

# Placebos in Pets

- Placebo- “I shall please”
  - Nocebo- “I shall cause harm”



## Placebo

An inert medical intervention known not to have a specific physiologic effect on the condition being treated. Often a control treatment in a clinical trial.

- Placebo- “I shall please”
  - Nocebo- “I shall cause harm”



## Placebo Effect

Beneficial effects, or the appearance of benefit, associated with medical treatment and not attributable to direct, specific physiologic effects of the treatment. Improvement in patients in the placebo arm of a clinical trial.

# History of Placebos

- Medical Dictionary 1811

“Medicine adapted more to please than to benefit the patient”

- Hogarth, 1801
  - Possibly first placebo-controlled trial
  - Perkins tractors
  - Crossover design

“what wonderful effects the passions of hope and faith, excited by mere imagination, can produce on disease”





# History of Placebos

- 18<sup>th</sup>- early 20<sup>th</sup> centuries
  - Commonly used to comfort patients
  - Bread pills, colored water, inert injections
  - Seen as effective treatment
- Mid to late 20<sup>th</sup> century
  - Increased research on placebo effects
  - Widespread use in clinical trials
  - Declining use in clinical practice due to ethical concerns
    - Deception of patients
    - Medical paternalism
    - Growing belief that not truly effective treatment



# History of Placebos

- Late 20<sup>th</sup> to early 21<sup>st</sup> Century
  - Truly effective?
  - Deception?
  - Ethical?



Powerful or Powerless Placebo?





# Powerful Placebo

- Beecher, 1955
  - 35% responders
  - “A high degree of therapeutic effectiveness in treating subjective responses.”
  - Also affected stress physiology
  - Potential “toxic effects”
  - Clinical experience thus not very reliable measure of efficacy



# Powerful Placebo

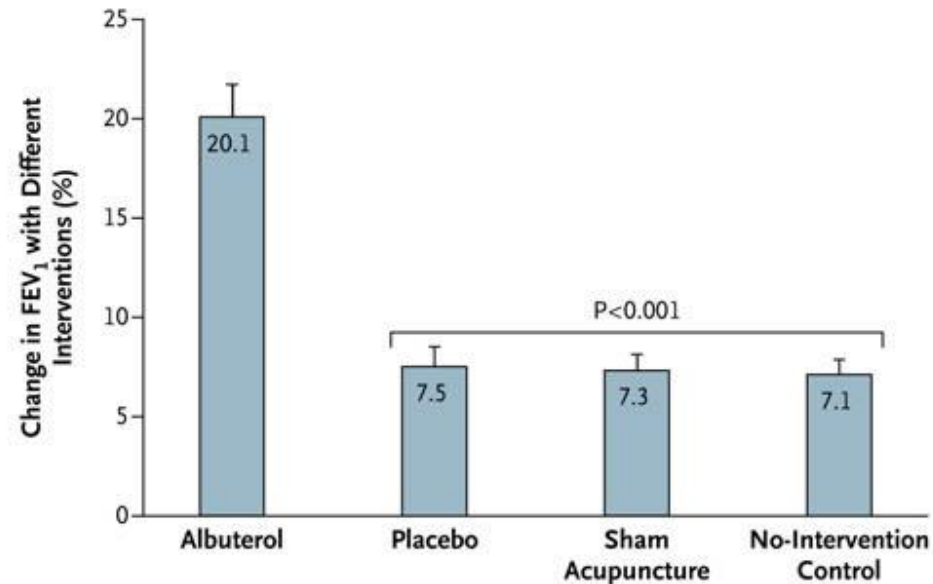
- Kaptchuk, 2015
  - “no evidence can shrink tumors”
  - “rarely cure”
  - “genuine biopsychosocial effects”
  - Symptomatic benefits still worth having
  - Can achieve benefits without deception
  - “mind-body self-healing process”



# Powerless Placebo

Wechsler, et al, 2011

- Patients with asthma
- Random series of treatments
  - No treatment
  - Albuterol inhaler
  - Placebo inhaler
  - Sham acupuncture



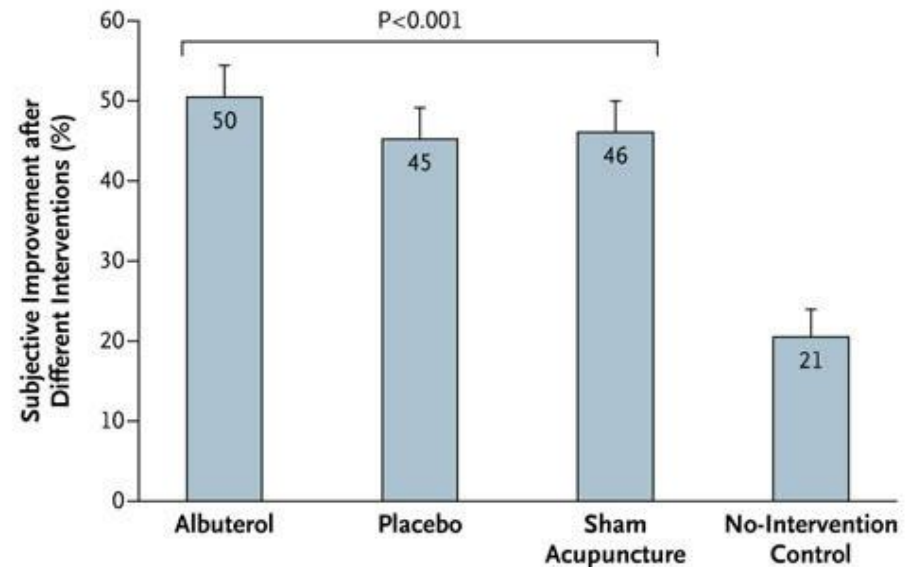
**Figure 3.** Percent Change in Maximum Forced Expiratory Volume in 1 Second (FEV<sub>1</sub>) with Each of the Four Interventions.

The relative improvement in FEV<sub>1</sub> achieved with albuterol was significantly greater than that achieved with each of the other three interventions ( $P < 0.001$ ). No other differences among the four experimental conditions were significant. T bars indicate standard errors.

# Powerless Placebo

Wechsler, et al, 2011

- Patients with asthma
- Random series of treatments
  - No treatment
  - Albuterol inhaler
  - Placebo inhaler
  - Sham acupuncture



**Figure 4.** Percent Change in Subjective Improvement with Each of the Four Interventions.

The relative improvement in subjective outcomes, assessed with the use of a visual-analogue scale (with 0 indicating no improvement and 10 indicating complete improvement), was significantly greater with the albuterol inhaler, placebo inhaler, and sham acupuncture interventions than with the no-intervention control ( $P<0.001$ ). No other differences among the four experimental conditions were significant. T bars indicate standard errors.

# Powerless Placebo

- Hrobjartsson, 2001,2004

- Systematic reviews of hundreds of clinical trials

“No significant effects on objective or binary outcomes...possible small benefits in studies with continuous subjective outcomes and for the treatment of pain.”

“Possible small effect on patient-reported continuous outcomes, especially pain, could not be clearly distinguished from bias.”

“Outside the setting of clinical trials, there is no justification for the use of placebos.”



# Powerless Placebo

- Cochrane Review, 2010

- Systematic reviews of hundreds of clinical trials

“Placebo treatments produced no major health benefits”

“On average they had a modest effect on outcomes reported by patients, such as pain”

“The effect on pain varied from large to non-existent, even in well-conducted trials. Variations in the effect of placebo was partly explained by variations in how trials were conducted, the type of placebo used, and whether patients were informed that the trial involved placebo.”





# Characteristics of Placebos

- No direct, specific effects
- Impact subjective outcomes more than objective outcomes
  - pain
  - nausea
  - anxiety, depression
  - tumor growth
  - mortality
  - most clinical laboratory values
  - autonomic outcomes (BP, BG, HR, etc.)
- Continuous more than binary variables



# Characteristics of Placebos

- Weaker than specific effects
  - smaller effect size
  - shorter duration
- Independent of specific effects
  - additive for effective treatments
  - illusory for ineffective treatments



# Characteristics of Placebos

- Depend on presentation
- Personnel
  - Lab coat versus t-shirt
  - Positive, negative, neutral messaging
- Intervention
  - Injection > pills
  - Branded > generic
  - Expensive > cheap

More intensive and theatrical placebos generate greater effects



# Characteristics of Placebos

- Other predictors
- Patient
  - Expectations, previous experiences
  - Symptom severity and history
  - Age?
  - Gender?
  - Genes?
- Study design features
  - True quantification requires no-treatment group
  - Parallel designs > crossover design

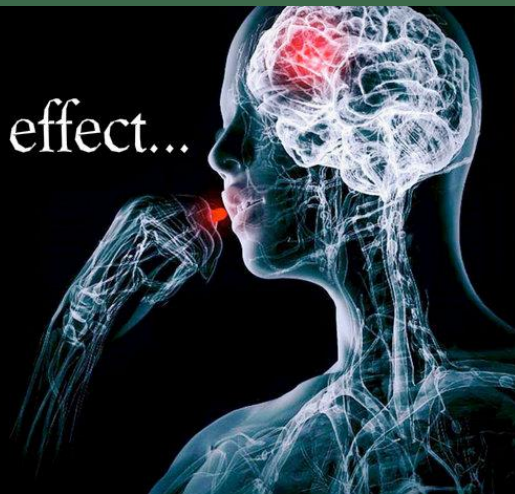




# How Does the Placebo Effect Work?

- Expectation and Belief
- Conditioning effects
- Endogenous opioids/endorphins?
- Other neurophysiologic mechanisms

The placebo effect...  
it's all in  
the mind?





## Mimicking the Placebo Effect



# Mimicking the Placebo Effect

Non-specific factors that generate the appearance of response to treatment

- Natural course of disease
  - Regression to the mean
  - Spontaneous resolution
- Concurrent treatment
- Clinical trial effects (Hawthorne Effect)
  - Response bias
  - Other uncontrolled bias
  - Compliance with treatment
  - Overall better care



# Placebo Effects in Animals?

- Clinical Trials
  - Pain (NSAID trials)
  - Pruritis and skin lesions
  - Anxiety
  - Headshaking
  - Seizure frequency
- Dogs, cats, horses
- Subjective measures > objective measures
- Parallel design > crossover design
- Open label > blinded



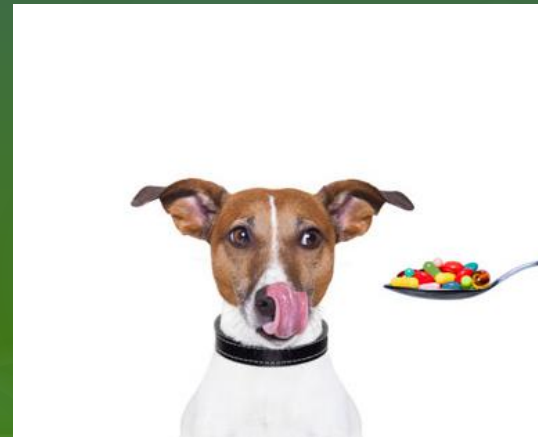


# Placebo Effects in Animals- Mechanisms

- Caregiver Placebo

Conzemius & Evans, 2012

- 58 dogs with OA and lameness
- Placebo group from an NSAID vs placebo RCT
- Randomized, double-blinded (owners and vets)
- Assessments
  - Owner questionnaire
  - DVM physical exam
  - Force plate analysis



# Placebo Effects in Animals- Konzemius & Evans, 2012

- Caregiver placebo effect-

“A sham medical intervention that causes pet caregivers (owners or veterinarians) to believe the treatment they provided to the pet improved the pet’s condition.”

“Owner responded the dog had improved when the dog’s GRFs were unchanged or had worsened, and owner responded the dog was unchanged when GRF had worsened”



# Placebo Effects in Animals- Konzemius & Evans, 2012

- Owner survey
  - 50% reported improvement
  - 10% reported worsening
  - Caregiver placebo 57%
- Vet Exam
  - 45% improved lameness/pain
  - 14% worse lameness/pain
  - Caregiver placebo 40%-45%
- Force Plate
  - $\geq 5\%$  change
    - 12% improved
    - 9% worse
  - $\geq 10\%$  change
    - 2% improved
    - 2% worse



# Placebo Effects in Animals- Conzemius & Evans, 2012

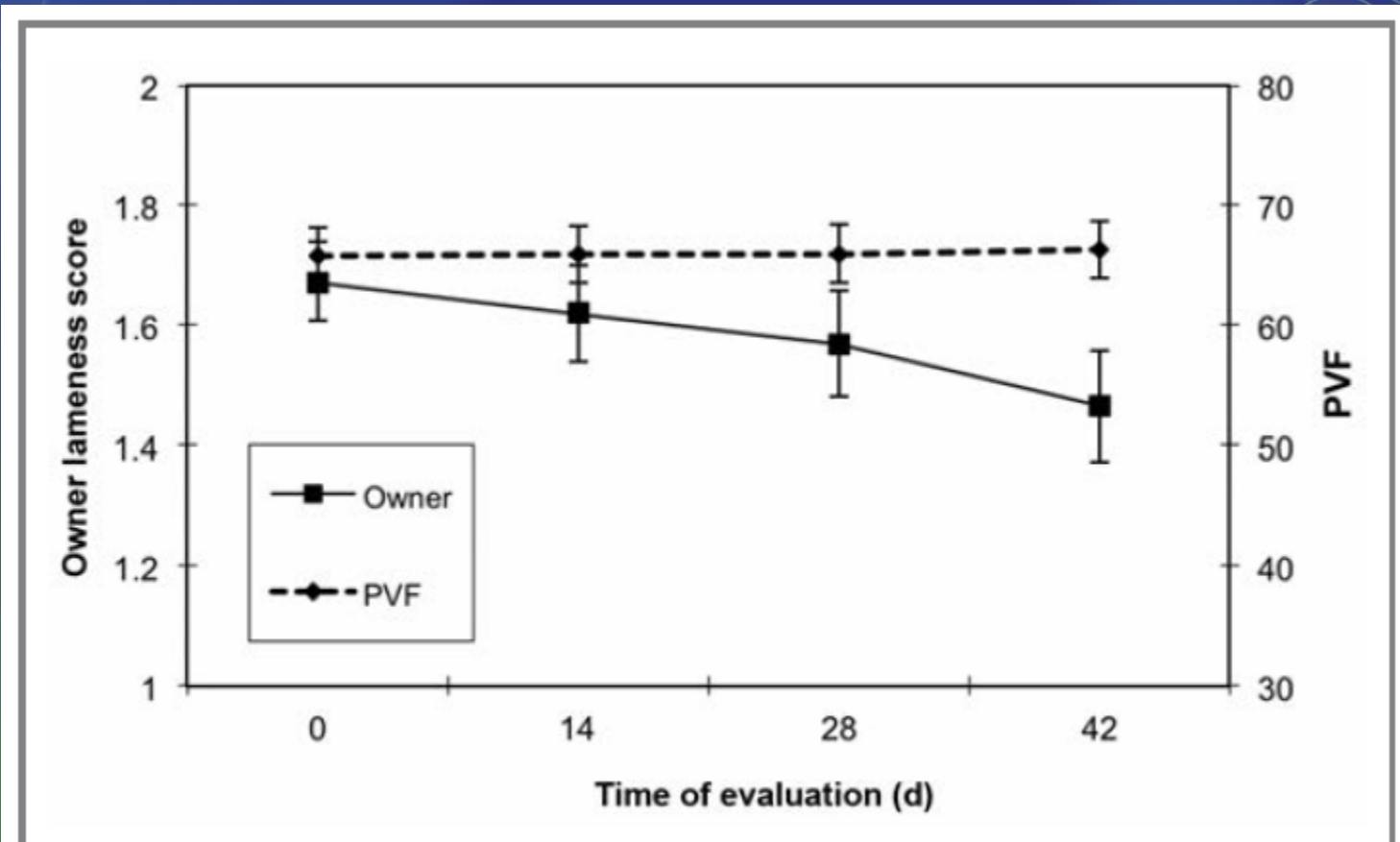


Figure 1—Mean  $\pm$  SE lameness evaluation score for 58 dogs with lameness secondary to osteoarthritis evaluated over time as generated by owners and force platform (PVF). These data were not normally distributed.



# Placebo Effects in Animals- Gruen, Dorman, Lascelles, 2017

- 96 cats in 5 OA studies
- Drug and non-drug interventions
- All double-blinded
- Similar outcome measures
  - DVM exam
  - Client-specific Outcome Measures (CSOM)
  - Accelerometry
    - "Success"  $\geq 10\%$  increase over baseline
    - "Failure"  $< 10\%$  increase over baseline



# Placebo Effects in Animals- Gruen, Dorman, Lascelles, 2017

- Effect Size
  - Difference in mean/pooled SD (Cohen's d)
    - Small 0.01
    - Medium 0.50
    - Large  $\geq 0.80$



# Placebo Effects in Animals- Gruen, Dorman, Lascelles, 2017

- Caregiver placebo effect-

“effects that alter the rating of outcomes provided by clinicians, caregivers or the family”

“Cats given placebo that were classified as CSOM successes without having an increase in activity were considered to have ‘improved’ due to the caregiver placebo effect.”



# Placebo Effects in Animals- Gruen, Dorman, Lascelles, 2017

- Placebo-by-proxy effect-

“a caregiver’s belief that the animal is receiving an effective medication alters their interaction with the animal and manifests as a real beneficial effect for the animal.”

“Cats that were given placebo and classified as CSOM and activity count successes were considered to have improved due to a placebo-by-proxy effect.”





# Placebo Effects in Animals-Gruen, Dorman, Lascelles, 2017

**TABLE 3: Effect sizes for the placebo period, treatment period and treatment over placebo by study**

Study	Effect size (95% CI)		
	Placebo	Treatment	Treatment over placebo
Diet	1.93 (1.16 to 2.70)	1.33 (0.65 to 2.02)	-0.35 (-0.98 to 0.28)
DQ	1.71 (1.12 to 2.30)	1.40 (0.81 to 1.96)	-0.35 (-0.87 to 0.16)
FMPI	0.97 (0.16 to 1.78)	1.40 (0.42 to 2.37)	0.35 (-0.48 to 1.18)
Low-dose	1.05 (0.50 to 1.60)	1.09 (0.53 to 1.64)	0.09 (-0.43 to 0.60)
Antibody	1.20 (0.25 to 2.16)	2.06 (1.34 to 2.77)	0.74 (-0.02 to 1.50)

FMPI, Feline Musculoskeletal Pain Index



# Placebo Effects in Animals-Gruen, Dorman, Lascelles, 2017

- On CSOM 87% of cases showed some improvement
- 50-70% of cases met study criteria for effective Tx
- Caregiver Placebo- 43% (9%-63%)
- Placebo-by-proxy- 24% (11%-45%)



# Placebo Effects in Animals-Gruen, Dorman, Lascelles, 2017

**TABLE 4: Summary of proportion of overall Client-Specific Outcome Measure (CSOM) success during placebo treatment (CSOM+) as well as breakdown of CSOM and activity (Activity+) successes and failures (CSOM– and Activity–) by study**

Study	N	Overall CSOM+	CSOM+/Activity+	CSOM+ /Activity–	CSOM– /Activity+	CSOM– /Activity–
Diet	19	0.74	0.11	0.63	0.00	0.26
DQ*	28	0.70	0.33	0.37	0.11	0.19
FMPI	11	0.54	0.45	0.09	0.18	0.27
Low-dose	29	0.66	0.21	0.45	0.03	0.31
Antibody	9	0.67	0.11	0.56	0.00	0.33
Overall	96*	0.68	0.24	0.43	0.06	0.26

\*One cat excluded due to accelerometer malfunction; n=96 for overall CSOM, n=95 for CSOM/Activity  
FMPI, Feline Musculoskeletal Pain Index



# Placebo Effects in Animals- Muñana, Zhang, Patterson, 2010

- Meta-analysis of 3 double-blinded, placebo-controlled trials in 34 epileptic dogs
  - Add-on medication
  - Diet
  - Surgical implant
- 2 crossover and 1 parallel study (diet)
- Owner diary used to establish seizure frequency
- Responders defined as  $\geq 50\%$  decrease in seizure frequency





# Placebo Effects in Animals- Muñana, Zhangh, Patterson, 2010

- Seizure frequency reduction
  - Crossover studies- 26% and 29%
  - Parallel study- 46%
  - Not all reductions statistically significant
- Responders- 29%
- Did not control for non-specific clinical trial effects

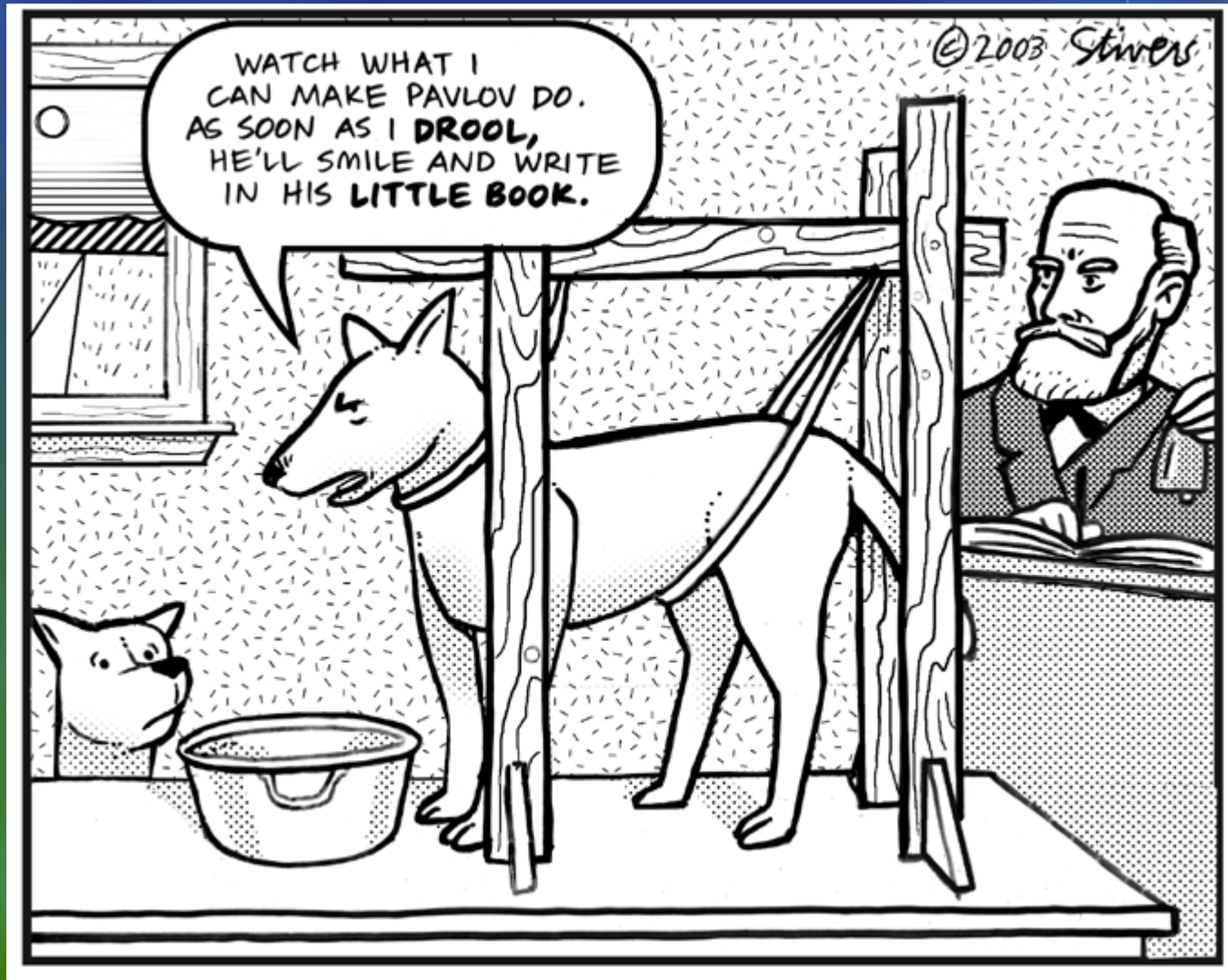


# Placebo Effects in Animals- Mechanisms

- Caregiver Placebo
- Non-specific clinical trial effects
  - Better overall monitoring and care
  - Compliance with concurrent treatment
  - Placebo-by-proxy
- Natural course of disease
  - Spontaneous resolution
  - Regression to the mean
- Conditioning
- Human interaction

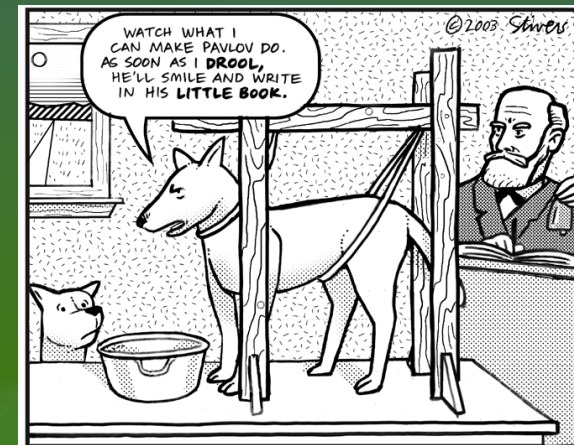
# Placebo Effects in Animals- Mechanisms

- Conditioning



# Placebo Effects in Animals- Mechanisms

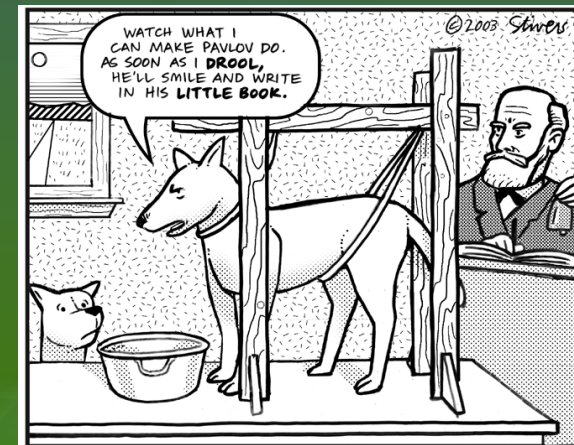
- Conditioning
  - Unconditioned stimulus/response
  - Conditioned stimulus/response
- Examples
  - Morphine in dogs
    - US- morphine
    - CS- environment/injection (saline)
    - UR/CR- vomiting/nausea/lethargy
  - Pain, nausea, agitation, lethargy, BG, gastric pH, opioid effects and withdrawal, immune function (mostly nocebo in lab studies)





# Placebo Effects in Animals- Mechanisms

- Conditioning as Placebo
  - US- effective medical Tx
  - UR- symptomatic improvement
  - CS- medical environment/treatment
  - UR- symptomatic improvement
- Requires Hx of effective Tx
- Familiarity with Tx experience



# Placebo Effects in Animals- Sümegi, Gácsi, Topál, 2014

- Conditioned placebo effect in dogs decreases separation-related behaviors
  - 28 dogs with separation anxiety
  - Procedure
    - Baseline- separation condition
    - Conditioning- same setup but no separation and pre-treated with either oral acepromazine or placebo repeated 3 times
    - Test- separation condition, both groups pre-treated with placebo

# Placebo Effects in Animals- Sümegi, Gácsi, Topál, 2014

- Conditioned placebo effect in dogs decreases separation-related behaviors
  - Conditioned dogs showed
    - Less active anxiety
    - More passive behavior





# Placebo Effects in Animals- Mechanisms

- Human Interaction





# Placebo Effects in Animals- Mechanisms

- Human Interaction
  - Lowers HR
  - Reduces physiologic stress response
  - Reduces autonomic response to painful stimuli
  - May affect productivity, reproduction, post-surgical recovery, disease resistance
- Positive handling vs Negative handling



# Placebo Effects in Animals- Implications



# Placebo Effects in Animals- Implications

- Research Studies
  - Placebo effects/mimics ARE relevant to animal studies
  - Always have a placebo control!!
  - Try to have multiple controls
    - No-treatment
    - Positive control
  - Bias control (blinding, randomization, etc.)
  - Objective outcome measures
  - Crossover design vs parallel design

# Placebo Effects in Animals- Implications

- Clinical practice
  - Are they really getting better?
    - Caregiver placebo
  - Did our treatment work?
    - Natural history/regression to the mean
    - Placebo-by-proxy
    - Non-specific treatment effects
  - Can we take advantage of placebo effects?
    - Conditioning
    - Human interaction
    - Placebo-by-proxy
  - Ethical issues