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Bern, September 8th and 9th 2010

CISDEM
CÁTEDRA IBEROAMERICANA-SUIZA
DE DESARROLLO DE MEDICAMENTOS

➔Patient Compliance in the Focus of Pharmaceutical Care

Prof. Dr. Kurt Hersberger

Pharmaceutical Care Research Group

University of Basel

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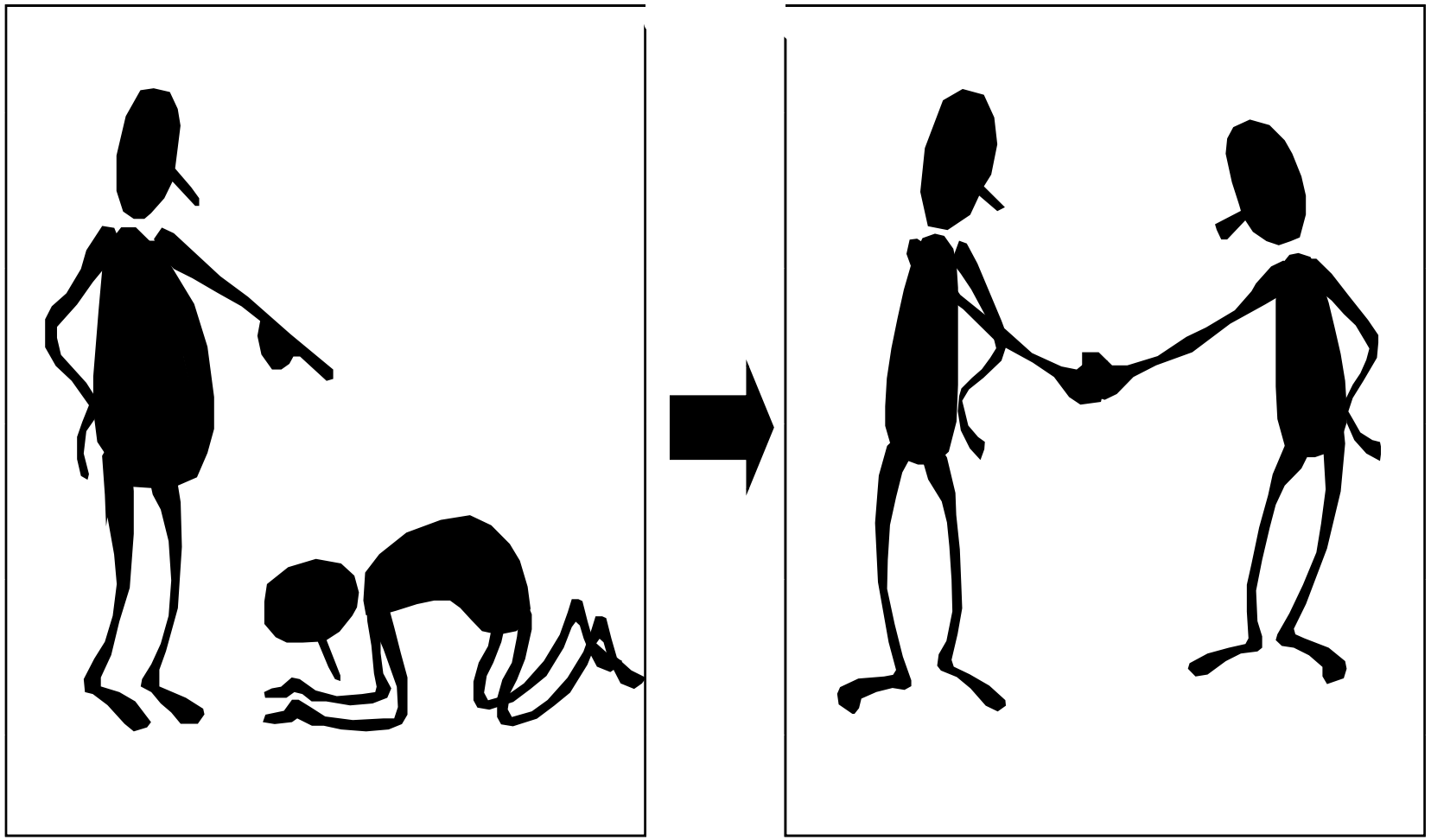
BASEL

Compliance model

Concordance model



Definitions

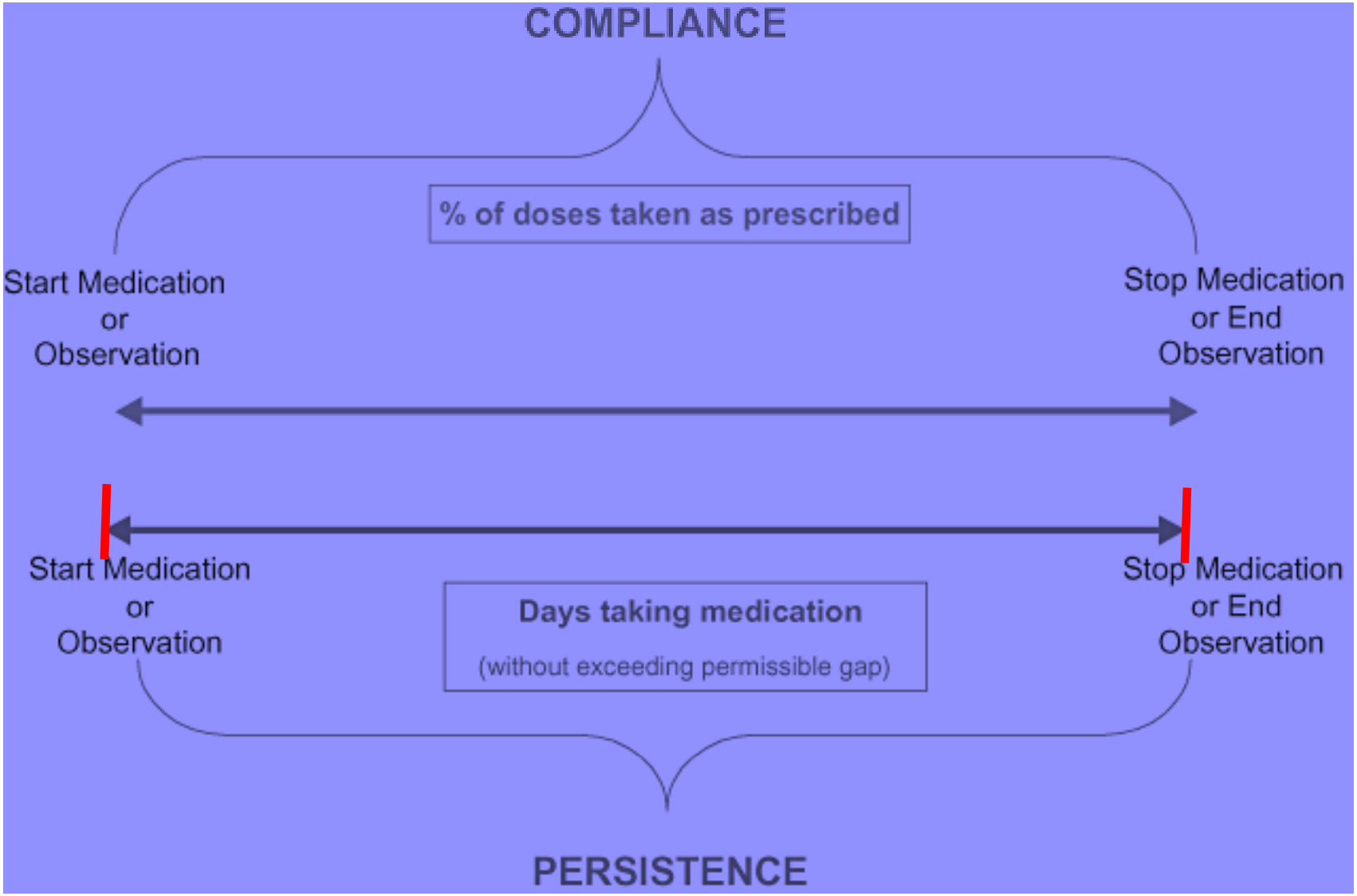
Patient compliance: « Voluntary cooperation of the patient in following a prescribed regimen » (Mesh, Year introduced: 1975)

Medication adherence: « Voluntary cooperation of the patient in taking drugs or medicine as prescribed. This includes timing, dosage, and frequency »
(MESH; Year introduced: 2009)

ISPOR 2008 (International Society for Pharmacoeconomics and Outcomes Research):

Medication compliance: « **(synonym: adherence)** refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking. »

Medication persistence: « Accumulation of time from initiation to discontinuation of therapy, measured by time metric »



Cramer, J. A., Roy, A., Burrell, A., Fairchild, C. J., Fuldeore, M. J., Ollendorf, D. A. and Wong, P. K. (2008), Medication Compliance and Persistence: Terminology and Definitions. Value in Health, 11: 44–47.

Non-compliance affects virtually all disease areas (n=569 studies)

TABLE 2. Average Adherence in Studies of 17 Disease Conditions

	No. of Studies	Mean Adherence (percent)*	Random Effects 95% Confidence Interval for Mean Adherence (percent)
HIV disease	8	88.3	(78.9, 95.2)
Arthritis	22	81.2	(71.9, 89.0)
Gastrointestinal disorders	42	80.4	(73.9, 86.2)
Cancer	65	79.1	(75.9, 84.2)
Seizures/brain disorders	9	78.4	(52.4, 95.7)
Genitourinary and STDs	17	77.0	(65.4, 86.9)
Skin disorders	11	76.9	(66.5, 85.9)
Cardio vascular diseases†	129	76.6	(73.4, 79.8)
ENT and mouth disorders	30	76.1	(68.6, 82.8)
Blood disorders (not leukemia)	7	75.6	(45.9, 95.7)
OB-GYN	19	74.8	(64.2, 84.2)
Infectious disease	34	74.0	(67.5, 80.0)
Eye disorders	15	72.6	(61.8, 82.3)
End-stage renal disease	20	70.0	(56.8, 81.6)
Pulmonary diseases	41	68.8	(61.1, 76.2)
Diabetes	23	67.5	(58.5, 75.8)
Sleep disorders	16	65.5	(54.3, 75.8)

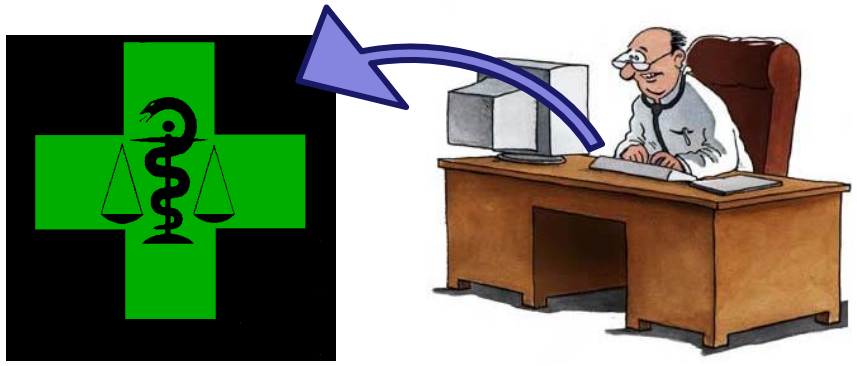
DiMattero MR. Patients' adherence : review of 50 years of research. Med Care. 2004;42(3):200-9

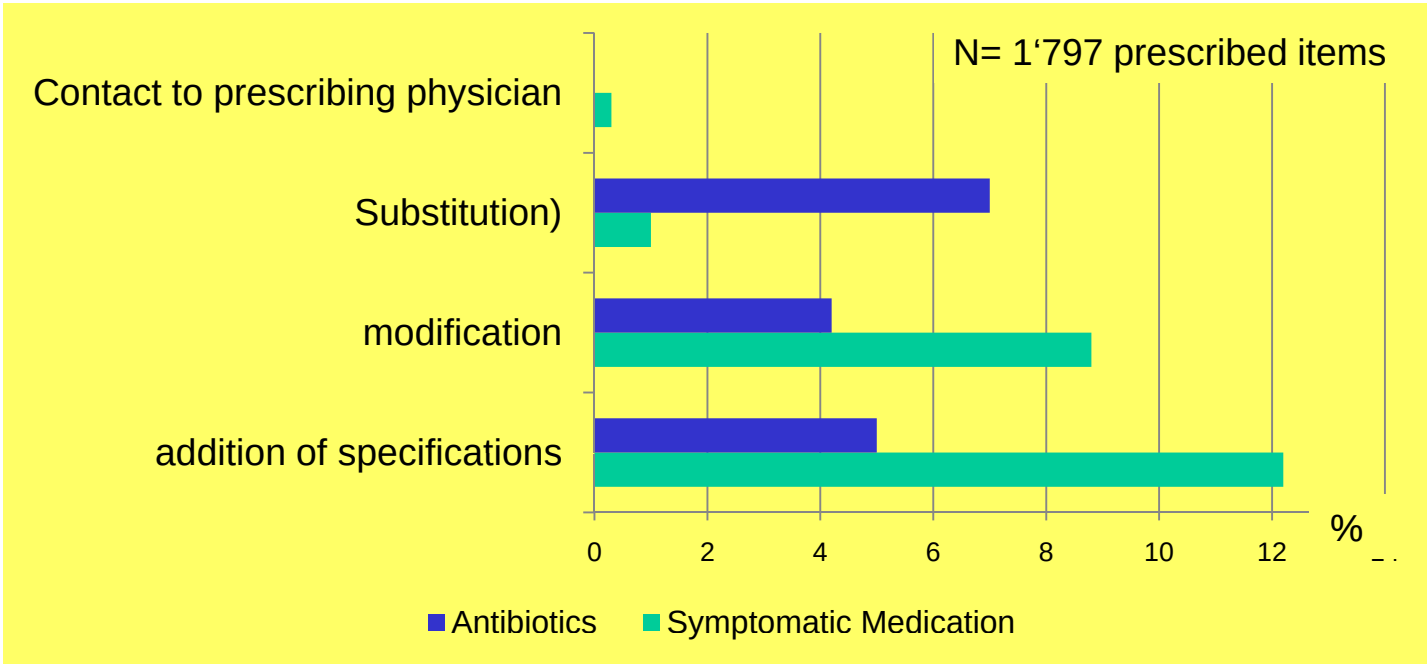
Prescriptions in Swiss community pharmacies

In general:

- 20.9% newly prescribed items
- 74.6% repeat prescriptions
- 4.5% provision in advance

Gregorini F. Master thesis Pharm Sci, Basel 2007

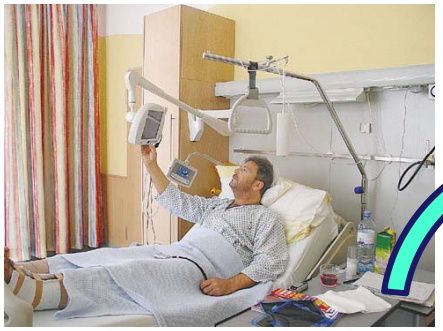




Prescribed medications and pharmacy interventions for acute respiratory tract infections in Swiss primary care (ARTIME- study)

Hersberger K et al. J Clin Pharm Ther, 2009;34:387–395

“Intention to treat” vs. “as treated” in daily life



Frequent interventions / modifications

Prescribed ≠ dispensed ≠ used

Prescription validation in Switzerland
(Rezeptvalidierung)

„Delivery-Check“
(Bezugs-Check):
Each prescription: sFr. 3.25
- Medication history
- Check accumulation / SM
- Check interactions

2 Perspectives
- **Pharmaceutical Care**
- **Technical control** (with respect to direct charging the assurance)

„Drug-Check“ (Medikamenten-Check):
Each dispensed item: sFr. 4.30
- Prescription check
- Ev. possibility of repeated dispense
- Dosage / Limitations
- Interactions
- Risk factors / contraindications
- Contact with prescriber
- Check for misuse
- Patient counselling
- Choice of optimised package size
- Need for immediate provision
- Modifications

Special Cases:
- Single repetition / Repetition over time
- Provision in advance
- Provision without prescription

Polymedication Check (45 tax points = ca. €30.-)

Limitations:

- **Only for patients on ≥ 4 prescribed drugs over ≥ 3 months**
- **Only if patient agrees, but independently from prescriber**

Elements of new service

- Instruction of the patient on use of ALL drugs he uses
- Together with the patient a written protocol has to be filled which documents for each drug
  - dosing regimen and important recommendations
  - check for motivation, experiences and difficulties of the patient
  - counselling on potential side effects and drug interactions
  - discussion of compliance goals and documentation of agreed objectives
- This protocol has to be signed by the patient who receives a copy
- **If patient agrees the pharmacy can dispense the drugs in a Dosette or weekly blister pack for a maximum period of 3 months (continued service needs to be prescribed) (20 TP per week = ca. €13.-)**
- Repetition of Polymedication check at the earliest after 6 months = max. 2x / year
- This service has to be performed exclusively by a pharmacist

Levels of Pharmaceutical Care

Level 1

AD HOC
unstructured opportunistic
POS-Intervention
Counselling at the point of sale

Level 2

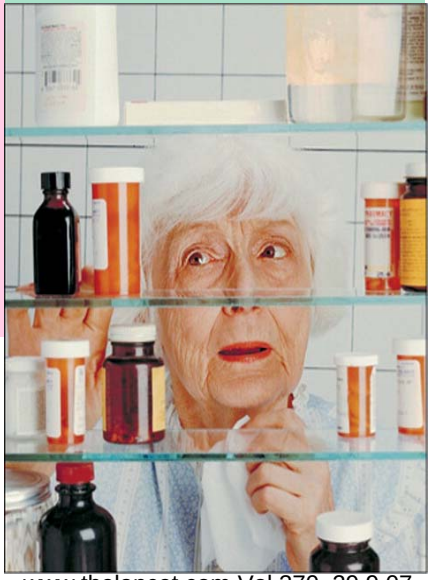
TELEPHONE INTERVIEW
Structured counselling with respect to prior POS-intervention; some days later

Level 3

MONITORING
Prearranged counselling session with medication review and ev. clinical assessment

Level 4

HOME VISIT
Comprehensive assessement of patient self-management

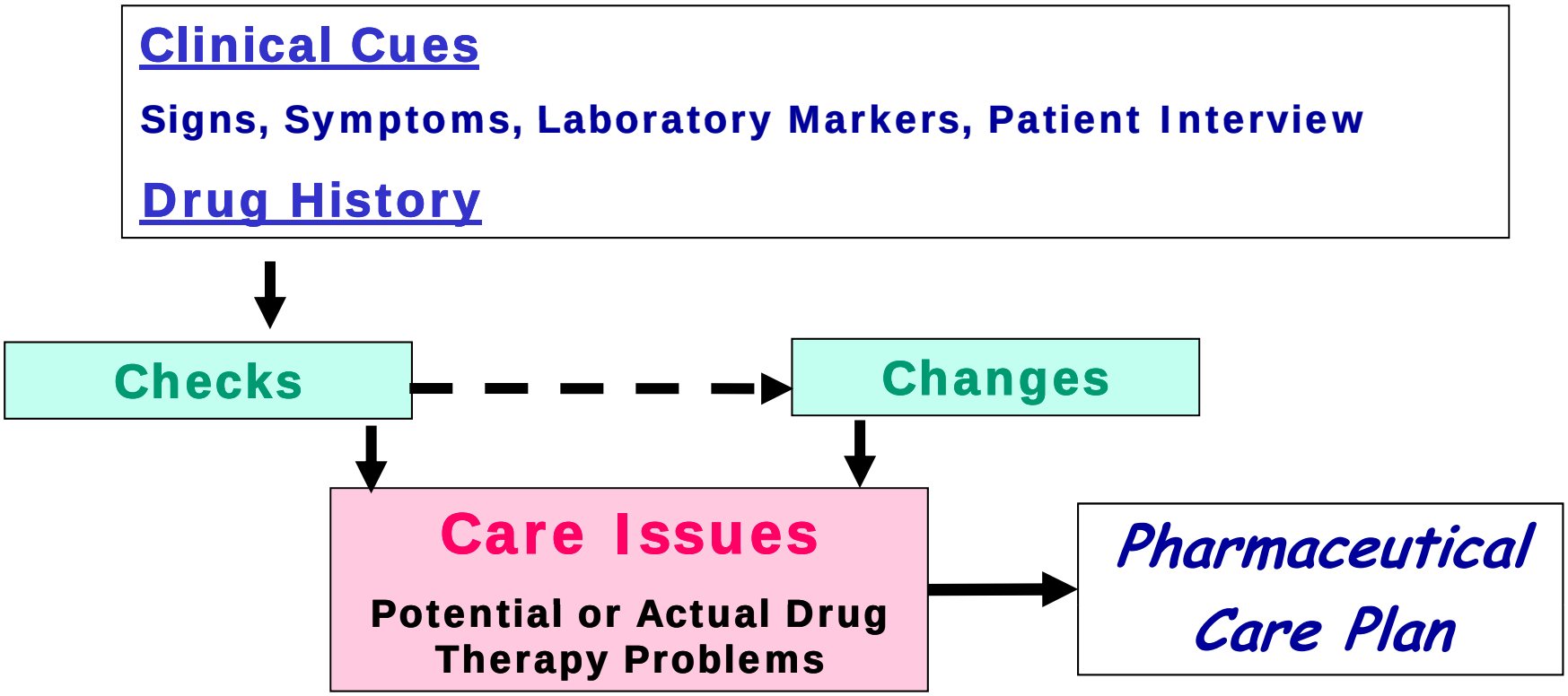


www.thelancet.com Vol 370 29,9.07

Pharmaceutical Care Issues

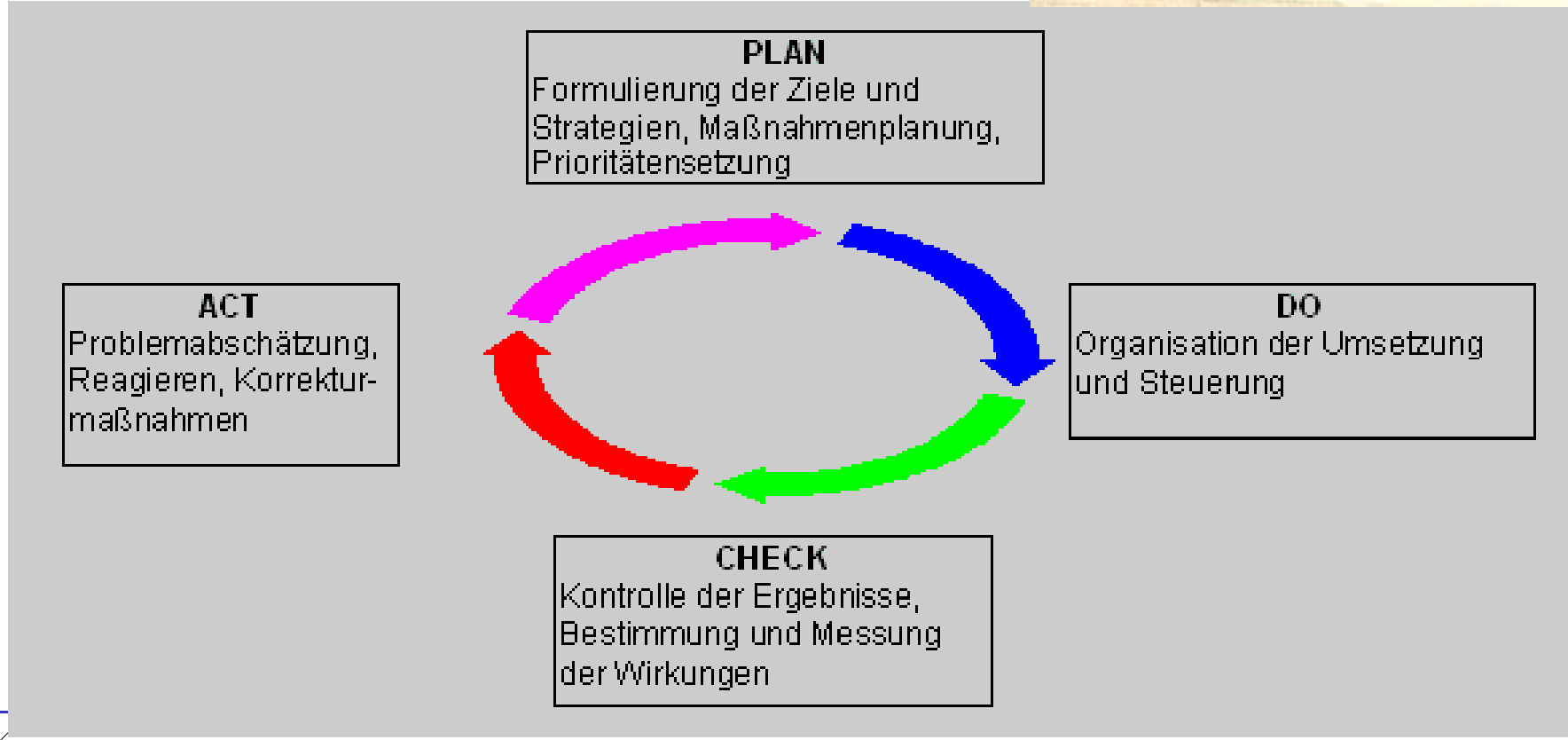
(adapted from S. Hudson, University of Strathclyde, Glasgow, UK)

Systematic evaluation & monitoring of drug therapy:



W.E. Deming (1900-1993)

PDCA - Principle (Plan, Do, Check, Act)



Concept Polymedication Check

All drugs (Focus on RX, but self-medication if considered important)

Check

A. Clarification of need for counselling on drug use

(Unclarity within treatment plan, duplication, problems with drug „handling“)

1. Patient knows how (Wissen, wie)
2. Patient knows why (Wissen, weshalb)

B. „ Compliance question“ ?

3. Do you ever forget to take this medicine?

C. Need for Dosette/weekly blister pack?

D. Need for intensified compliance counselling / support?

E. Need for advanced medication review ? (clinical review)

Act & Plan

I. Instruction / Motivation to perform treatment plan

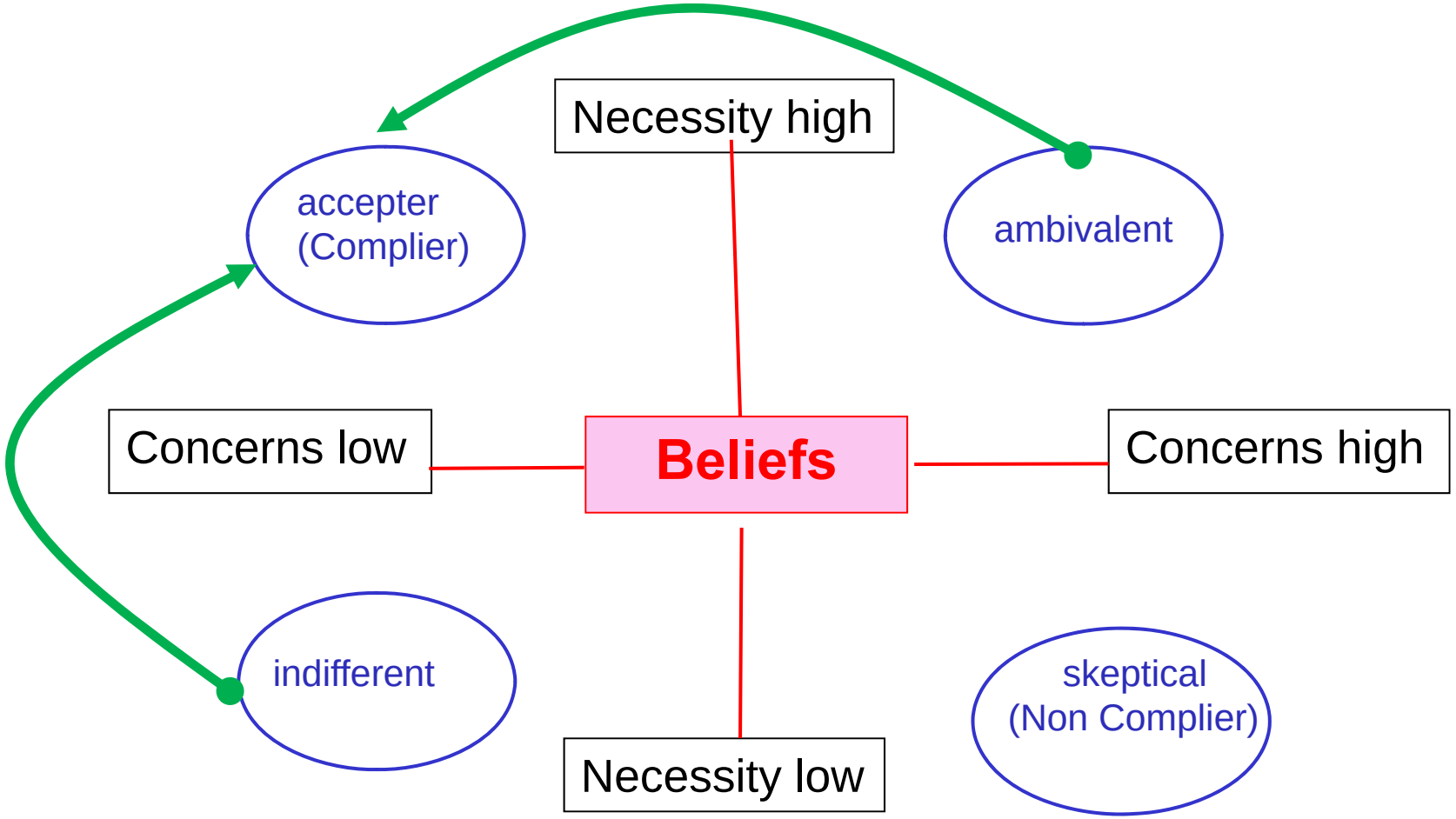
K. Follow-up (e.g. next PM-Check)

L. Ev. filling a Dosette

M. Ev. clarification treatment plan with prescriber

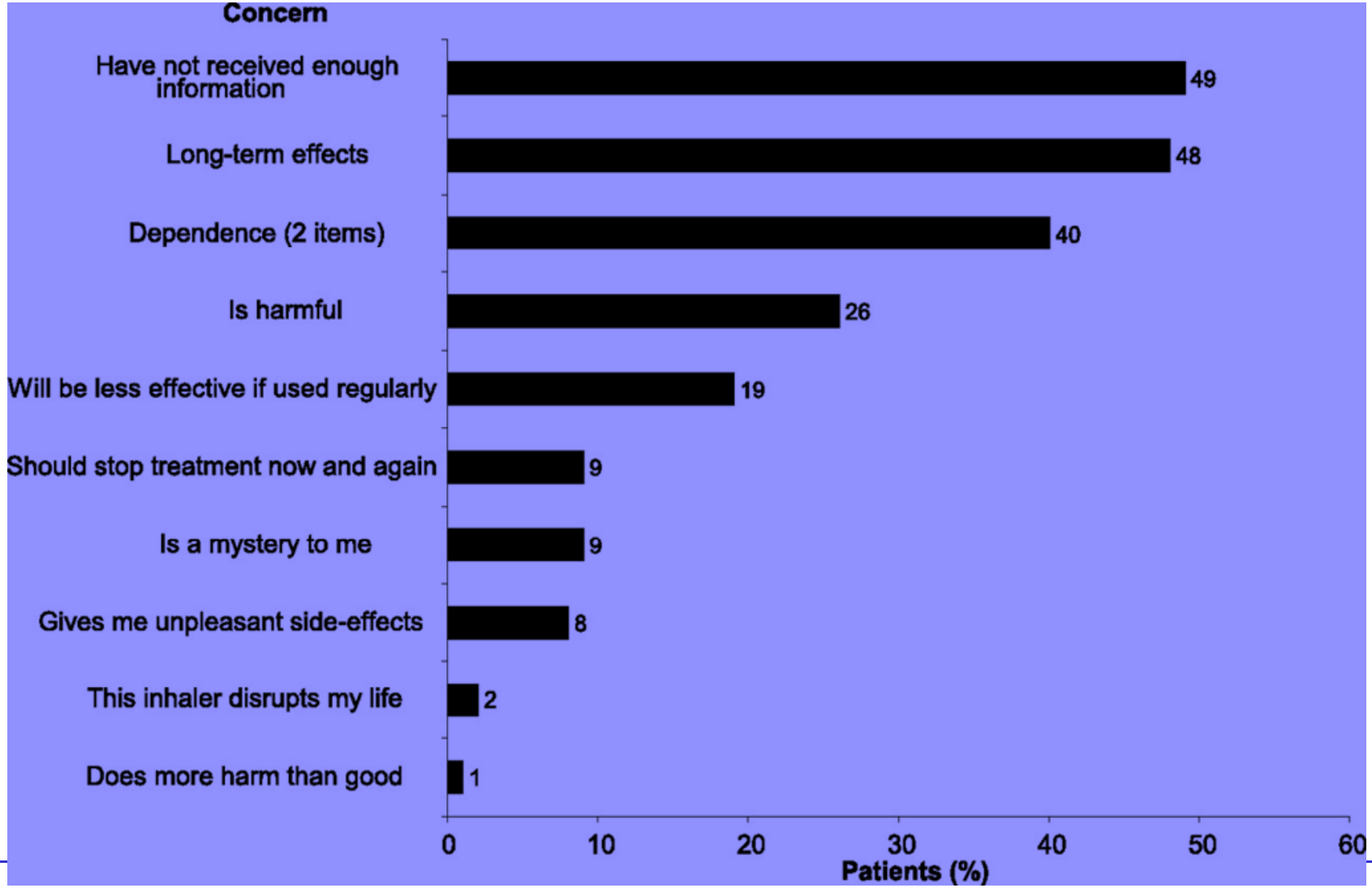
Looking at some research projects

Reasons for non compliance: necessity vs. concerns



Horne R. Chest 2006;130:65S

Profile of concerns about the use of ICS among 100 primary care patients with asthma



Horne, R. Chest 2006;130:65S-72S

Compliance with Glivec® (imatinib): Pattern of refill in community pharmacies

Master Thesis 2009

Person in support: Dr. Isabelle Arnet
Pharmaceutical Care Research Group
Universität Basel

Rationale

TABLE 2. Studies of Adult Adherence to Oral Antineoplastic Agents Over Time

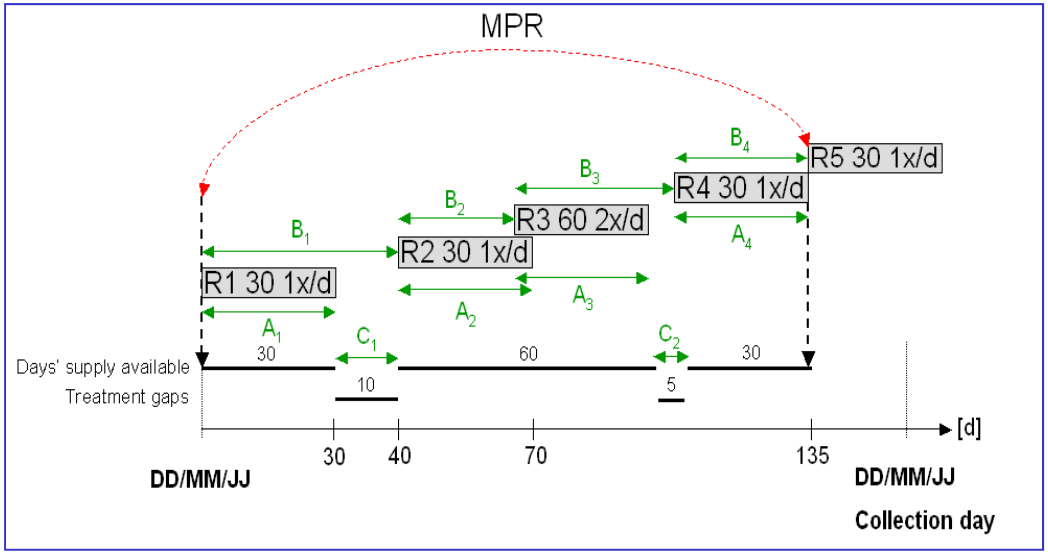
YEAR	CANCER	NO.	ORAL THERAPY	ADHERENCE OR PERSISTENCE MEASURE	ADHERENCE OR PERSISTENCE RATE	TIME PERIOD	STUDY
1987	Hematologic malignancy	108	Prednisone and allopurinol	Serum metabolites	Prednisone: 26.8% Allopurinol: 16.8%	6 mo	Levine 1987[50]; Richardson 1988
1990	Breast cancer	51	Cyclophosphamide and/or prednisone	Self-report that 90-110% taken	53% overall with both drugs	6 mo	Lebovits 1990[21]
1992	Lymphoma	21	Chlorambucil, prednisolone, or dexamethasone	Microelectronic monitoring system (MEMS)	100% (standard deviation [SD]: 20.6%)	852 d	Lee 1992[52]
1993	Breast cancer	26	Tamoxifen	Self-report Pill count	97.9% (SD: 3%) by self-report; 92.1% (SD: 9.8%) by pill counts;	Mean of 2.92 mo	Waterhouse 1993[48]
1993	Small ce						
1996	Ovarian						
2000	Colon c						
2002	Breast cancer	53	Tamoxifen	Self-report	76% missed <1 dose per wk	6 mo	Murthy 2002[5]
2003	Breast cancer	2,378	Tamoxifen	Prescription refill records	77% filled prescriptions that covered at least 80% of doses over the 1st y; 50% did so by 4th y	4 y	Partridge 200
2005	Breast cancer	110	Tamoxifen	Self-report	88% adherent	Not stated	Grunfeld 200
2006	Myelodysplastic syndrome	90	Topotecan	MEMS	90%	5-10 d	Klein 2006[59]
2006	Breast cancer	131	Tamoxifen	Self-report	55% reported nonadherence to medication frequently or occasionally	Single point in time	Atkins 2006[60]
2007	Breast cancer	2,816	Tamoxifen	Prescription refill records	77.9% at 1 y; 64.8% at 3.5 y	3.5 y	Barron 2007[61]
2007	Breast cancer	1,633	Tamoxifen	Clinical notes, audit records, cancer registry data, prescription records	93% median (95% confidence interval, 84-100%)	2.4 y	Thompson 20
2008	Breast cancer	12,391	Anastrozole	Prescription refill records	78-86% of d were covered by filled prescriptions in Year 1; 62-79% of d	3 y	Partridge 200

Results (N=19): Refills & Beliefs

- range: R5 – R82
- mean R: 27.7 / pat.
- mean t: 2.5 years

MPR = 95.7% ± 11 (70-113%)

CMG = 11.7% ± 8 (4-30%)



➔ Difficulties at start of the therapy

Concerns:	2.5 ± 1.0
Necessity:	4.5 ± 0.6
(max. 5)	

Combination of pharmacological biomarkers and compliance monitoring to detect contributing factors to drug resistance - a study design

Walter Philipp[1], Arnet Isabelle[1], Kort Willem[2], Hersberger Kurt E[1]
[1]Pharmaceutical Care Research Group, University of Basle, Switzerland
[2]The Compliers Group International BV, DSM TCG, Eindhoven, The Netherlands

Background

The term "drug resistance" describes any condition that prevents a patient from displaying the expected clinical outcome despite adequately prescribed drug therapy. Non compliance is one of the most important possible contributors. A persistent lack of biomarker response under assured compliance **(= non response)** can uncover other factors to resistance with clinical, cellular and pharmacogenetical background.

Many studies aimed to investigate drug resistance omit to distinguish between non response and non compliance. The combination of a reliable compliance measurement technique with pharmacological biomarker quantification (Fig. 1) is mandatory to study drug resistance.

Outstanding interest has been attracted by the phenomenon of antiplatelet drug resistance with aspirin and clopidogrel.

The present study design, adapted to antiplatelet resistance, can be taken as a template for the investigation of drug resistance in general.

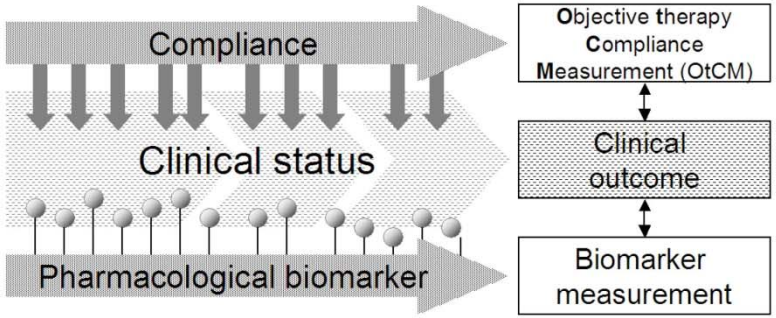


Fig 1: Relationship between compliance, biomarker and clinical status

Objective

1. To develop a model for the investigation of drug resistance
2. To adapt the model to the phenomenon of antiplatelet drug resistance

Methods: Technical Details

Compliance monitoring technology

Compliance is electronically monitored with the OtCM technology (Objective therapy Compliance Measurement, The Compliers Group, Eindhoven, The Netherlands) attached to a time-specific blister pack containing all solid oral drugs (Pharmis GmbH, Beinwil a. S., Switzerland).

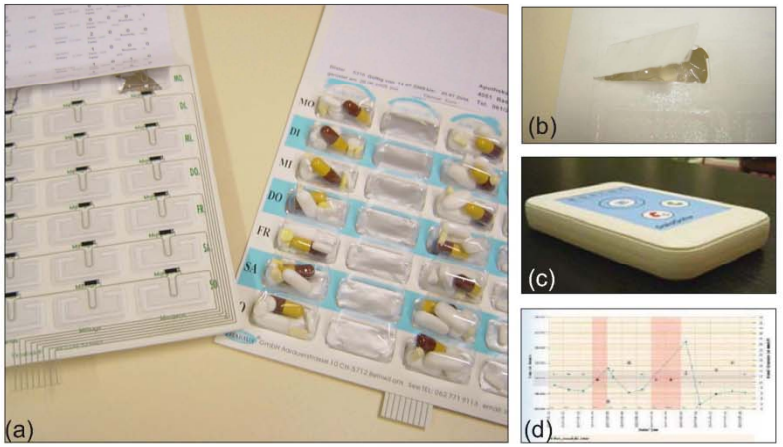
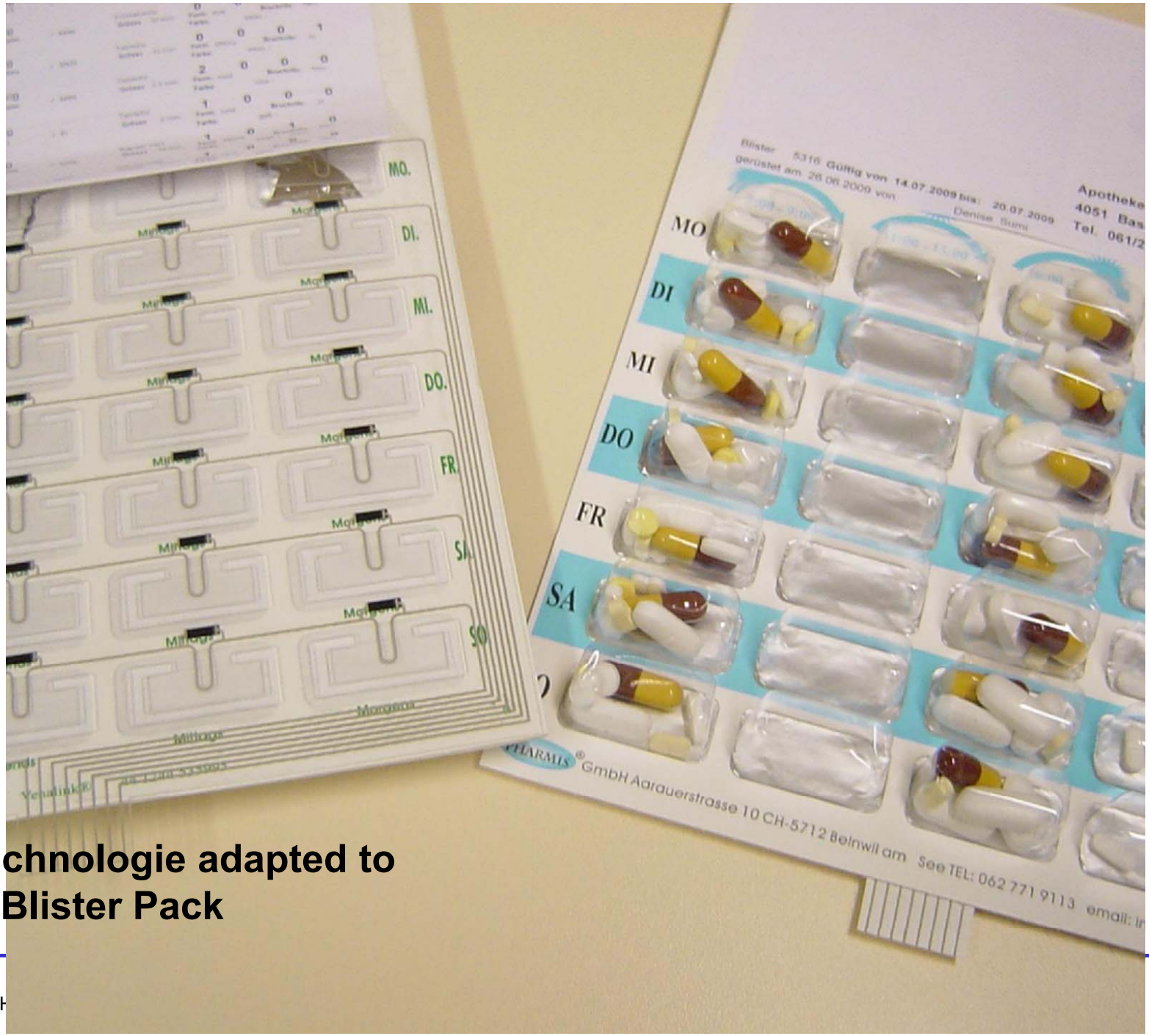


Fig. 3: (a) Pharmis® blister pack with attached OtCM label, (b) drug removal registration, (c) RFID chip readout and data transmittance by DataGator® and readout, (d) overview on compliance events in the OtCM database

Pharmacological biomarkers

Pharmacological biomarkers are biological markers for the evaluation and improvement of drug efficacy and safety. As an element in drug resistance studies, biomarkers have to fulfil several requirements, and specific characteristics have to be taken into account (Tab. 1).

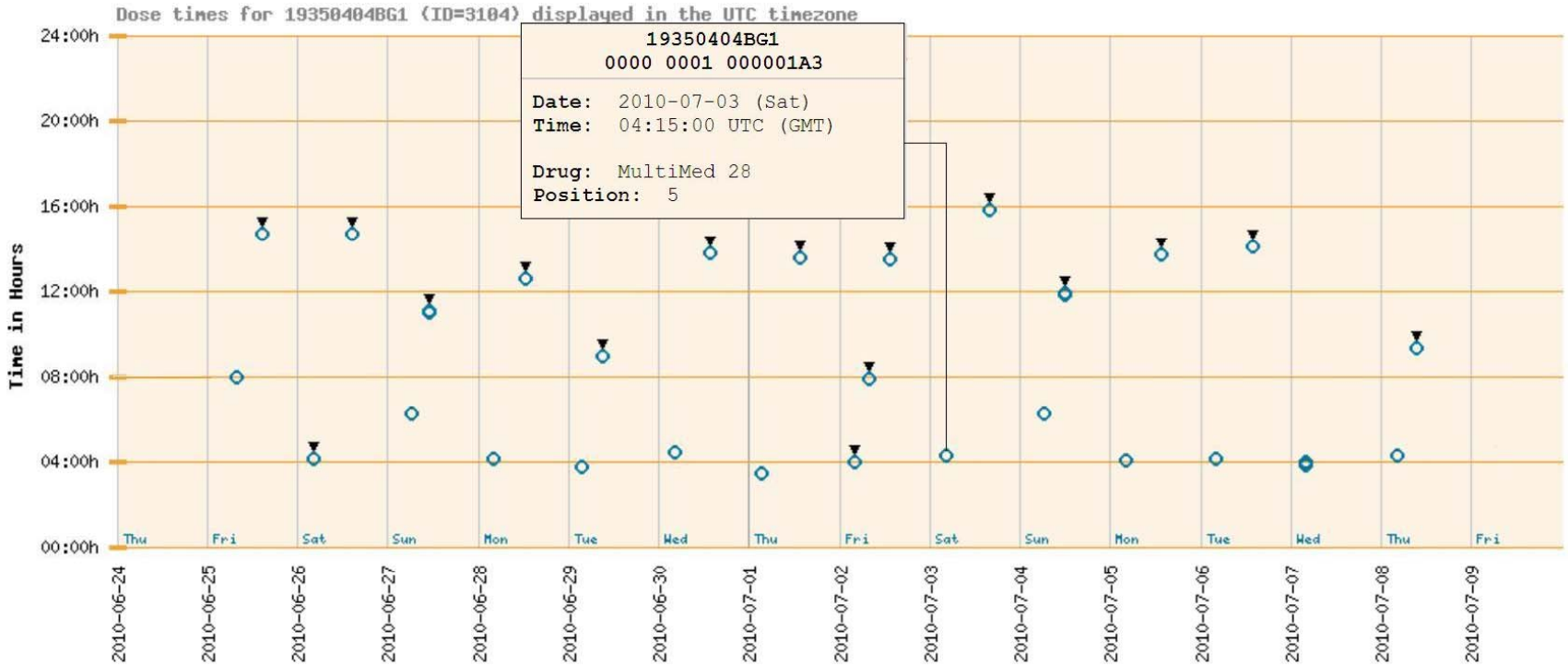
A. Established association with clinical therapy failure
• biomarker studies with clinical endpoints
• clinically determined reference intervals
B. Analytical performance characteristics of the measurement method



OtCM™ Technologie adapted to Pharmis® Blister Pack

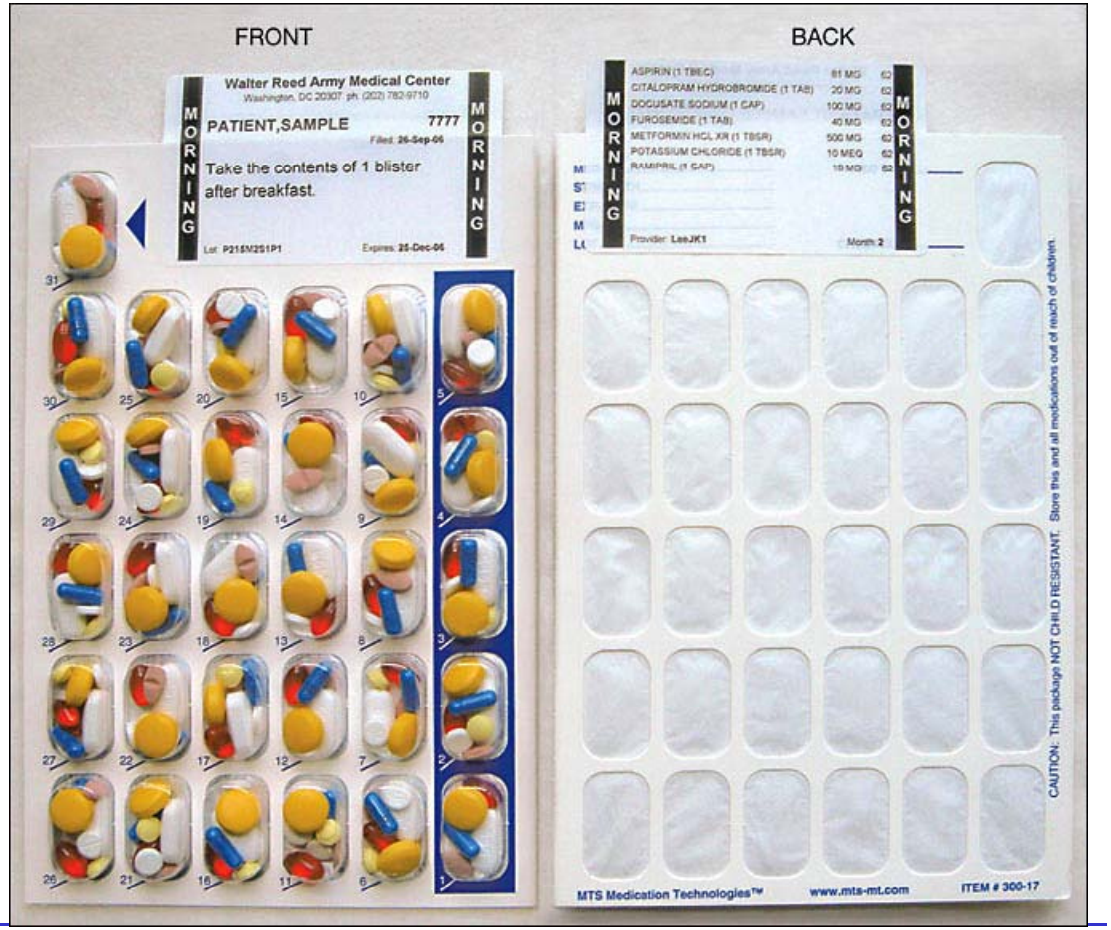
Patient with

1 dose morning
2 doses evening (blistered separately in two positions: evening / night)

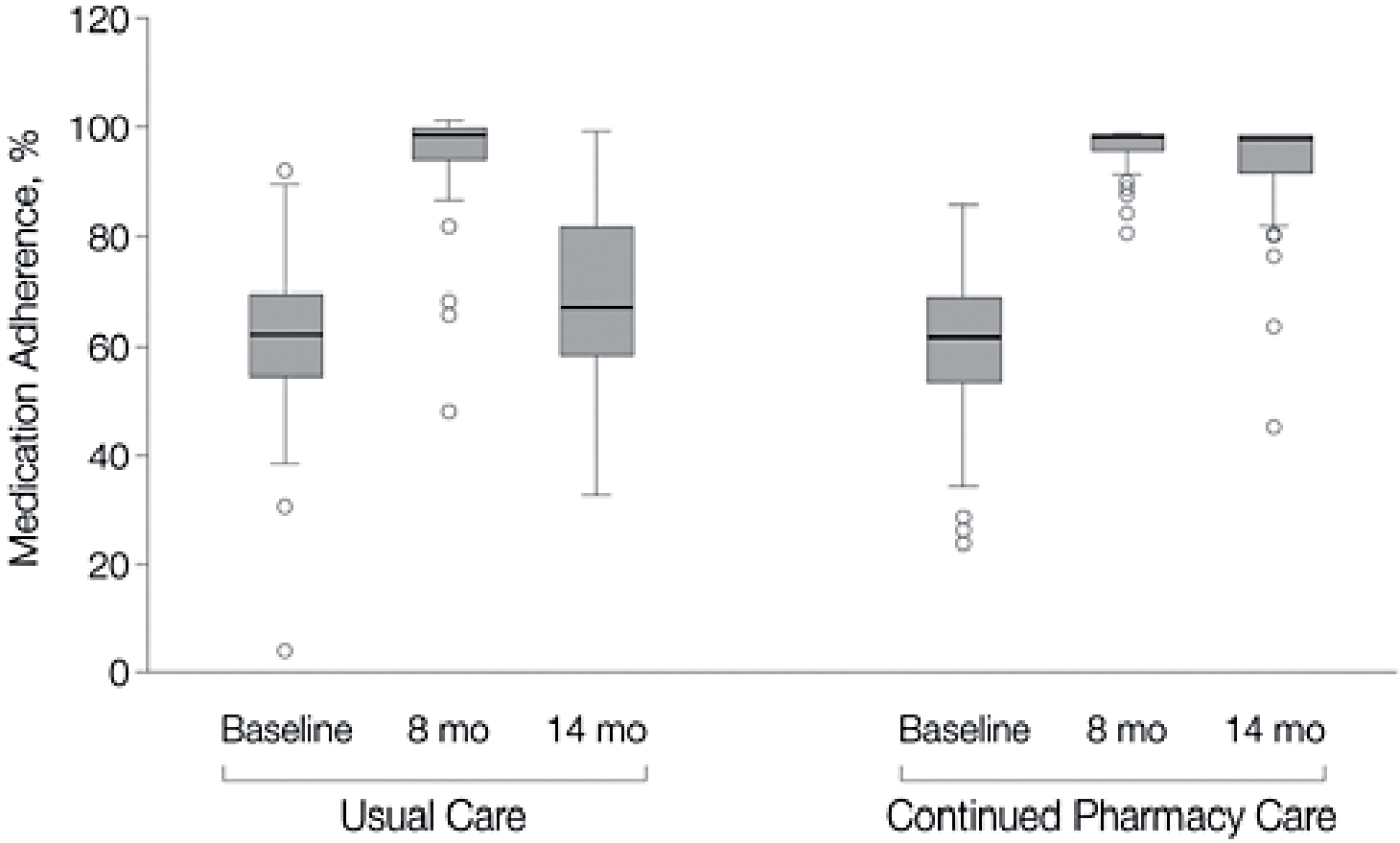


Effect of a Pharmacy Care Program on Medication Adherence and Persistence, Blood Pressure, and Low-Density Lipoprotein Cholesterol. A Randomized Controlled Trial (FAME-study) Lee J. K. et al. JAMA 2006

- patients aged 65 years or older
- taking at least 4 chronic medications
- 6-month intervention phase:
  - **standardized medication**
  - **education**
  - **regular follow-up by pharmacists**
  - **medications dispensed in timespecific packs**



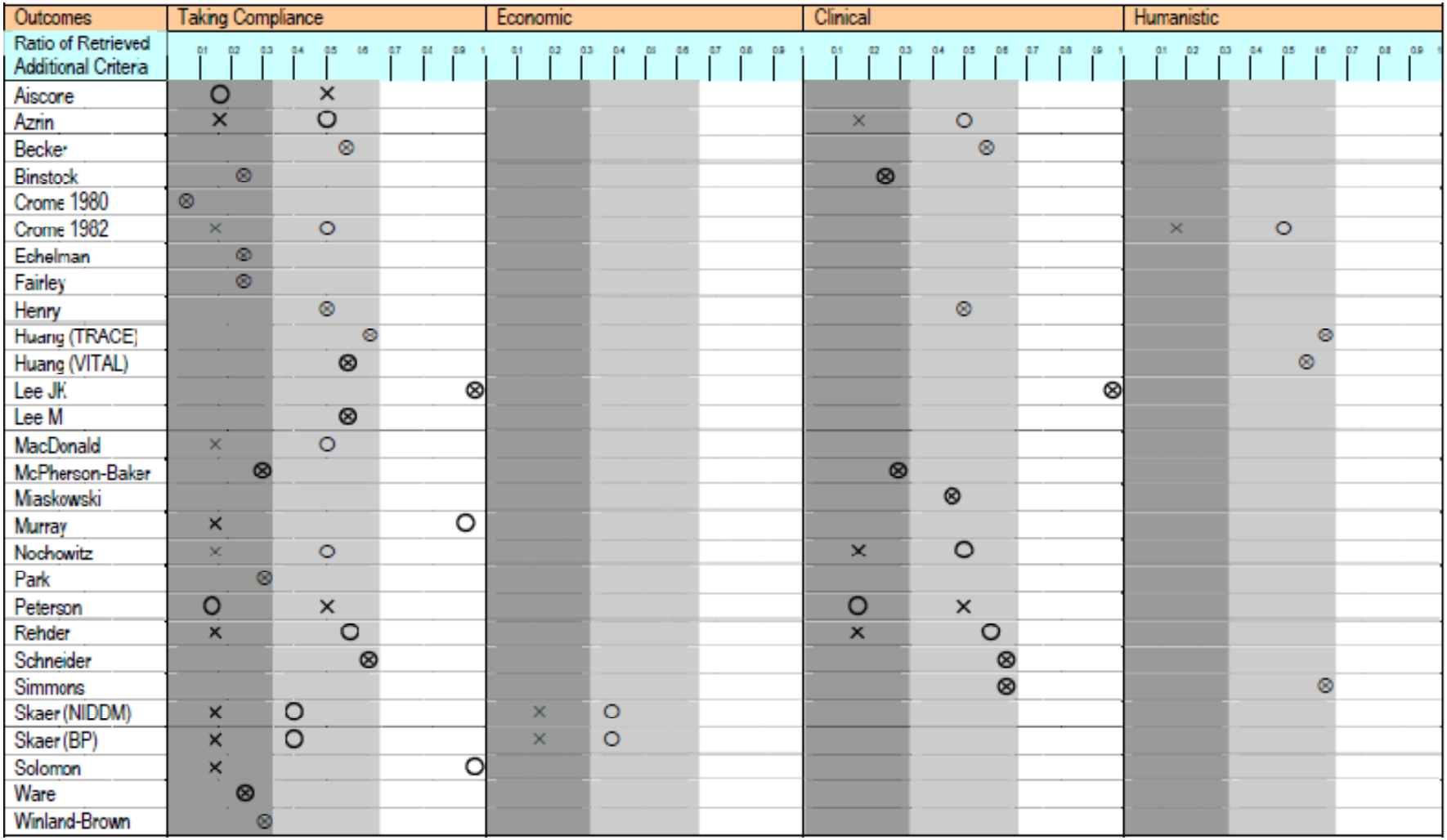
Medication Adherence During the Randomized Trial (Phase 2) for the Continued Pharmacy Care and Usual Care Groups
Lee J. K. et al. JAMA 2006



Blood Pressure: (133.2 [14.9] to 129.9 [16.0] mmHg; p =0.02)
LDL-Cholesterin: (91.7 [26.1] to 86.8 [23.4] mg/dl; p=.001)

Impact of Drug Reminder Packaging on Compliance – Where are the Research Gaps?

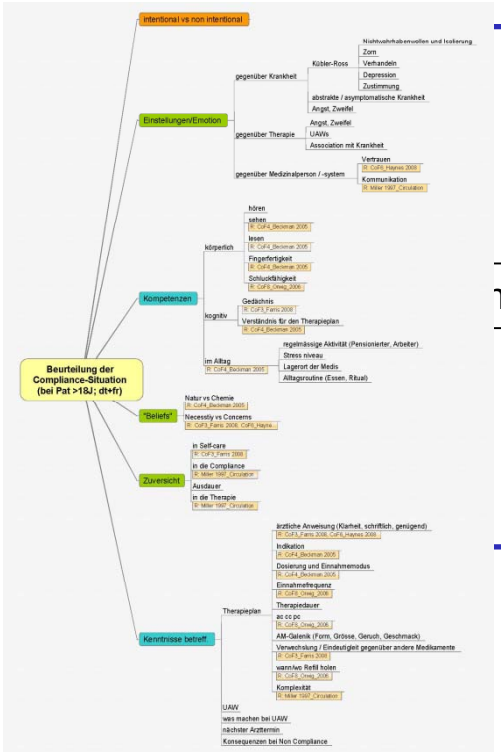
Fabienne Boeni, Katja Suter, Isabelle Arnet, Kurt E. Hersberger

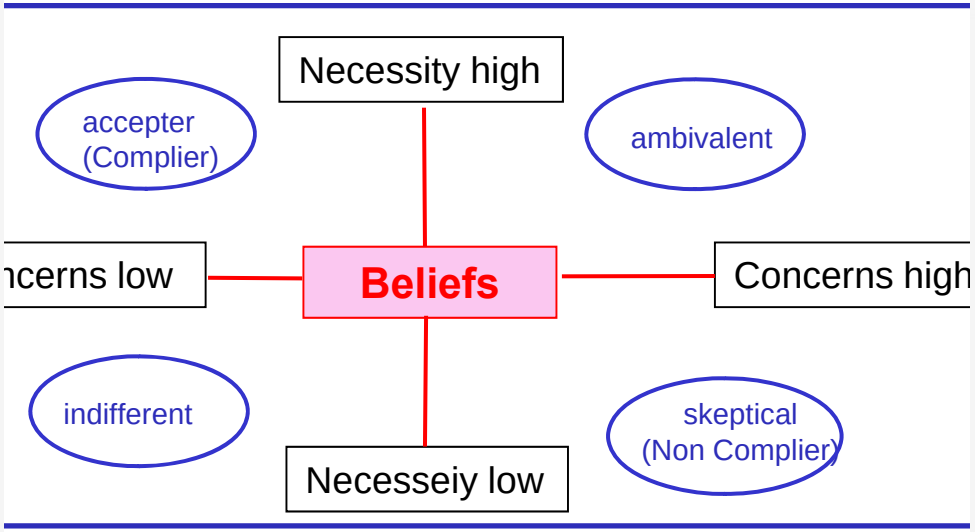


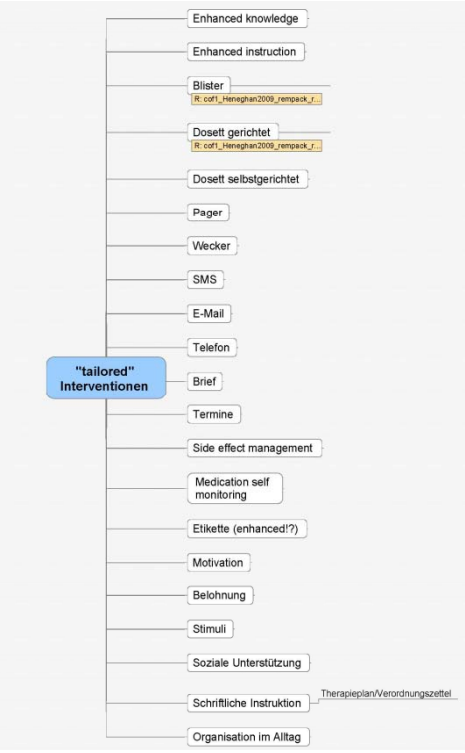
(„pouches“, „bubble pack“)

Compliance Factory

Screening → Intervention → Monitoring







Framework for Pharmaceutical Care

In patient contacts the community pharmacy team screens for pharmaceutical care issues arising from 4 situations

a. requests in self-medication (incl. presentation of symptoms)

b. dispense of prescribed drugs (first or repeat)

c. clinical patient assessment (e.g. BP measurement)

d. transition between institutions

Pharmaceutical care can be delivered in 4 different settings framing 4 levels of care

1. Ad hoc in the pharmacy
2. By phone
3. Scheduled in the pharmacy
4. At patient‘s home

At each level of pharmaceutical care different types of medication review can be performed (according to patient‘s needs) and including drugs from self-medication

I. Technical prescription (drug therapy) review

II. Medication use review focusing on compliance and concordance

III. Clinical medication review (integrating medical history and clinical assessment)

Framework for Pharmaceutical Care Research

„The Compliance Factory“ (Individualised compliance assistance)

Focus on patients after hospital discharge (eg. MI, Stroke, TIA)

Situation

a) **Requests in self-medication (incl. presentation of symptoms)**
b) **Dispense of prescribed drugs (first or repeat)**
c) **Clinical patient assessment (e.g. BP measurement)**
d) **Transition between institutions**

Levels of care

1. **Ad hoc in the pharmacy**
2. **By phone**
3. **Scheduled in the pharmacy**
4. **At patient‘s home**

Types of medication review

I. **Technical prescription (drug therapy) review**
II. **Medication use review (compliance and concordance)**
III. **Clinical medication review**

Screening:

➔Intentional
➔Unintentional

➔Needs
➔Concerns

Intervention

➔Motiv.Interviewing
➔Dosette
➔Blister packs
➔SMS reminder
➔Monitoring
➔…

➔Level of care ?

Pharmaceutical Care & Personalised Medicine

The NEW ENGLAND JOURNAL of MEDICINE

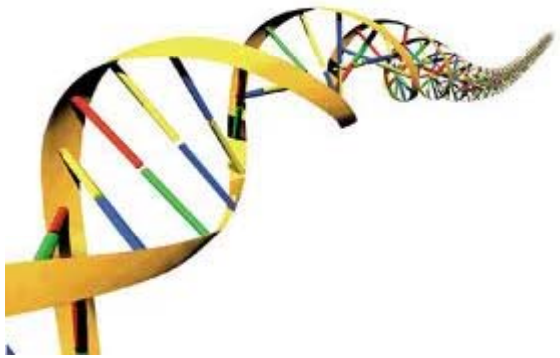
Examples of FDA-Approved Drugs and Companion Diagnostics in Clinical Practice.*

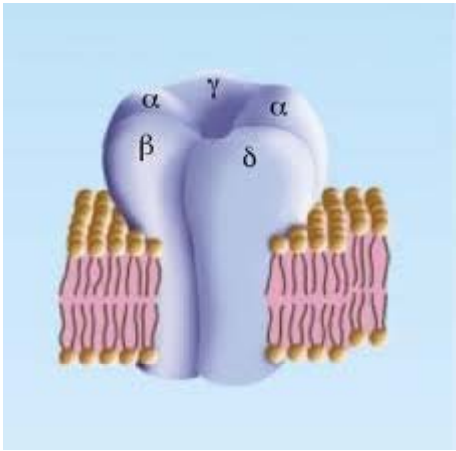
Approved Drug	Mechanism	Approved Companion Diagnostic
Herceptin (trastuzumab)	Targets HER2 to treat metastatic breast cancer	HER2 immunohistochemistry tests, HER2 gene-amplification tests
Erbitux (cetuximab)	Targets EGFR to treat metastatic colorectal cancer	EGFR immunohistochemistry test
Gleevec (imatinib)	Targets the cell-surface tyrosine kinase receptor c-kit in gastrointestinal stromal tumors	c-kit immunohistochemistry test

The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

Pharmaceutical Care & Personalised Medicine



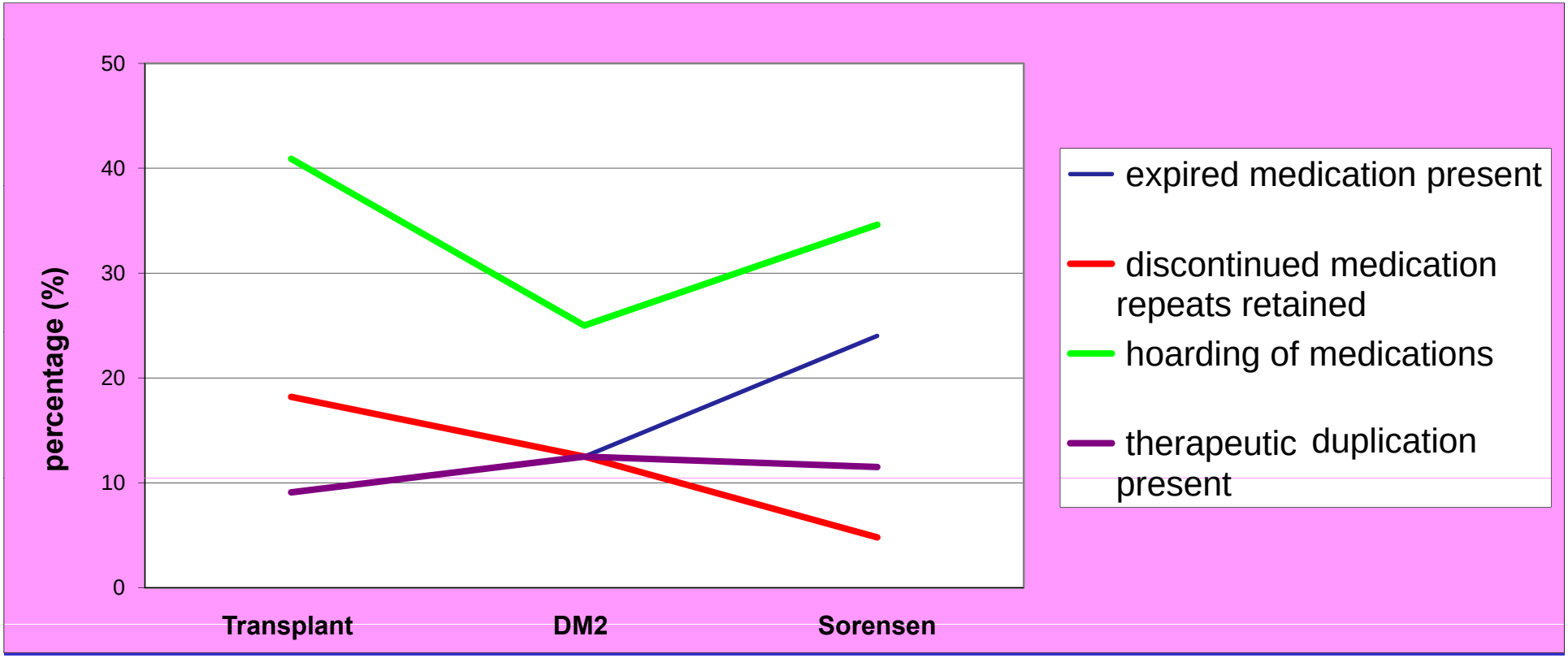


Prevalence of medication-related risk factors

A convenient sample of chronically ill patients after transplantation (n=22) or with diabetes Type 2 (n=31), taking ≥4 medications.

Home visits by trained 5th year pharmacy students together with a Master student or a PhD student

P.Eichenberger, PWS, in press



Medication management by diabetes patients

UNI BASEL

Prof. Dr. K. Hersberger

Masterthesis B. Sleyska 2008

Conclusions

- ⇨ Compliance is a major issue for pharmaceutical care
- ⇨ We need evidence based interventions to improve compliance
- ⇨ Compliance improvement needs an individually tailored approach
- ⇨ We must boost „personalised“ medicine
- ⇨ Personalised medicine must be enlarged with a comprehensive patient perspective

Thank you

Kurt Hersberger

Isabelle Arnet

Esther Spinatsch

Rudolf Bruppacher

Patrick Eichenberger

Seraina Mengiardi

Markus Messerli

Fabienne Böni

Philipp Walter

Markus Lampert