Choosing a placebo

EAPC Research Forum
Trondheim 2008

Claudia Bausewein

Department of Palliative Care, Policy & Rehabilitation
King's College London

History

- Religious context
  - Psalm 116: Placebo Domine (“I will please the Lord”)

- Medical context
  - 1772 William Cullen (leading British physician of 18th century): “a method for pleasing and comforting difficult or incurable patients”
  - First half 19th century: inert substances used in comparative clinical trials
  - Beginning 20th century: inert substances used as controls in pharmacological experiments

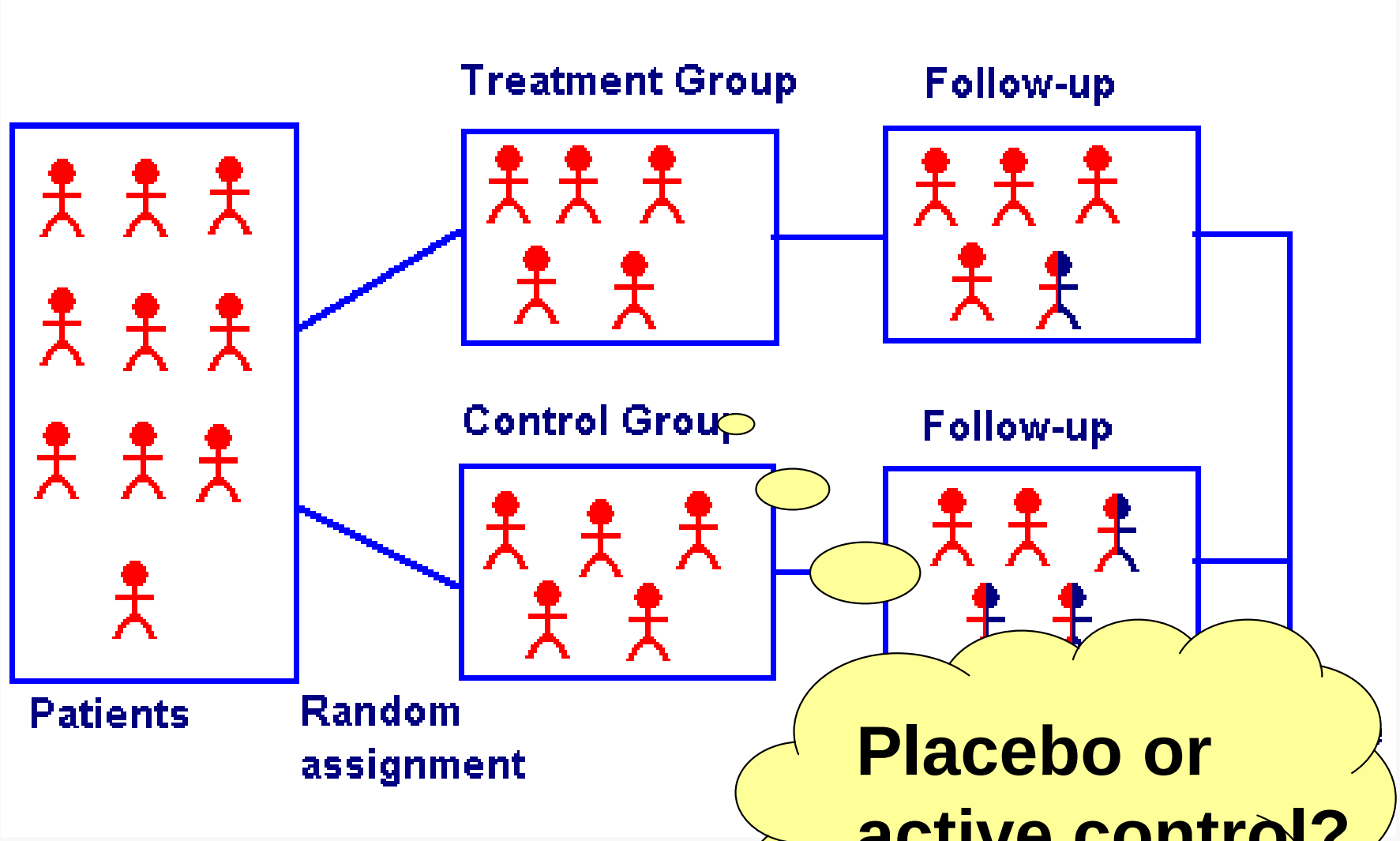
Definition

= inactive or ineffective treatment or formulation

- Synonyms: inert, sham, dummy, non-specific

- Traditional practice of prescribing inert interventions
- Clinical trials
  - double-blind **placebo**-controlled RCT as gold standard to rigorously show treatment efficacy
  - control treatment with a similar appearance to study treatments but without their specific activity (Hróbjartsson NEJM 2001)
  - to control for psychological effects of treatment

Gold standard: RCT



Types of placebo

- Pharmacological
  - e.g. drug (lactose tablet)
  - “active placebos”: treatment with some pharma-cological or physiological activity (benzodiazepines or anti-muscarinics in analgesic trials)
- Physical
  - e.g. manipulation: procedure with machine that was turned off (sham TENS)
- Psychological
  - e.g. non-directional conversation: “attention placebo”

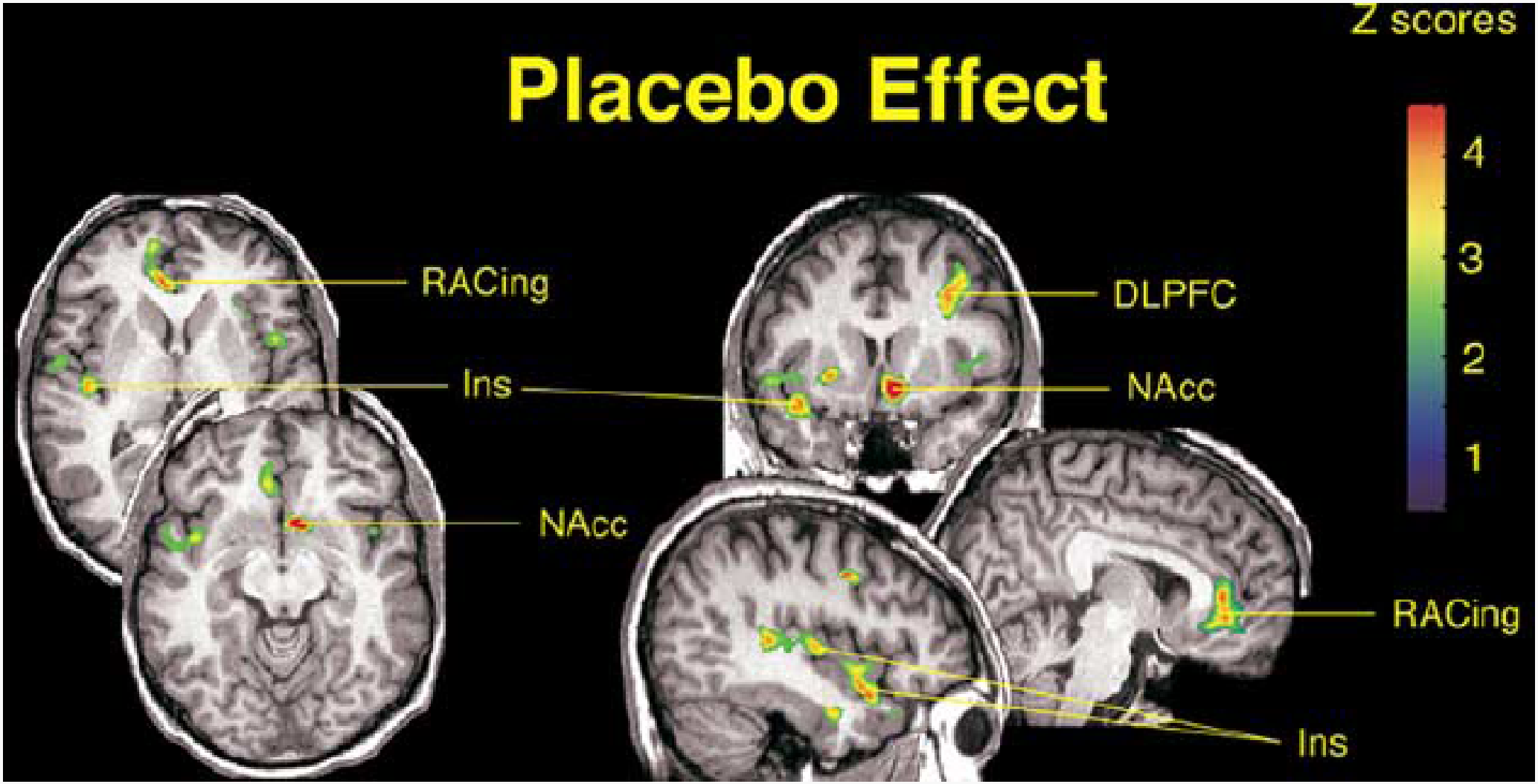
“The” placebo effect

- Dependant on patients’ expectations, interaction with doctors, context of study, different for different diseases

- Size of placebo effect
  - between 35% (Beecher JAMA 1955) and 80% (Kirsch Prev Treatment 2002)
  - significant correlation of placebo with improvement rated in treatment group (Walach BMC Med Res Meth 2005)
  - no evidence that placebo interventions in general have clinically important effects; possible small effect on patient-reported continuous outcomes, especially pain (Hróbjartsson NEJM 2001, CDSR 2004)

Placebo effect - Neurobiology

- Placebo-induced expectation of motor improvement activates endogenous dopamine in Parkinson patients (de la Fuente-Fernandez Science 2001)
- Placebo-induced metabolic changes seen in PET in depressive patients (compared to fluoxetine) (Mayberg Am J Psych 2002)
- Placebo analgesia blocked by opioid-antagonist naloxone (Levine Lancet 1978)



Effects of placebo on the activation of μ-opioid receptor–mediated neurotransmission

Benedetti J Neurosci 2005

Components of placebo effect

- RCT to determine patients' response to placebo treatment
- Irritable bowel syndrome (n=262)
- Trial arms (6 weeks): waiting list, acupuncture with minimal interaction or with defined positive patient-practitioner relationship

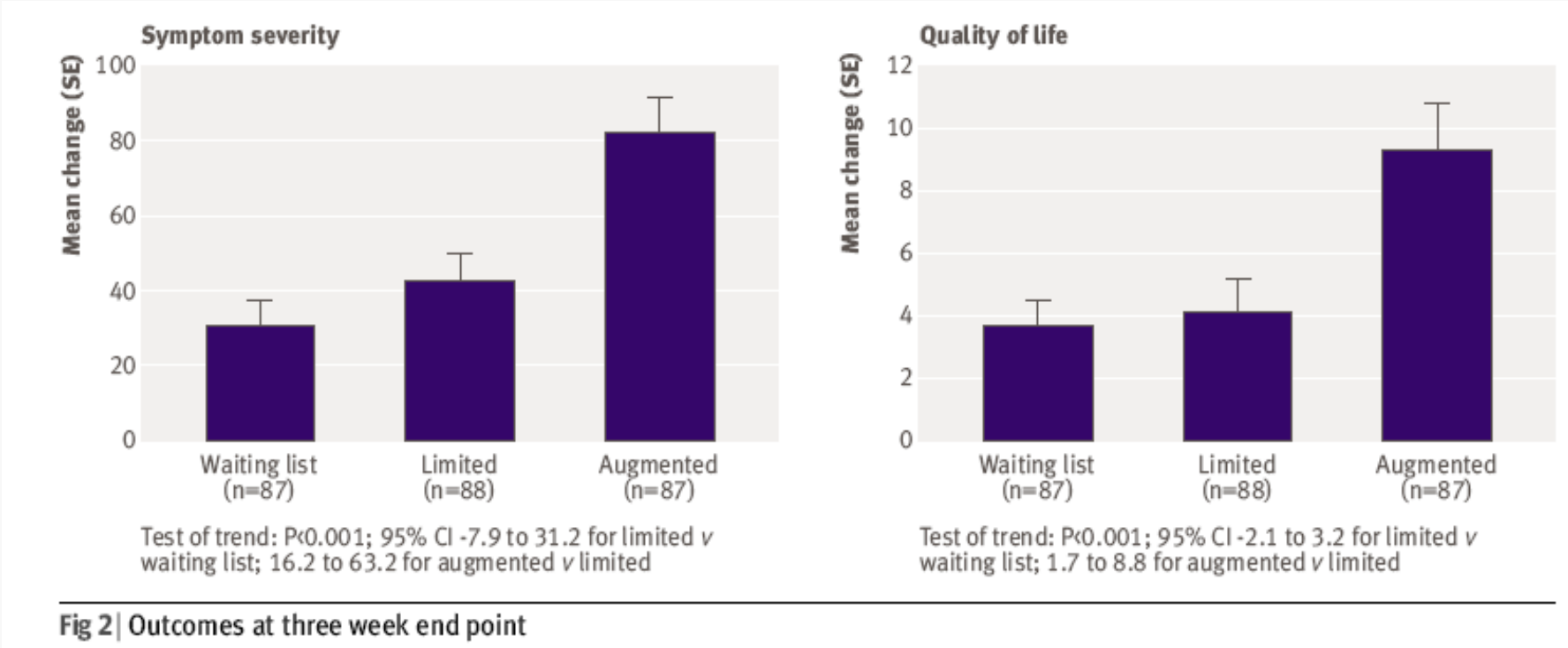


Fig 2 | Outcomes at three week end point

Kaptchuk BMJ 2008

Placebo effect also depending on…

- Clinical setting, cognitive and affective communication, ritual of administering treatment ("contextual healing") (Miller FG J R Soc Med 2008)
- Meaning of placebo to patients and investigators (Keefe, Pain 2008)
- Impact of instructions
  - "50/50 chance of receiving real medication or placebo" versus "received drug is know to significantly reduce pain in some people" (Chung KS, Pain 2007)

Drug trials: choice of placebo

- Chemically inert similar-looking pill with no active chemicals
- Even saline and sugar pills have physiological properties (Sievenpiper Br J Clin Pharmacol 2007)
- Double-blinding necessary
- Colour of drugs (de Craen BMJ 1996)
  - red, yellow, and orange coloured drugs associated with a stimulant effect, blue and green related to tranquillising effect

Non-pharmacological interventions: choice of placebo

- Placebo for acupuncture, surgery, psychotherapy…?
- Experience based/ complex interventions (Hart Neuropsych Rehab 2008)
  - nearly impossible to be compared to true placebo
  - blinding difficult for treater and participant
  - placebo-analogue
    - plausible treatment theoretically irrelevant to problem (control non-specific effects such as attention, cognitive stimulation, social contact, expectancy of improvement)
    - attention control: e.g. phone calls, to balance amount of exposure to study personnel; but therapeutic alliance important correlate in psychotherapy interventions

RCT: hand-held fan versus wristband

- Aim: To test the effectiveness of a hand-held fan over time in relieving breathlessness in breathless COPD and cancer patients and to explore the experience of patients who use it
- Methods: RCT embedded in longitudinal study examining the experience of breathlessness over time
- Randomisation findings:
  - randomised: intervention (hand-held fan) n = 38, control (wristband) n = 32 (2 declined, wanted fan)
  - refusal of randomisation n = 39 (beliefs in ineffectiveness of intervention or control 20/39, 3/20 wanted fan)

control

intervention

???

Patients‘ feedback (n= 38)

- Hand-held fan
  - Positive experiences: 11/23 patients *(“very helpful, don’t want to miss it anymore, makes life much easier”, “very good, use it regularly”)*
  - Negative experiences: 7/23 patients (2/23 fan defect, 1/23 sensitive towards the air draught produced by the fan)

- Wristband
  - Positive experiences: 5/15 patients *(“reassuring to wear it”, “I rely on it”)*
  - Negative experiences 4/15 patients *(“it is foolish”),* 2/15 patients reported side-effects in form of skin irritations, 2/15 patients did not use it of whom one complained that the wristband did not fit

Conclusions

- “Placebo” is a rather complex topic
- Variety of factors attributed to placebo effect
- Contextual healing even bigger role in palliative care?
- Choice of placebo in an RCT needs as much consideration as intervention

"First, we'll try a placebo."