

Voltaire 1694-1778 in Paris

- Ärzte verschreiben Medikamente, von denen sie wenig verstehen,
- um Krankheiten zu behandeln, von denen sie noch weniger verstehen
- bei Leuten, von denen sie überhaupt nichts verstehen...

- Die ärztliche Kunst besteht darin, die Patienten zu unterhalten, während die Natur ihren Dienst an den Krankheiten tut...



„Placebo domino in regione vivorum“ Psalm 116, 9

- Fehlübersetzung “Ich will dem Herrn gefallen” statt: “Ich will einhergehen vor dem Herrn”
- In der mittelalterlichen Liturgie eröffneten diese Verse die Vesper für die Verstorbenen
- Professionelle Kläger wurden gemietet, um Vesper zu singen
“Placebosingen” derogative für unterwürfige Schmeichler: "Flatterers are the Devil's chaplains, always singing Placebo“ Geoffrey Chaucer: The Parson's Tale
- Anfangs 19. Jhdt: „Placebo“ als Medikament “mehr um den Patienten zu erfreuen, als ihn zu heilen”



Pneumoniestudie über 14 Jahre, ca. 380 Patienten
(Joseph Dietl 1849)

<u>Therapieart</u>	<u>Letalität</u>
Aderlass durch Blutegel	20.4%
Weinsteinbrechmittel	20.7%
Placebo	7.4%

Beecher, H. K.

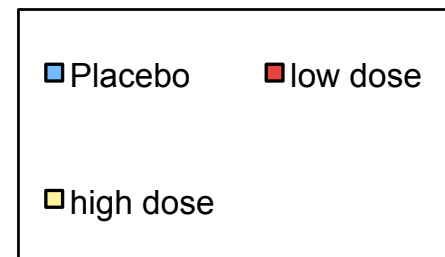
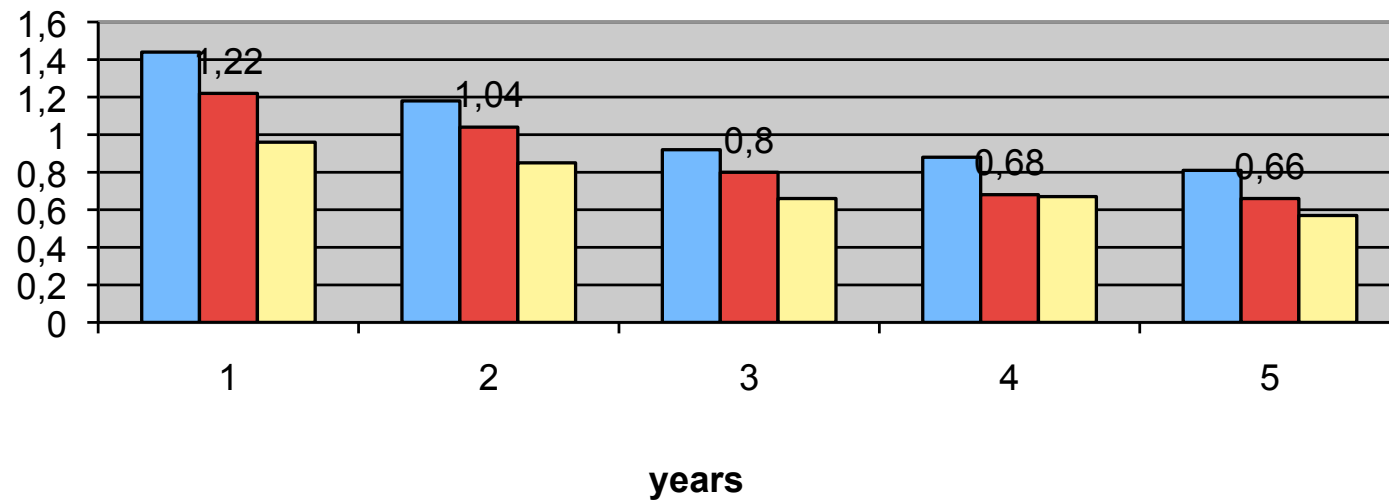
The powerful placebo

JAMA 1955; 159:1602-1606

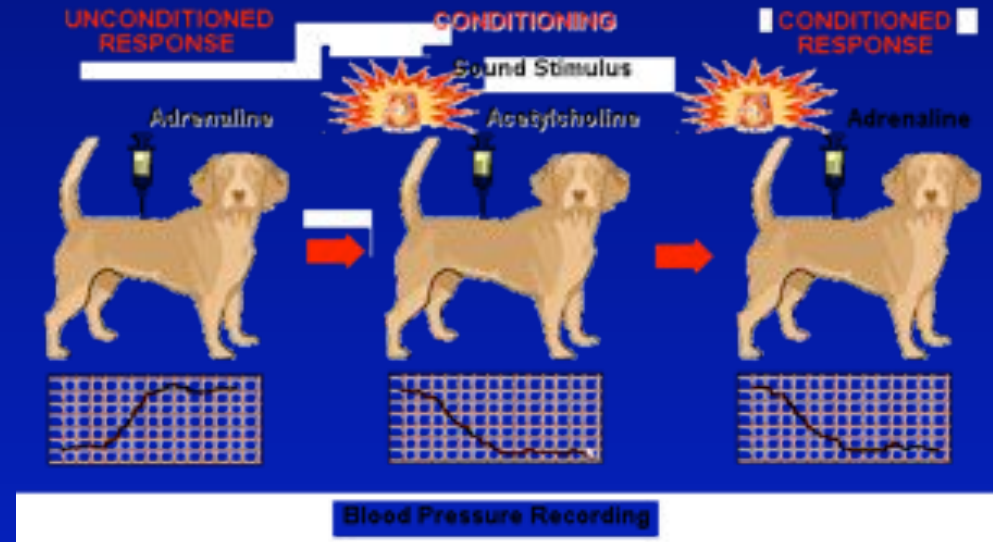
- among the most frequently cited papers
- reported on twenty-six studies
- arrived at an average placebo response rate of 32.5 percent
- responsible for the double-blind study design as the universal standard



Beta-Interferon: Annualized relapse rate



Placebo-Neurologie



- 1. Therapeutische Handlungen finden in einem komplexen psychosozialen Kontext statt
- 2. Placebobehandlung dient dem Studium dieses psychosozialen Kontextes
 - Erwartung des klinischen Nutzens
 - Pavlov'sche Konditionierung
- 3. Tatsächliche psychobiologische Placebo-wirkung = Unterschied zwischen Gruppe mit Placebo und Gruppe ohne Behandlung

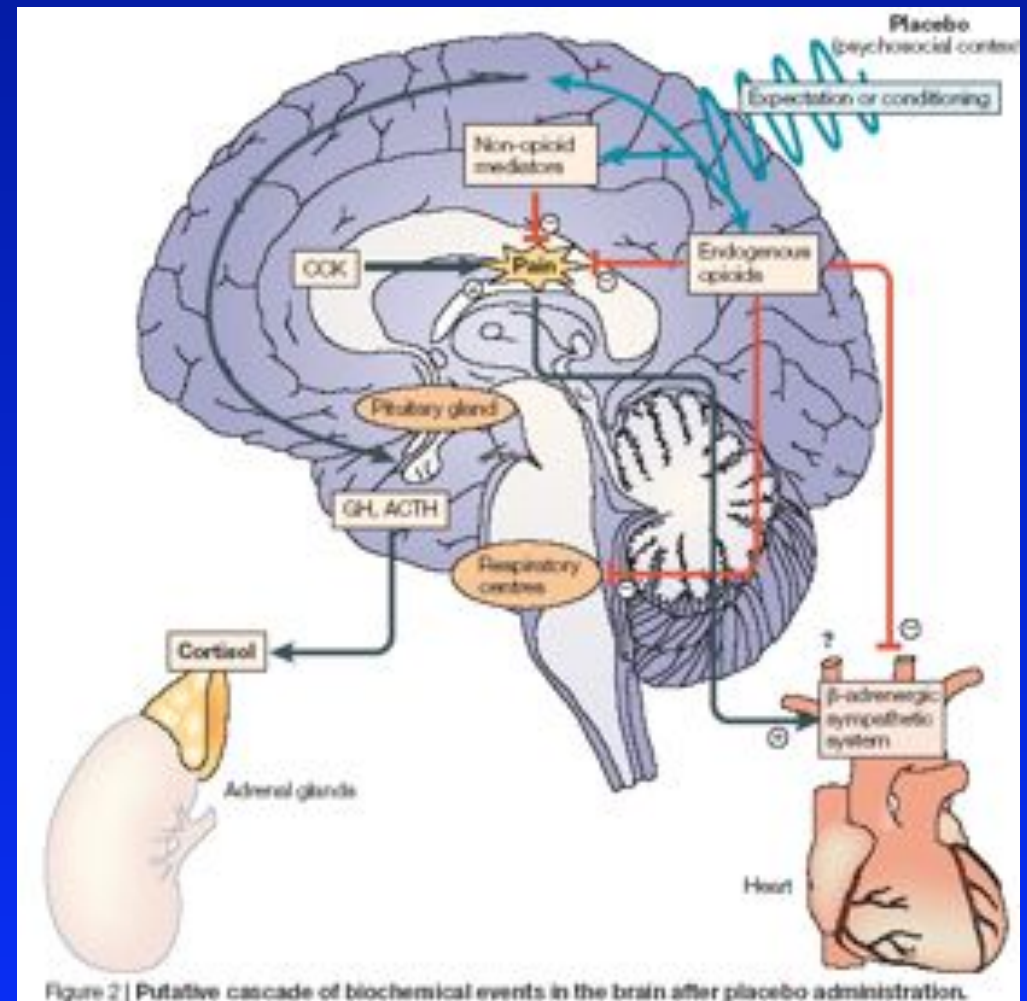
Guess et al (eds.) The Science of Placebo: Towards a Scientific Research Agenda BMJ Books London UK 2002

Placeboforschung

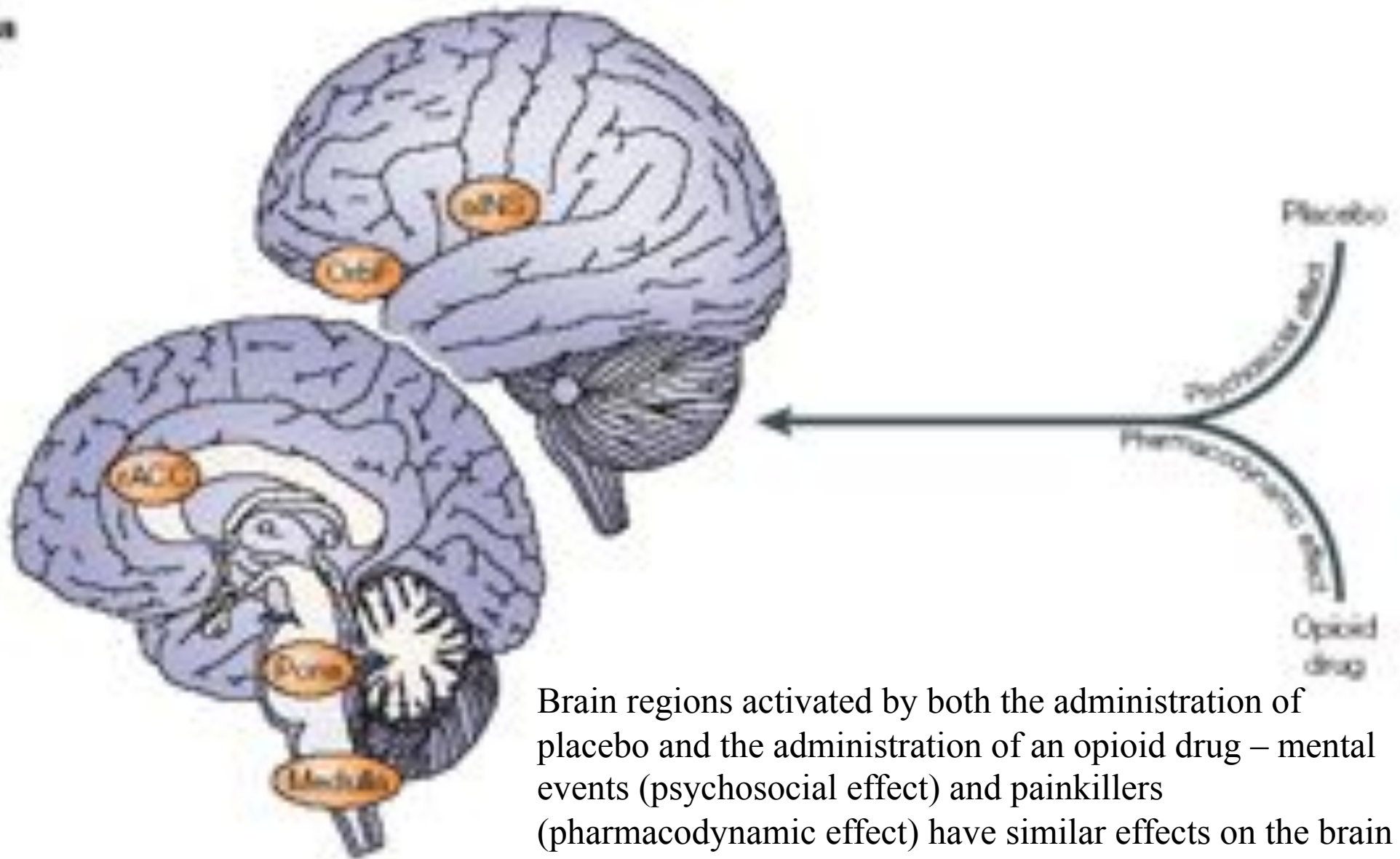
- bezweckt
 - Verständnis von Körper-Seele Interaktionen
 - Verbesserung der klinischen Praxis und der Lebensqualität der Patienten
 - Entwicklung neuer Pläne für Klinische Studien
- ABER
 - Unterstreicht die Instabilität der menschlichen Psyche
 - Tendenz zu Manipulation
 - Gefährliche Rechtfertigung von Täuschung, Lug & Trug, Quacksalberei

Placebonetz und Biochemie

- Placebo-aktiviertes endogenes Opioidsystem produziert Opiod-NW: (Atemdepression, verminderte beta-adrenerge Reaktionen)
- Cholecystinin (anti-endogenes Opioid): Interaktion zwischen komplexen sozialen Stimuli aus der Umwelt (z.B. Sicherheit) und endogenem Opioidsystem



Colloca L, Benedetti F: Placebos and painkillers: is mind as real as matter? Nat Rev Neurosci 2005; 6: 545 - 552



Brain regions activated by both the administration of placebo and the administration of an opioid drug – mental events (psychosocial effect) and painkillers (pharmacodynamic effect) have similar effects on the brain

b Increased activity during anticipation



c Decreased activity during placebo analgesia



Figure 3 | Summary of brain imaging studies showing the different brain regions that are involved in placebo analgesia.

b) Brain regions activated by placebo (cognitive-evaluative network)

c) Decreased activity in brain regions involved in pain processing

Overt vs. covert treatment

- Telling that a painkiller is injected (saline solution) is as effective as 6-8 mg morphine
- Analgesic dose required to reduce pain by 50% much higher for hidden infusions than for open ones and intensity of postop pain much higher in patients who received hidden infusions as compared to open ones. Differences could be eliminated by naloxone

Routine medical practice



Treatment simulation with placebo



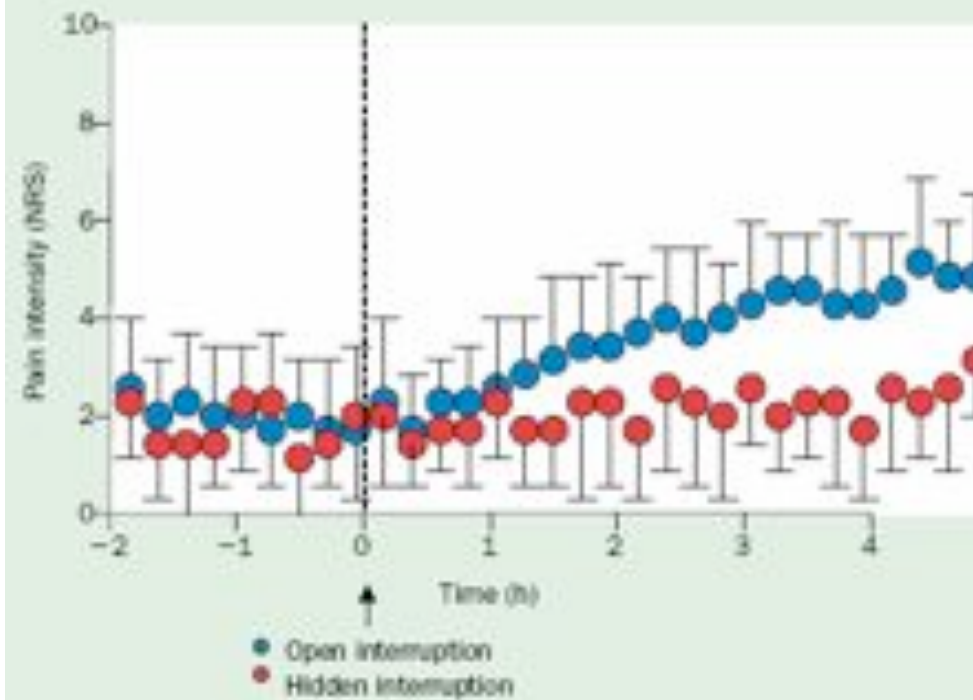
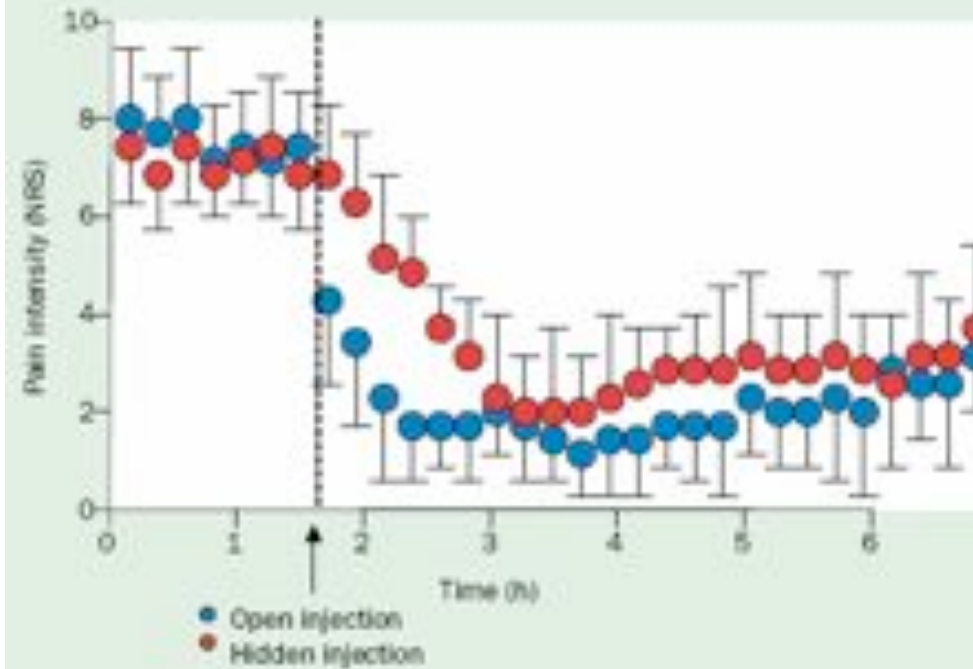
Hidden dose of active treatment

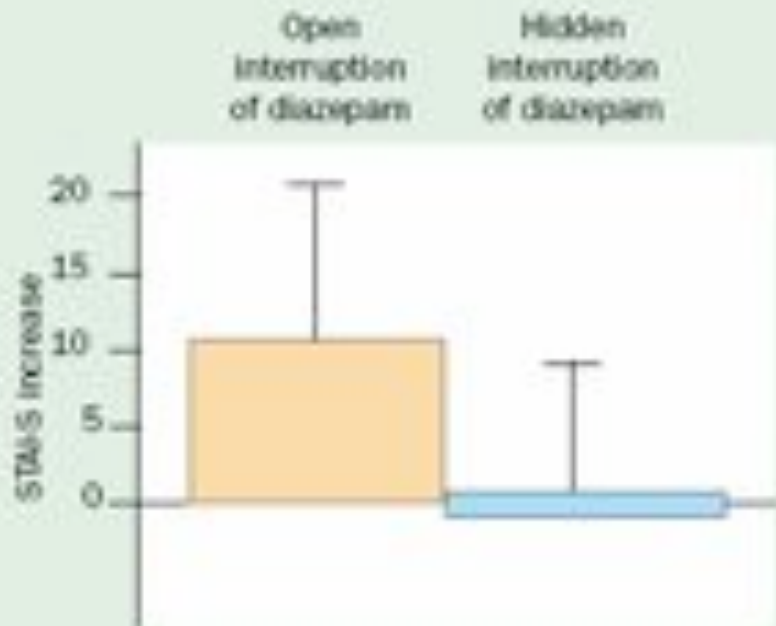
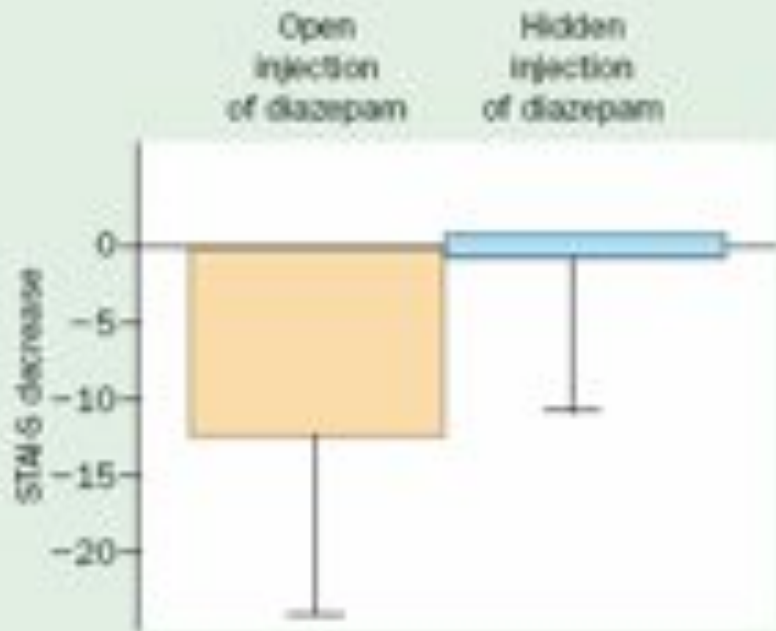


Postoperative pain: Open vs. hidden administration of morphine treatment (10 mg)

Benedetti F et al: Open versus hidden medical treatments: the patient's knowledge about a therapy affects the therapy outcome

Prevention & Treatment online sept 2004





Postoperative anxiety

State Trait Anxiety decrease in 2 h after open and hidden doses of diazepam (10 mg)

Benedetti F et al: Open versus hidden medical treatments: the patient's knowledge about a therapy affects the therapy outcome

Prevention & Treatment online sept 2004

Klinische Bedeutung

- Wissen um eine Behandlung, Anwesenheit der Therapeuten, Erwartungshaltung sind wichtig (stark geprägt durch Arzt-Patienten Beziehung)
- Erwartungshaltung gegenüber Behandlung nützt nur, wenn diese tatsächlich erfolgt (Offener Behandlungsabbruch führt zu deutlicherer Symptomverschlechterung als versteckter)
- Colloca L et al: Overt versus covert treatment for pain, anxiety, and Parkinson's disease *Lancet Neurol* 2004; 3: 679 - 84

Hrobjartsson A, Gotzsche PC: Is the Placebo Powerless? An analysis of clinical trials comparing placebo with no Treatment
The New England Journal of Medicine; 2001; 344: 1594 - 1602

- Meta-study of 114 studies involving placebos found "little evidence in general that placebos had powerful clinical effects...[and]...compared with no treatment, placebo had no significant effect on binary outcomes, regardless of whether these outcomes were subjective or objective. For the trials with continuous outcomes, placebo had a beneficial effect, but the effect decreased with increasing sample size, indicating a possible bias related to the effects of small trials"
 - Includes studies across 40 different maladies („analogous to evaluating efficacy of active drug by combining results from studies of effects on different disease processes“)
 - Only pain with large enough pool for separate analysis showed placebo effect

Plazebostudien: Probleme

- *Spontane Verbesserung*
 - Besonders bei Krankheiten mit fluktuierendem Verlauf
- *Symptomfluktuationen („regression to the mean“)*
 - Studieneintritt mit stärkeren Symptomen als durchschnittlich im Krankheitsverlauf – Besserung auch ohne Intervention zu erwarten
- *Günstige Wirkung zusätzlicher Behandlungen und besserer Pflege und Nachsorge während Studie*
- *Skaleneffekt (scaling bias) bei subjektiven outcomes*
 - Verwendung von Skalen mit mehr Graden, um Verbesserungen zu messen, als um Verschlechterungen
- *Höflichkeitsantworten oder experimentelle „Unterwerfung“*
 - Studienteilnehmer kennt die erwünschte Antwort

Placebomechanismen

- Endorphinfreisetzung als Reaktion auf Placebostimulus (“Opioidmodell”)
- Gelernte Reaktion auf medizinische Intervention (“Konditionierungsmodell”)
- Bewusster vermittelte Reaktion (“Bedeutung” oder Erwartungsmodell)
- Spezialform von Belohnungssystem

Placeboeffekt: Erwartung einer Besserung
=> Förderung von Selbstheilungskräften

- Persönliche Vorerfahrung
- Erwartung an das Behandlungsverfahren
- Wissen, dass die Behandlung stattfindet
- Nachvollziehbare Wirktheorie
- Autorität und Glaubwürdigkeit von Berichten
- Empfehlungen von Freunden

Humphrey N: Great expectations: The evolutionary psychology of faith-healing and the placebo response Proc 27th Intl Congress Psychol 2000

Optimism and Cardiovascular Death

(The Zutphen Elderly Study)

Cohort of 545 men, 64-84 yrs, followed over 15 yrs

Free of pre existing CV disease or cancer

The first 2 years of observation were excluded

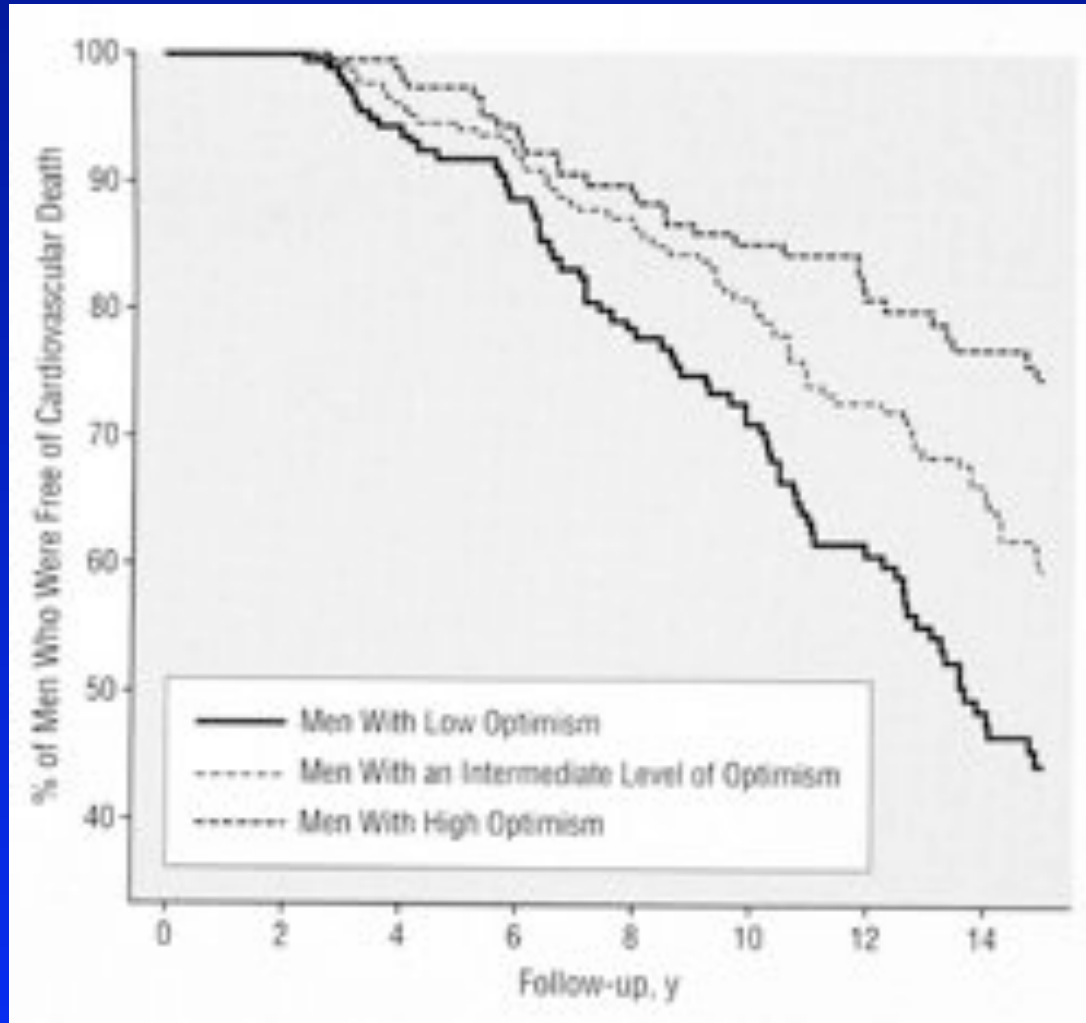
1985, 1990, 1995 and 2000 the optimism was assessed by questionnaire:

Optimist tertile: HR for CV mortality: 0.45 (0.26-0.68)

Arch Intern Med 2006; 166:431

Optimism and Cardiovascular Death

(The Zutphen Elderly Study)



-55%

Arch Intern Med 2006; 166:431

Adherence and Outcome

CHARM study: Candesartan in heart failure

Double blind RCT with candesartan vs placebo in 7,599 pts

Median follow-up 38m

Def: Good compliance: >80% of the study medication taken

Def: Bad compliance: <80% of the study medication taken

Lancet 2005; 366: 1989

Adherence and outcome

pts with candesartan: 10% lower mortality than pts on placebo (p=0.032)

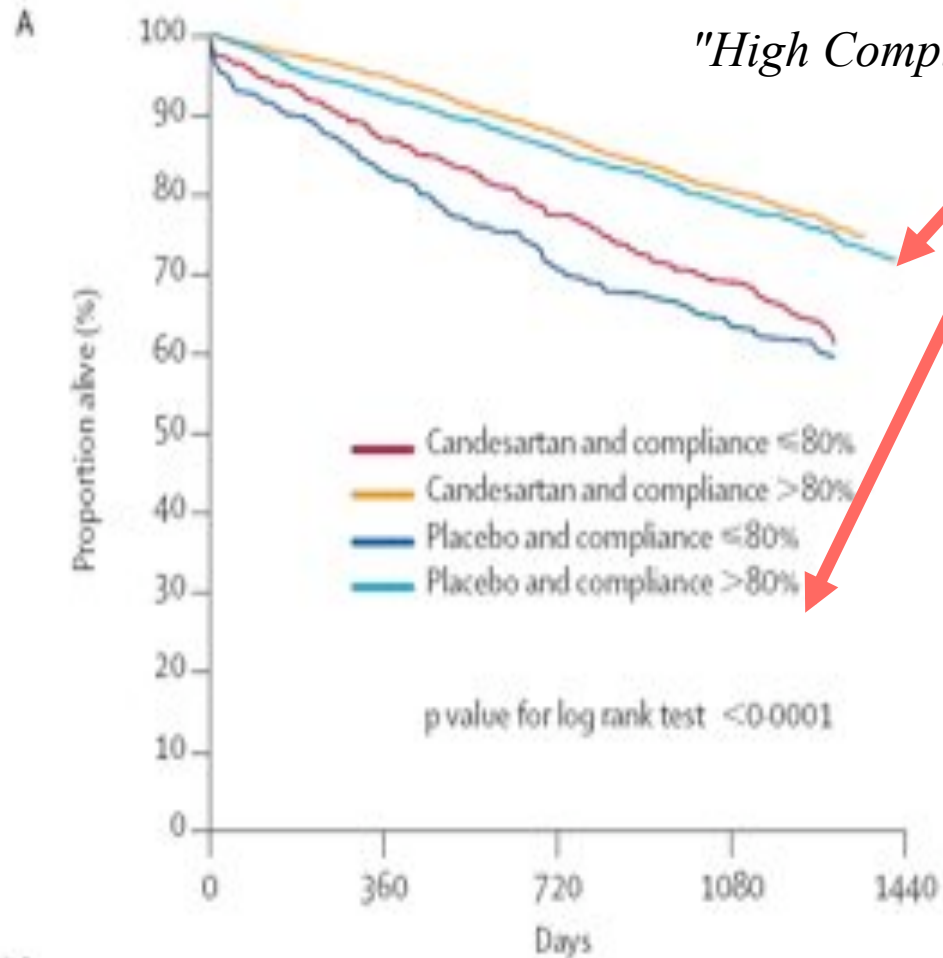
high adherence to placebo had a 3.5x greater effect
than overall effect of candesartan:

High adherence to placebo: HR 0.64 (CI: 0.53-0.78)

High adherence to candes.: HR 0.65 (CI: 0.55-0.81)

Good adherence is associated with a lower risk of death, irrespective of the assigned treatment

Lancet 2005; 366: 1989



"High Compliance with Placebo"

Numbers at risk

	0	360	720	1080	1440
Candesartan and compliance ≤ 80	493	426	380	249	
Candesartan and compliance > 80	3310	3137	2891	1967	
Placebo and compliance $\leq 80\%$	435	359	306	209	
Placebo and compliance $> 80\%$	3361	3106	2864	1951	

Lancet 2005; 366: 1989

Adherence and Outcome

High adherence...even if to placebo...
was associated with a 35% lower mortality
than low adherence in congestive heart failure

Lancet 2005; 366: 1989

Adherence and outcome

Adherence is a marker for adherence to other effective treatments than the study medication or adherence to other behaviour that affect outcome

Disease severity (EF or NYHA class) is not associated with adherence

Lancet 2005; 366: 1989

Adherence may be associated to optimism?

Adherence and outcome

Other studies with similar findings:

1) *CDP: Coronary drug project research group. Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project*

NEJM 1980; 303:1038

2) *BHAT: Treatment adherence and the risk of death after myocardial infarction*

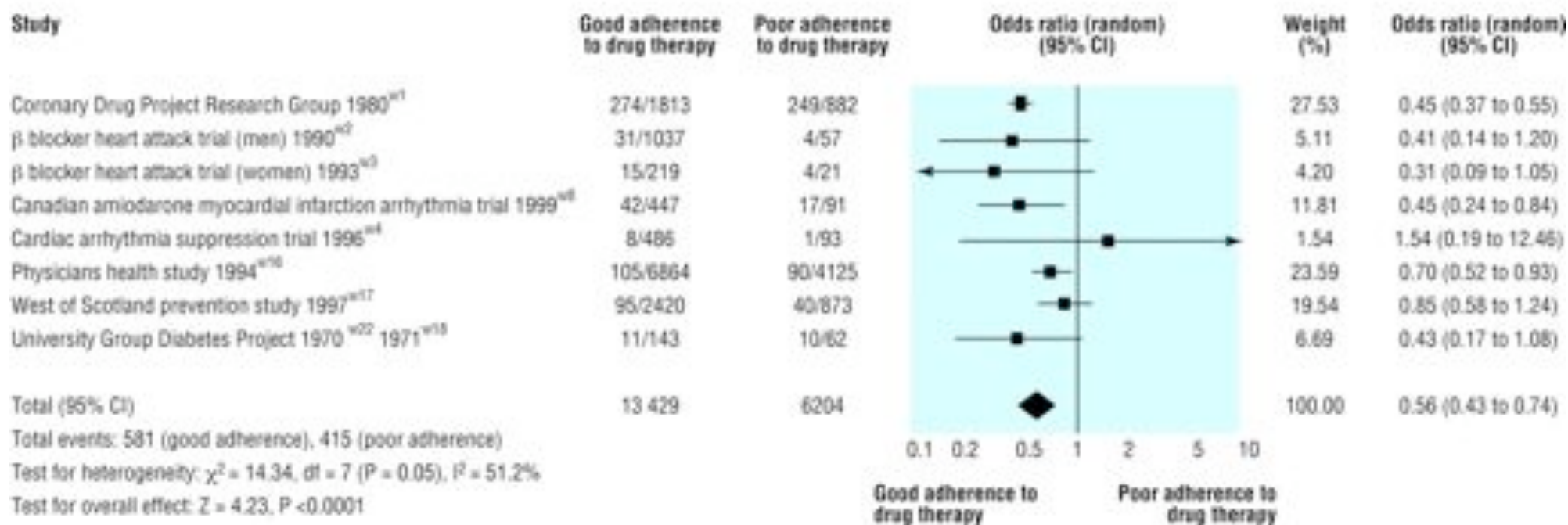
Lancet 1990; 336:542

3) *CAMIAT: Poor adherence to placebo or amiodarone-Therapy predicts mortality: Results from the CAMIAT study*

Psychosom Medicine 1999; 61:566

Association between adherence to placebo and mortality

Simpson, S. H et al. BMJ 2006;333:15



- About one in four people do not adhere well to prescribed drug therapy
- Poor adherence is a critical barrier to treatment success and remains an important challenge to healthcare professionals
- Good adherence to drug therapy is associated with positive health outcomes
- association between adherence to placebo and mortality: healthy adherer effect, where adherence to drug therapy may be a surrogate marker for overall healthy behaviour

Betty Chewning: The healthy adherer and the placebo effect BMJ 2006; 333: 18-19

- ...” that healing lies not in the treatment but rather in patients' emotional and cognitive processes of "feeling cared for" and "caring for oneself.“
Barrett B, Muller D, Rakel D, Rabago D, Marchand L, Scheder J.
Perspect Biol Med 2006;49: 178-98.
- The meanings people attach to the "pill" and "behaviour of the healer" are the key to the mind-body connection leading to health outcomes.
- The association with lower mortality could arise from positive interaction between these healthy adherer and placebo related effects.
- Implications for doctors' decisions and encounters?
 - Traditionally, the healer's greatest tool has been to listen and build on the patient's story and its meaning to determine the most appropriate healing ceremonies, rituals, and therapies.
 - Coupled with other patient centred approaches, practice based on these hypotheses could yield extra value in treatment regimens that patients agree to, believe in, and will sustain over time.
 - Patients' adherence to treatments would show that they were caring for themselves while their clinical encounters would reinforce that their doctors were caring for them.

Noceboeffekte

Patient

- Mangelnde Motivation
- Misstrauen
- Erwartung einer Verschlimmerung
- Krankheitsgewinn
- Fehlende Mitarbeit
- Ängstlichkeit
- Ideologie

Behandler

- Schlechte Informationsvermittlung
- Fehlende Empathie
- Keine Zeit, kein Interesse
- Schlechter Ruf
- Ängstigende Beipackzettel
- Nebenwirkungsreiche Behandlung

“Any therapeutic meeting between a conscious patient and a doctor has the potential of initiating a placebo effect”. The mere act of interviewing and examining a patient before enrollment in the study may have a placebo effect

Hróbjartsson, A. The uncontrollable placebo effect. *Eur J Clin Pharmacol* 1996; 50: 345–348

Benedetti F: How the doctor's words affect the brain *Eval Health Prof* 2002; 25: 369 - 382



THE LANCET

Volume 366 Number 9480 Pages 95-176 July 9-15, 2005

www.thelancet.com

“If everything has to be double-blinded, randomised, and evidence-based, where does that leave new ideas?”

See Correspondence page 122

KVG Art. 32
Die Leistungen müssen
wirksam
zweckmässig
wirtschaftlich
sein.

Die Wirksamkeit muss
nach **wissenschaftlichen**
Methoden
nachgewiesen sein

valēns, entis, *adv.* enter (valeo) 1. stark, kräftig: bestia, iuvenis *O*; *met.* valentius spirare *O*. 2. gesund, wohlauf; *met.* animi. *met.* 3. stark, mächtig: opibus *N*, flamma *O*. 4. wirksam: causae *O*, carmina *H*.



Theophrastus Bobastus von
Hohenheim Paracelsus
(1493-1541)

„You must know that
the will is a powerful
adjuvant of medicine.“



Fragen

- 1) Ist es ethisch, Placebo-kontrollierte Studien durchzuführen bei Krankheiten (zB MS, Depression etc), für die teilweise wirksame Behandlungen bestehen ?
- 2) Placebo kann eine günstige Wirkung bei verschiedenen Krankheiten haben - ist es gerechtfertigt, eine Placebobehandlung anzuwenden?

Hill J: Placebo in clinical care – for whose pleasure? Lancet 2003; 362: 254

„Successfull placebo use may be even more of a problem than placebo failure, since maintaining the placebo effect can perpetuate the deceit by lying or avoiding legitimate questions patients may have about possible side effects, interactions with other agents, and other aspects of informed consent

- 3) Wenn die Wirkung (zB Verminderung der Schubrate bei MS) von Placebo nach einem Jahr ähnlich ist wie durch Verum ein Jahr zuvor – ist es gerechtfertigt, zu warten?

Questions

- 1) Is it ethical to conduct placebo-controlled trials in a disease (e.g. MS, depression etc) in which at least partly effective therapies are available?
- 2) Placebo may have a beneficial effect in many conditions - is it justified to use a treatment which is known to be a placebo?

Hill J: Placebo in clinical care – for whose pleasure? Lancet 2003; 362: 254

„Successfull placebo use may be even more of a problem than placebo failure, since maintaining the placebo effect can perpetuate the deceit by lying or avoiding legitimate questions patients may have about possible side effects, interactions with other agents, and other aspects of informed consent

- 3) When the effect in reducing relapse frequency in a progressive disease such as MS is similar for placebo one year later as it is for the Verum e.g. Interferons): is it justified just to wait for one year before treatment is initiated?

Der Placeboeffekt



