethics: Four key concerns



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a) The Greek tradition of ethics

Epicurus (341-270 BC): Ethics treats questions, what should be aimed at in practice and what should be avoided, questions of lifestyle and questions about the goals of life. What is happiness?

Aristotle (384-322 BC) wrote that humans, as rational beings, should not blindly follow traditional rules. They should critically question these and if necessary revise them. For this reason we need a philosophical reflection about how humans should act. – What is practical wisdom (phronesis)?

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b) Ethics as a critical discussion of morality: moral philosophy

Ethics as a critical examination and deliberation of moral norms, of what is said to be „good“ (desirable, valuable, right, just, evil, wrong ...) is not the same as applying given moral norms or values.

Doing ethics means to question morals and morality, to investigate its structure, its reasons, its contradictions, its limits.

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c) Moral perception

- A „case“ is an ethical situation, where different people are involved.
- The situation can be explored and desribed in different ways.
- For ethics we need to know/clarify what is salient in this situation. This must be done before reaching to a moral judgment.
- Anything contributing to, or encompassed within, the agent‘s salience-perception of the situation before she/he deliberates about what action to take is called „moral perception“.

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Methods as tools:

A tool for ethical discovery “helps us uncover ethically salient features of a situation that enrich our understanding of the nature of the ethical problem or question.”

Tools for ethical justification “are used to construct or to evaluate a set of reasons offered in support of a moral conclusion. They do so by employing some standard by which actions or states of affairs are to be judged better or worse, right or wrong.”

Tom Tomlinson: *Methods in Medical Ethics. Critical Perspectives.* Oxford: Oxford UP 2012, p. 213f. And 215

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Two ways of thinking in ethics

Deductive paradigm

- Theory is applied to concrete cases,
- Basic evidence is on the level of theory; universal rationality is key,
- Procedure: Search for the right norm that is sound, well-based in general principles, and applies to thi case.

Reflective paradigm

- Terms and concepts are developed inductively,
- Basic evidence is in concrete relationships; moral perception is key,
- Procedure: Develop arguments that can be explained and criticised, in order to certify that the principles used are sound for this context.

Glossary

Morals and morality: all values, value measures, rules and norms that guide us in regard to such questions as „What shall I do?“, „What my duty?“, „Are we allowed to do this?“ etc.

Ethics: the **critical** reflection about morals and morality, i.e. about what is good and evil, why it is good and evil, and about what we can or should expect from each others in society. (Critical reflection also includes **our own** practice how we *do* bioethics in society!)

Ethics of pharmacy: the search for the right ethical attitudes, norms and goals, which should guide us in the practice of pharmacy.

Ethos: A historically developed **coherent set** of moral attitudes, values and norms. The **ethos of science** is constitutive for identity (identitätsstiftend) for scientists. It belongs to the job profile (Berufsbild) and determines the self-image (Selbstverständnis). Ethics reflects about the contents of the ethos.

Case 1

Use of Laetrile in tumour patients

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Complementary and alternative medicine

- **Individual (non evidence-based) demands of a cancer patient**
  - **Versus**
- **Scientific and regulatory considerations**

Where is the limitation?

CAM in oncology day care units

Prospective study among patients (n=100), mean: 63 years old, 50% male, 50% female (Fort P et al. ASCO 2012; abstr e19555)

- **Questionnaire**
  - **Do you take any biological treatment concurrently?**
  - **Do you take any non-drug alternative medicine concurrently?**
- **Results**
  - **38% of patients used CAM. Of those: 45% homeopathy, 39% food supplements, 37% herbal medicine, 29% non-drug alternative medicine (acupuncture, magnetic healer, meditation)**
  - **29% took at least 3 different medicines, 61% herbal medicines (heard of it by friends & families, 75% bought it by internet* or by phone)**
  - **Food supplements: 48% bought it by pharmacy, 40% by phone, whereas 90% on homeopathy were advised by pharmacists**
- **Conclusion**
  - **Too many cases are advised by non-medical people**
  - **In 16% of cases, reduction of antitumor activity has to be expected**

*encouraging in vitro data, epidemiologic „indicators“, „expert“ opinion etc.

CAM - constituents

- **Vitamins*, physiological substrates, trace elements (orthomolecular medicine)**
- **Food supplements (e.g. shark cartilage)**
- **Phytomedicine (e.g. green tea)**
- **Traditional Chinese Medicine (TCM)**
- **Homeopathy**
- **Acupuncture**
- **Yoga**

*BURG APOTHEKE 2014: It is legally allowed to deliver Amygdalin (Vitamin B17, Laetrile) in case of a prescription if the quality is guaranteed
3 g/20 mL: 32 €, 6 g/40 mL: 60 €, 12 g/80 mL 115 €

Severe cyanide poisoning from CAM with amygdalin and pricot kernels in a 4-year old child

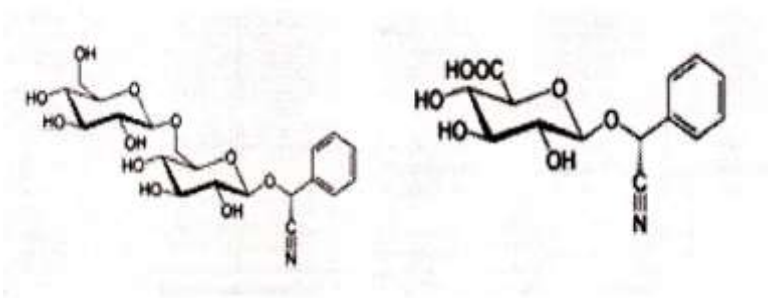
Sauer H et al. Wien Med Wochenschr 2015

- CTX pretreated 4-year old boy with a history of malignant brain disease. Based on poor prognosis, he was treated with CAM incl. Vitamins
- Transfer to emergency department because of sudden collapse. On arrival: agitation, unresponsiveness, encephalopathy, severe metabolic acidosis (pH: 7.12, pCO2: 45.7 mm Hg), lactate: 11.8 mM, glucose: 199 mg/dL
- Supportive intervention: fluid rescuscitation and oxygen. An yporgession of brain tumor was ruled out by MRI
- Anamnesis: IV Vitamin B17 (NovoDalin) 4 x 500 mg/d and consumption of 5-10 apricot kernels/day. In addition: Vitamin A, D, E, selenium and sulfur powder
- Toxicological analysis: ca. 2 h after last Vit.B17 administration: serum CN: 515 µg/L (normal: < 50 µg/L, toxic*: > 200 µg/L, lethal > 3 mg/L)
- Following sodium thiosulfate (2 g): rapid improvement within 2 hours, no long-term sequelae. After 3 d the patient could leave the department

*Mild: nausea, headache, metallic taste, drowsioness, hyperpnea; severe: convulsions, CV collapse, shock, pulmonary edema

Amygdalin & Laetril (IV form, synthesized/patented 1950)

Amgydalin = original form (ca. 8% m/m in apricot kernels), first isolated 1873
Vitamin B17 („pseudo-vitamin = it is not essential)



Release of Cyanide (via ß-Glucosidase as contaminant or impurity or via gut flora) results in inhibition of Cytochrome C Oxido-Reductase and intracellular breakdown of the respiratory chain (enery metabolism) – impairment of oxidative phosphorylation

FDA /NCI 1980s: - Clinical Trial in treatment of cancer – result: no signs of tumor regression:

Laetril for cancer: a systematic review of the clinical evidence

Milazzo S et al. Support Cancer Care 2007; 15: 583-95

- All types of clinical studies containing original clinical data related to the effectiveness or safety of Laetril interventions as a treatment. N = 36 met the inclusion criteria, however no controlled clinical trial was found.
- Conclusion: sound clinical data do not support beneficial effects of Lateril for cancer patients
- N**egative risk-benefit balance**

- Limitations of the systematic review:
  - Quality and paucity of data limits conclusiveness
  - Perhaps further data (unpublished) may exist
  - Very heterogenous data (different methodological desiagns, various forms/etiologies of cancer diseases)

Amygdalin/Laetril – regulatory considerations

- **ADKÄ Drug Safety: warning letter (37/2014)**
  - Do not use Amygdalin-containing drugs or products, ≥ 2 aprocot kernels have to be classified as critical
- **BfArM 10/2014**
  - Use of Amygdalin in human beings is very risky whereas clinical effectiveness as well as benefit in oncology have not yet been proven
  - Clinical efficacy = not proven, toxic effects = undoubted
  - Even when IV formulation (Laetril) may be associated with any increased CN levels (Oberverwaltunsgericht Hannover 2007*) , critical contaminants or impurities can never be excluded
- **BfArM Conclusion 2014: Delivery of Amygdalin-containg drugs is forbidden – on a regultory base - even in case of a physician´s prescription. § 5 AMG: possible damage *versus* no benefit**

***Single case decision (based on highly purified Laetril), no signs of in vitro toxicity (expert) which cannot be translated to other cases. In addition: in vitro to in vivo corrleation (toxicity) remains unclear (BfArM)**

Amygdalin influences bladder cancer cell adhesion and invasion in vitro

Makarevic J et al. (PLOS One Oct. 2014)

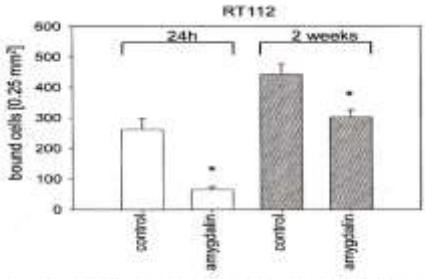


Figure 2. Adhesion of UMUC-3, TCCSUP and RT112 bladder cancer cells to immobilized collagen. Tumor cells were treated with 10 mg/ml amygdalin for either 24 h or for 2 weeks. Cells not treated with amygdalin served as the controls. 0.5×10^6 cells/well were added to immobilized collagen for 60 min. Mean number of adherent

Messages: Metastasis blocking was inveastigated…Integrin subtype was significantly and selectively altered by Amygdalin…anti-tumor benefits from amygdalin may dependent upon the cancer cell type
AMYGDALIN MAY SLOW METASTATIC PROGRESSION – PRECLINICAL DATA ARE UNDERWAY

Therapeutic use of tea derivatives

All that glitters is not gold (Mancuso & Barone; Blood 2012)


Grüner Tee antagonisiert die Wirkung von Bortezomib

- **Natural polyphenols antagonize the anti-myeloma activity of proteasome inhibitor bortezomib by direct chemical inactivation**
  - **Kim TY et al. BJH 2009**
- **Interaction of green tea EGCG with sunitinib: potential risk of diminished sunitinib bioavailability**
  - **Ge J et al. J Mol Med 2011**
- **Possible green tea-induced thrombotic thrombocytopenia purpura**
  - **Liatos GD et al. AmJ Health Syst Pharm 2010**

Cancer protection by Green Tea
Tao I et al.
Differential protective effects of EGCG in normal and oral cancer cells are related to differences in SIRT3 signaling
Mol Nutr Food Res 2015wepub

SIRT3: Sirtuin 3 = mitochondiral enzyme (HDAC)

Use of Laetrile in tumour patients – ethical questions

- Is a patient (or the family) in a position to make a balanced decision about using such a drug?
- What is the punchline in the proposal of Cancer Research UK?
- Is the approach proposed by Cancer Research UK reasonable?
- What are the underlying ethical considerations?
- What should in your view be the key ethical concerns?
- Should a terminal cancer patient have access to unproven therapies for psychological reasons (mental well-being)? And if yes, why? If not, why not?

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Case 2:

Cyp2C19-Genotyping to improve drug efficacy and tolerability

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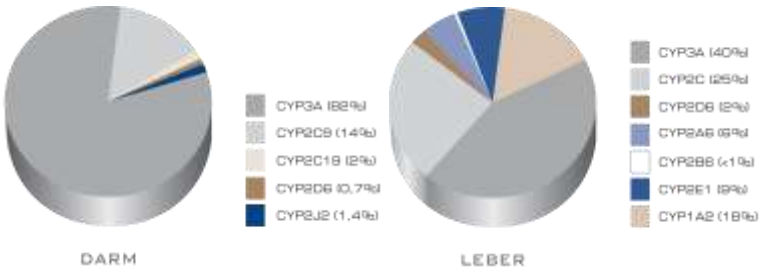
Pharmacogenetics – e.g. Cyp Isozymes

- **Predictive value (e.g. individual extent of biotransformation)**
  - **Versus**
- **Prognostic value and possibly undesired consequences**

Where is the limitation?

Focus: Extra- und intrahepatic distribution of Cytochrome P450 Isozymes



Modifiziert nach Paine MF et al.

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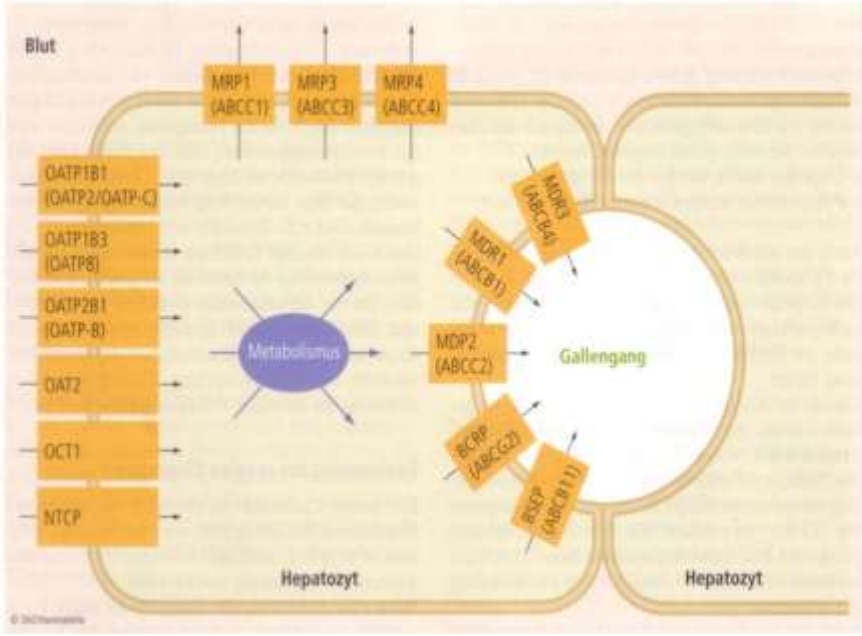
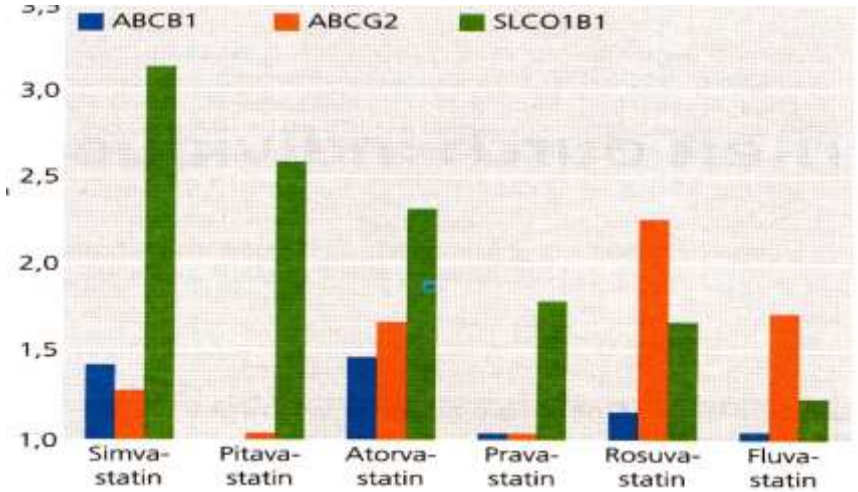
1. Mod. from Paine MF et al. Drug Metabolism and Disposition 2006; 34(5):880-886.



Statin levels in plasma and genetic polymorphisms of transmembranar carriers (e.g. SLCO1B1/OAT1B1)

Niemi M et al. Clin Pharmacol Ther 2010; 87: 130-3



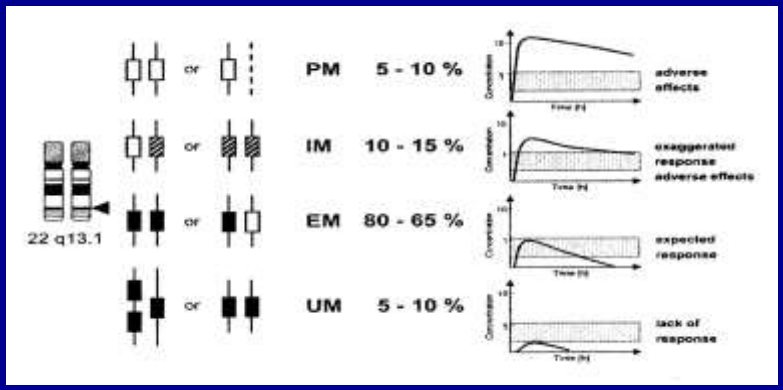
Current PK Genotyping Assays

AMPLICHIP
Challenges and limitations

- **OATP organic anion - influx pump (PK)**
- **OCT organic cation influx pump (PK)**
- **ABCB1 (MDR1, PgP) – efflux pump (PK)**
- **Cyp450 2C9, 2C19, 2D6 isozymes (PK)**
- **SULT1, UGT1A1 or GST-Phase-II-isozymes (PK)**
- **SCN5A – Sodium channels (heart tissue) (PD)**

Cytochrom P450-Isozyme Polymorphisms

(E.g. CYP2D6) mod. from Zanger, Raimundo & Eichelbaum)
Naunyn Schmiedeberg´s Arch Pharmacol 2004; 369: 23-37



Cave: marked interindividual variability of plasma levels (e.g. spartein) has to be considered in spite of recommended conventional dosages

E.g.: several antidepressants (clomipramine, nortriptyline,), neuroleptic agents (risperidone, haloperidol) tamoxifen, codein

Genetic variants associated with phenytoin-related severe cutaneous adverse actions (JAMA 2014epub)

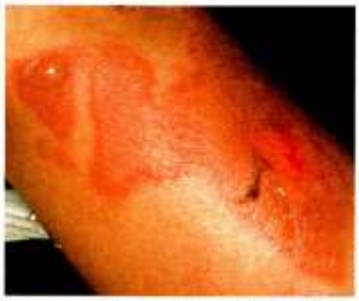


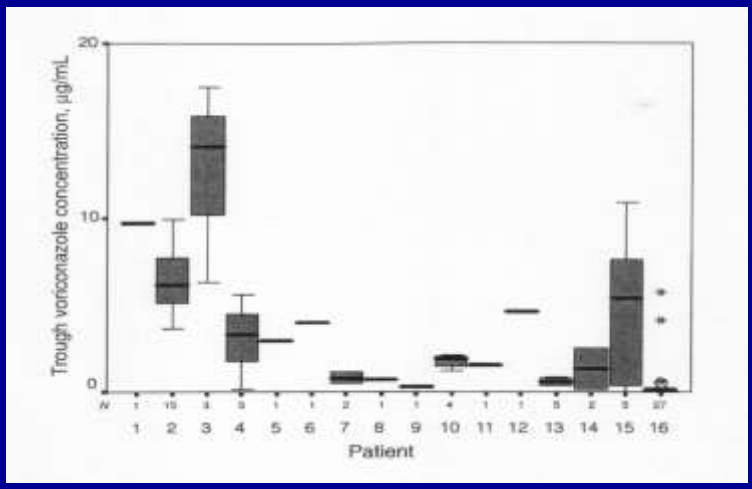
Foto: SPL/Agentur Focus

Die toxische epidermale Nekrolyse zählt zu den schweren Arzneimittelreaktionen, die durch eine großflächige Ablösung der Haut sowie der Schleimhäute, schwere systemische Begleiterscheinungen und durch eine hohe Mortalität gekennzeichnet ist.

- Variant **Cyp2C9*3** is associated with intolerability to Phenytoin- (SJS, TEN, increased mortality and DRESS)
- Mutation is located in 20% of patients in Malaysia or Japan
- Cyp2C9*3 results in 93-95%-decrease of phenytoin clearance with higher Phenytoin plasma levels than expected as well as increased formation of reactive intermediates

Inter- and intraindividual variability of VCZ c_{min}

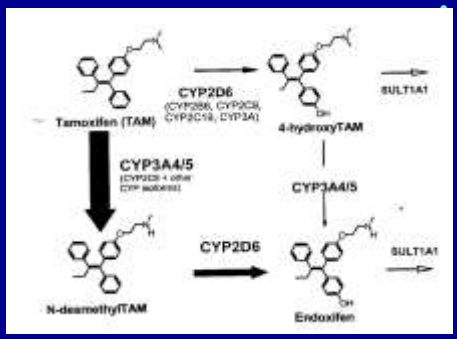
Experiences with Voriconazol oral (z.B. 2 x 200 mg/d)



Mod. from Boyd AE. et al. (CID 2004; 39: 1241-4)

Cyp2D6 Genotype, Antidepressant use, and Tamoxifen Metabolism during Adjuvant Breast Cancer Treatment

Zeruesenay YJ, et al. JNCI 2005; 97: 30-9



Flockhart et al.:

…5-year-disease-free survival for patients homozygous for inactivating 2D6 mutations was only 46%, compared with 83% for patients without the mutations (OS did not differ)

Avoid concomitant use of SSRI with 2D6 inhibiting potency

In addition: Cyp2C19 *17/*17 (URM) – ca. 9% of Caucasians – have been associated with better survival after adjuvant tamoxifen compared with carriers of other alleles

SULT1A1 *2/*2 triples the risk of death compared to other SULT1A1 genotypes (Lancet Oncol 2010)

Cyp2C19 Polymorphism and TDM of Voriconazole

(Obeng et al. Pharmacotherapy 2014; 34: 703-18)

Cyp2C19 genotype	Phenotype	White	African-American	Asian
*1/***17** and ***17/*17**	**Ultrarapid**	31%	33%	1%
*1/*1	Extensive	42%	39%	35-43%
*1/*2, *1/*3, *2/*17 *3/*17	Intermediate	19%	15%	43-46%
*2/*2, *2/*3, *3/*3	Poor	3%	7%	14-19%

Narita et al. (J Pediatr Hematol 2013): VCZ plasma levels are significantly correlated in children with Cyp2C19 geonotype

All patients with trough level > 5 µg/mL were PM or IM
Levels were higher in PM and IM compared to EM and UM
2 UM had very low levels (0.09 and 0.12 µg/mL)

Conclusion: Initial VCZ dose guided by Genotyping, TDM as patient-specific dosage recommendation (IA Treatment: > 0.5-1.5 µg/mL)

Cytochrome P450 2C19 (Cyp2C19) - Polymorphisms

- **Timm R et al.**
  - Association of cyclophosphamide pharmacokinetics to polymorphic cytochrome P450 2C19 (Pharmacogenomic J 2005; 5: 365-73)
- **Ishida Y et al.**
  - Eradication rate of Helicobacter pylori according to genotypes of Cyp2C19, IL-1ß and TNF (Int J Med Sci 2006; 3: 135-40)
- **Kropp S et al.**
  - Cytochrome P450 2D6 and 2C19 polymorphisms and length of hospitalization in psychiatry (Clin Lab 2006; 52: 237-40)
- **Hulot J-S et al.**
  - Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects (Blood 2006; 108: 2244-7)

Pros and cons: routine use of Cyp-Genotyping and TDM:

May the patient be alive? (Jornil J et al. Forensic Science Int 2013; 226: 26-31

- 34-year old male caucasian (1.65 m, 90 kg) was found dead lying in his bed at home (Jan. 2011). He was alive 4 h earlier, no note of suicide
- Background: Type-1 diabetes (since 2007: 10 IU/d Insulin detemir). History of psychiatric disease (depression, anxiety), in addition: severe shoulder and back pain
- Pill organizer: Venlafaxine 150 mg b.i.d. (ER), Pregabalin 300 mg o.d., Pantoprazole 20 mg o.d., Quetiapine 100 mg b.i.d., Simvastatin: 80 mg o.d. As needed: Oxycodone, Diazepam, Nitrazepam, Haloperidol, Zolpidem and Etodolac; 2-days before death: start with Penicillin V (1 Mio t.i.d.) based on suspiscion of pneumonia
- Because the death was unexpected – autopsy was performed: Result: Venlaxafine plasma levels remarkably high (4.5 mg/kg), whereas O-desmethylvenlafaxine and N-Desmethylvenlafaxine were low (0.02 mg/kg and 0.54 mg/kg) respectively. Genotyping: **Cyp2C19 PM as well as Cyp2D6 PM**
- **Conclusion: very probably, Venlafaxine-associated cardiovascular toxicity was the potentially lethal causative**

Cyp2C19 loss-of-function polymorphism is associated with an increased treatment-related mortality (TRM) in patients undergoing allogenic transplantation

(Elmaagaeli AH et al. BMT 2007)

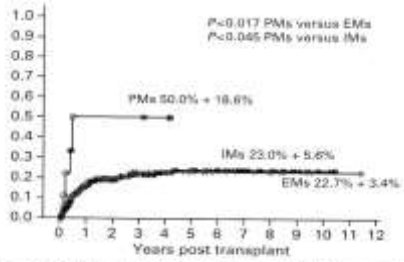


Figure 3 Estimates of transplant-related mortality. Poor metabolizers had the highest rate of TRM with 50% compared to extensive metabolizers and intermediate metabolizers.

Cyp2C19 PM developed 2-fold higer maximum serum creatinine and bilirubin values. In addition: Cyp2C19 PM correlates with TRM and higher morbidity (but not relpase rate, OS or GvHD)

Conclusion: Patients planned for allogenic PBSCT should be genotyped for Cyp2C19 before transplant to identify thiose with a high risk for individual risk of TRM

Cyp2C19-Genotyping to improve drug efficacy and tolerability - ethical questions

- Which are the two “horns” of the dilemma?
- Which ethical considerations are most relevant here?
- Decision-making takes place on several different levels: A healthcare system, a clinic, an individual doctor-patient-pharmacist-relationship, a patient within her or his family (etc.)
- How certain is the knowledge that we are dealing with at the different levels of decision-making?
- How would a non-consequentialist, a utilitarian, a virtue ethicist or a relationship ethicist argue?
- How should decisions be made? (How can the patient participate in the decision?)
- Is it something that the patient should decide about?
- Who is responsible for what?
- Do we have a duty to know our own genes?

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Self-assessment questionaire

1. Are you aware that ethical dilemmas play a role in daily pharmaceutical practice? (1....10)
2. Do you have knowledge how to deal with ethical dilemmas in pharmaceutical practice? (1....10)
3. Should a pharmacist fill any prescription and prepare extemporeanously any medicinal product despite of ethical concerns? (1....10)

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