

# Can basic and clinical research on placebo lead to evidence-based clinical trials?

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# Evidence from basic and clinical research

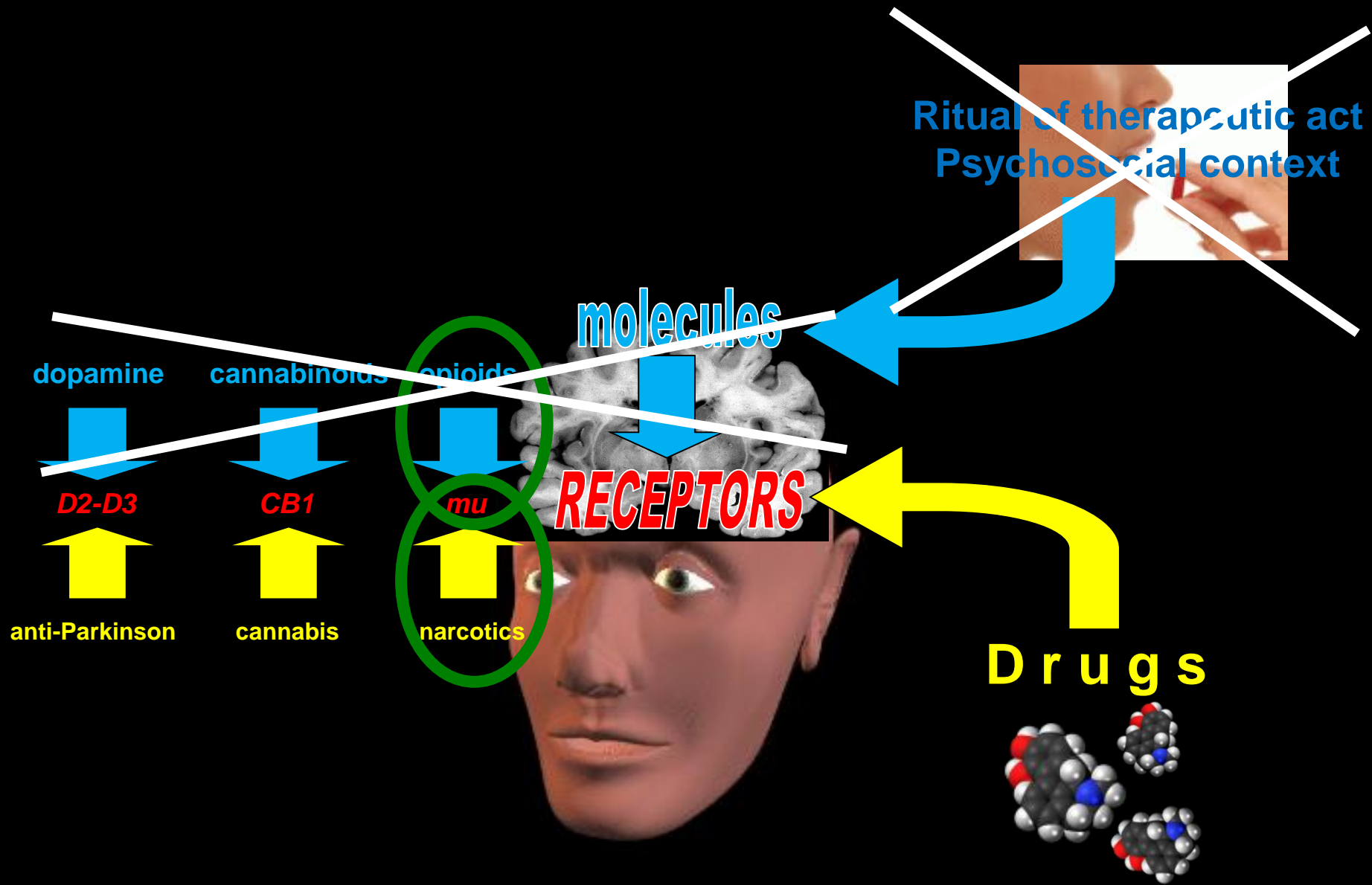
## OVERVIEW

**Patients' expectations are crucial for the therapeutic outcome**

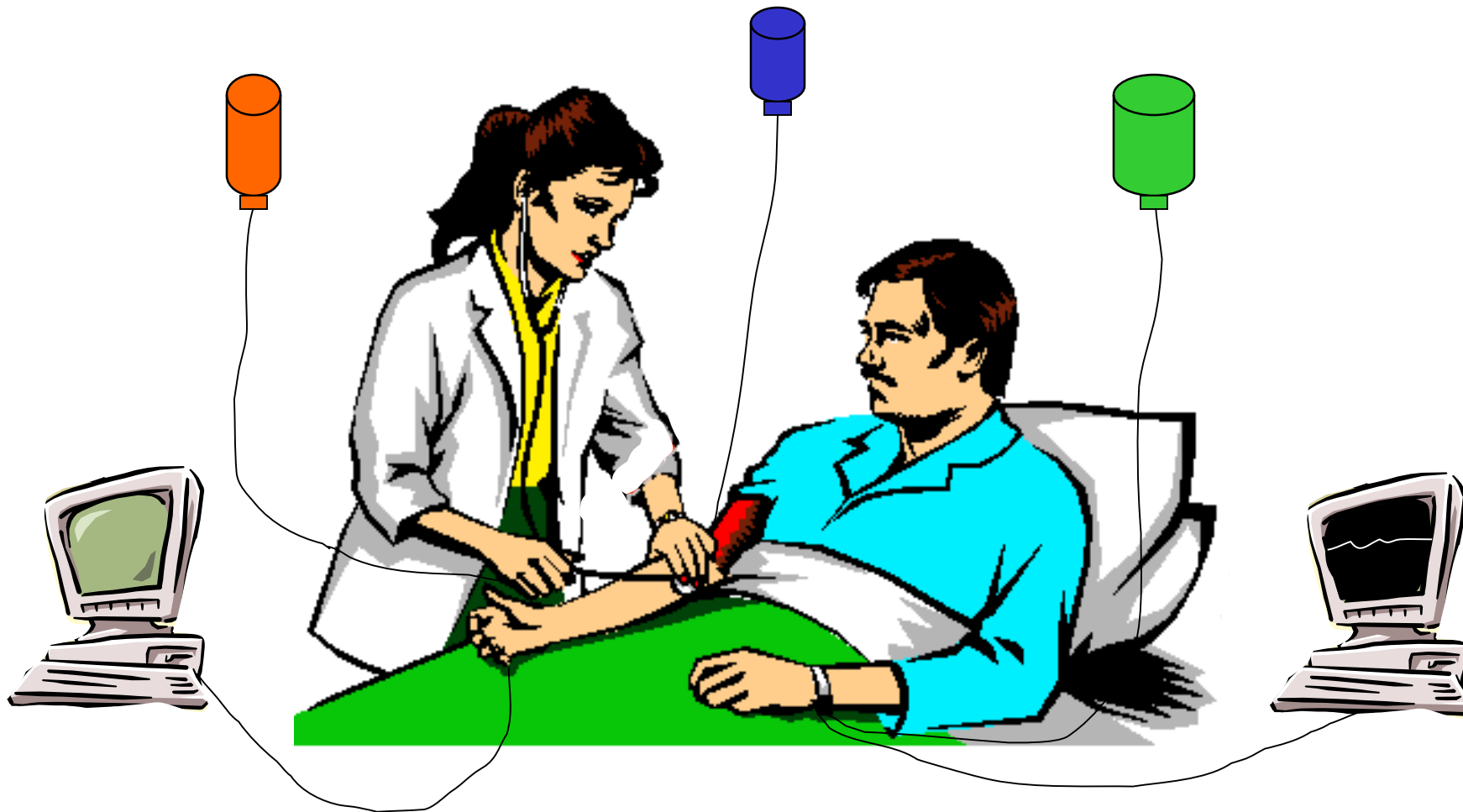
**Repeated exposure to drugs may lead to substantial placebo responses**

**Communication across participants may affect the therapeutic outcome**

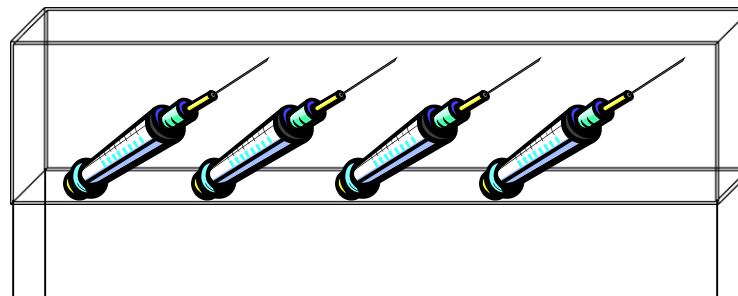
**Placebo responders and nonresponders can be identified *a priori***



Benedetti (2008) *Annu Rev Pharmacol Toxicol*  
 Benedetti (2014) *Neuron*



Benedetti et al (1995) *Lancet*  
Colloca et al (2004) *Lancet Neurol*  
Benedetti et al (2016) *Lancet Neurol*

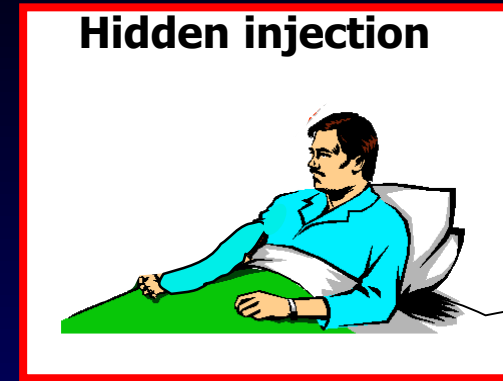
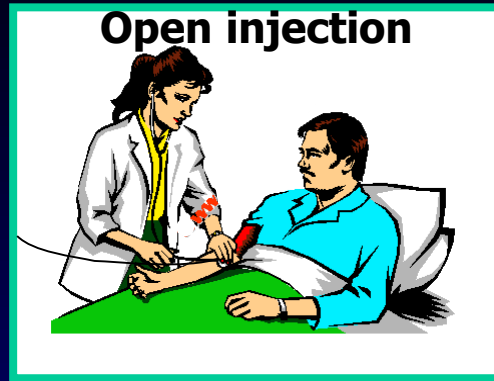


# No expectation

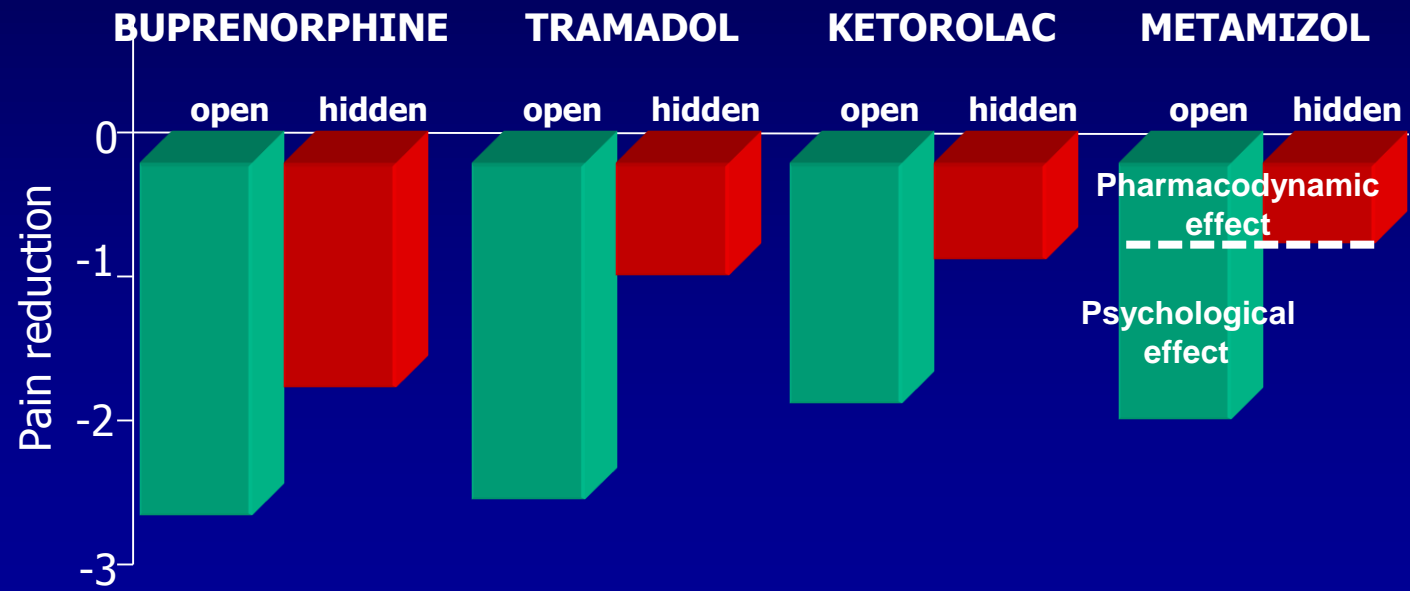


Benedetti et al (1995) *Lancet*  
Colloca et al (2004) *Lancet Neurol*  
Benedetti et al (2016) *Lancet Neurol*

No expectation



computer



Benedetti et al (1995) *Lancet*  
Colloca et al (2004) *Lancet Neurol*  
Benedetti et al (2016) *Lancet Neurol*

# TRIAL Met#2

(Colloca and Benedetti, *Nature Rev Neurosci* 6: 545-552, 2005)

Is metamizol (300 mg) effective in post-thymectomy pain?



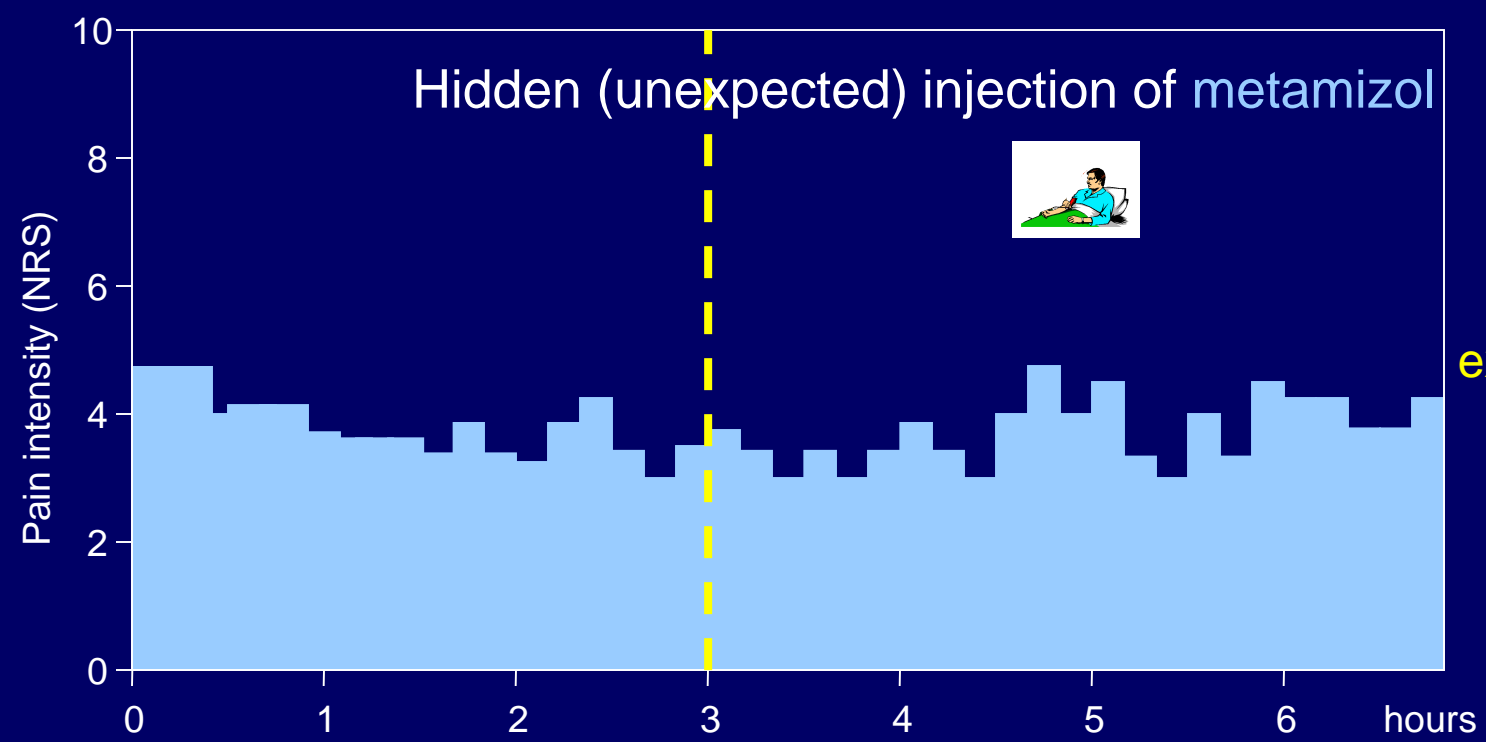
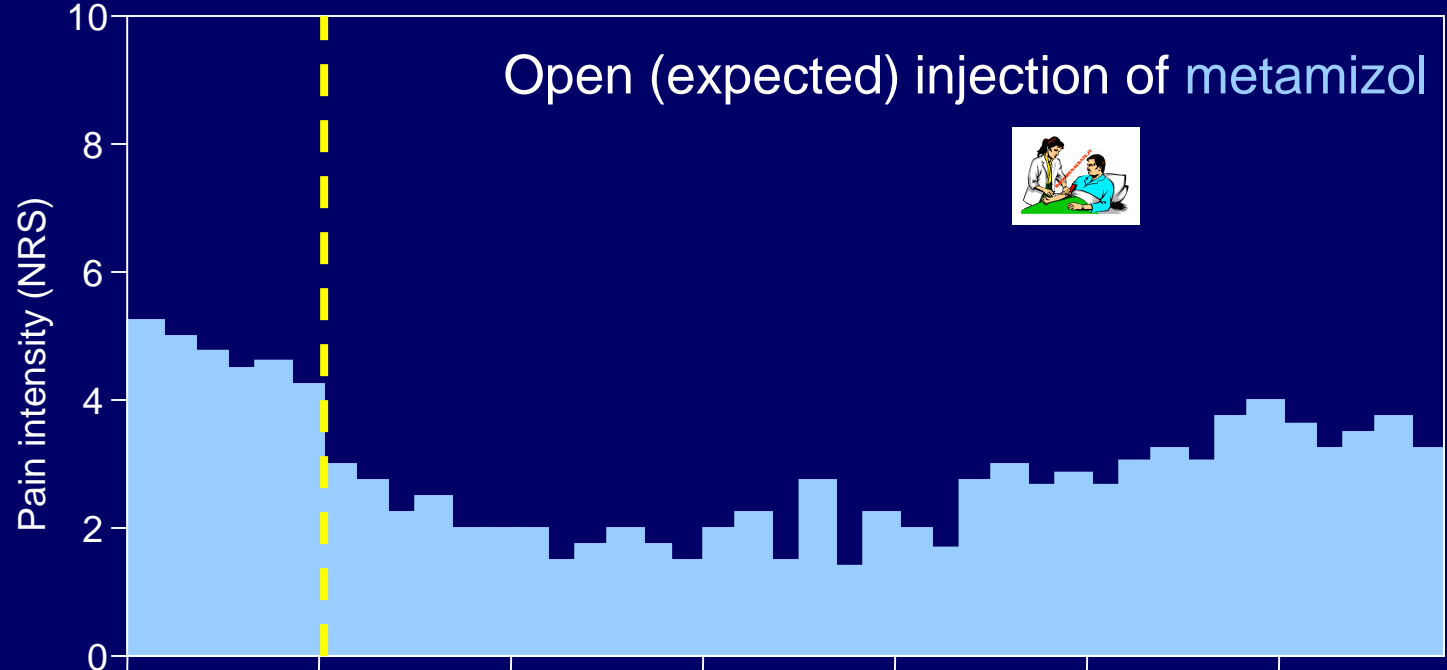
Open metamizol injection group (N=10)



Hidden metamizol injection group (N=10)

Informed consent "You will receive metamizol but you don't know when"

Double blind





GET

R e m i f e n t a n i l

TOLD

Saline

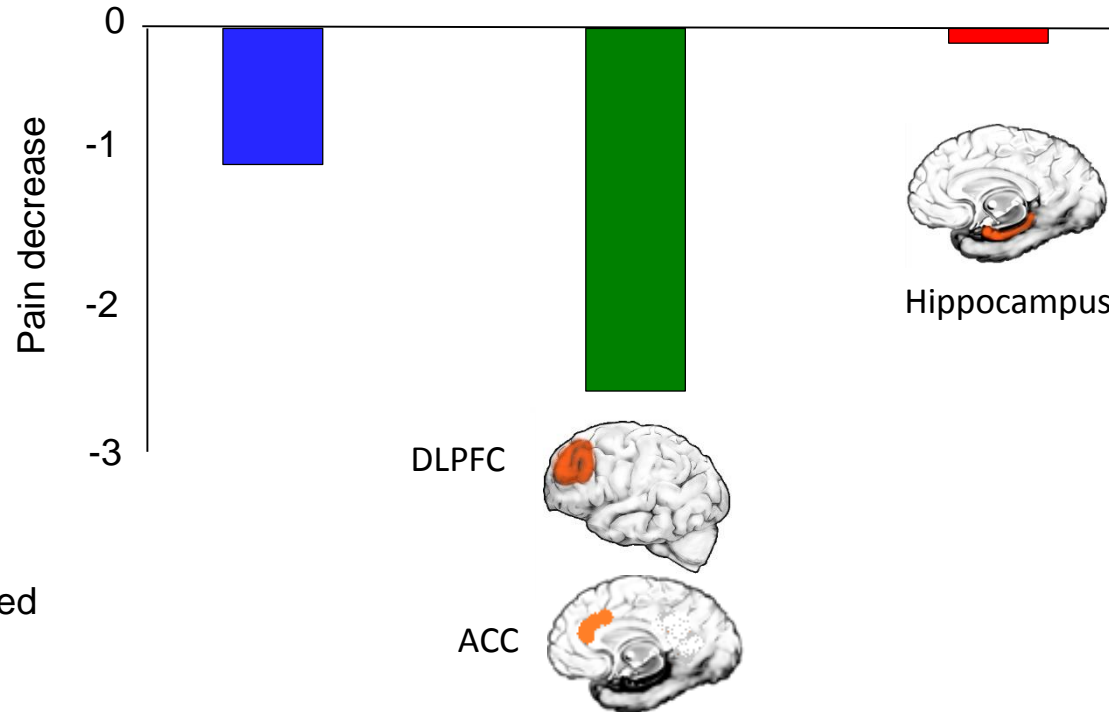
Remifentanil

Interruption

No  
expectation

Positive  
expectation

Negative  
expectation



# Evidence from basic and clinical research

## OVERVIEW

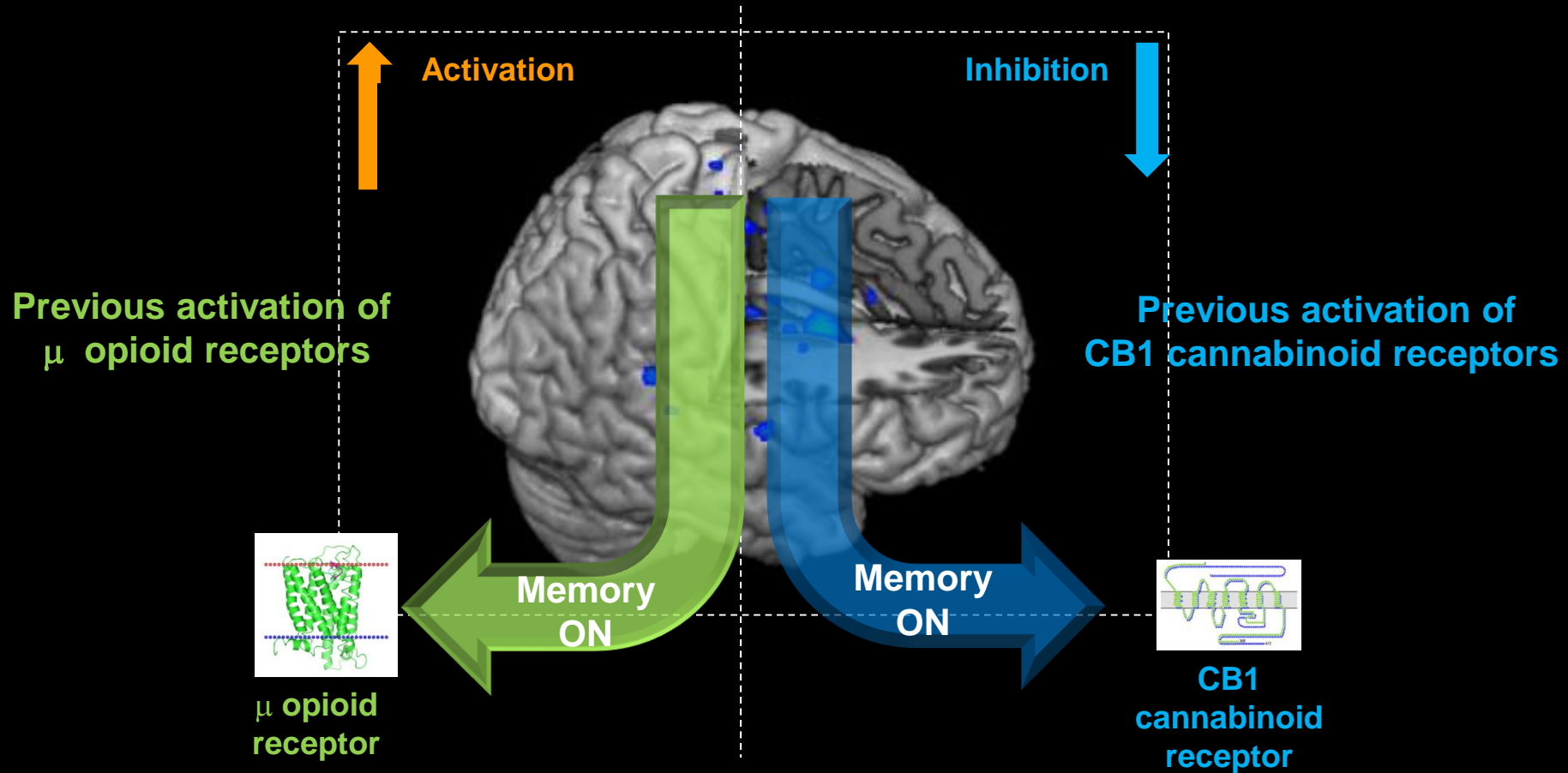
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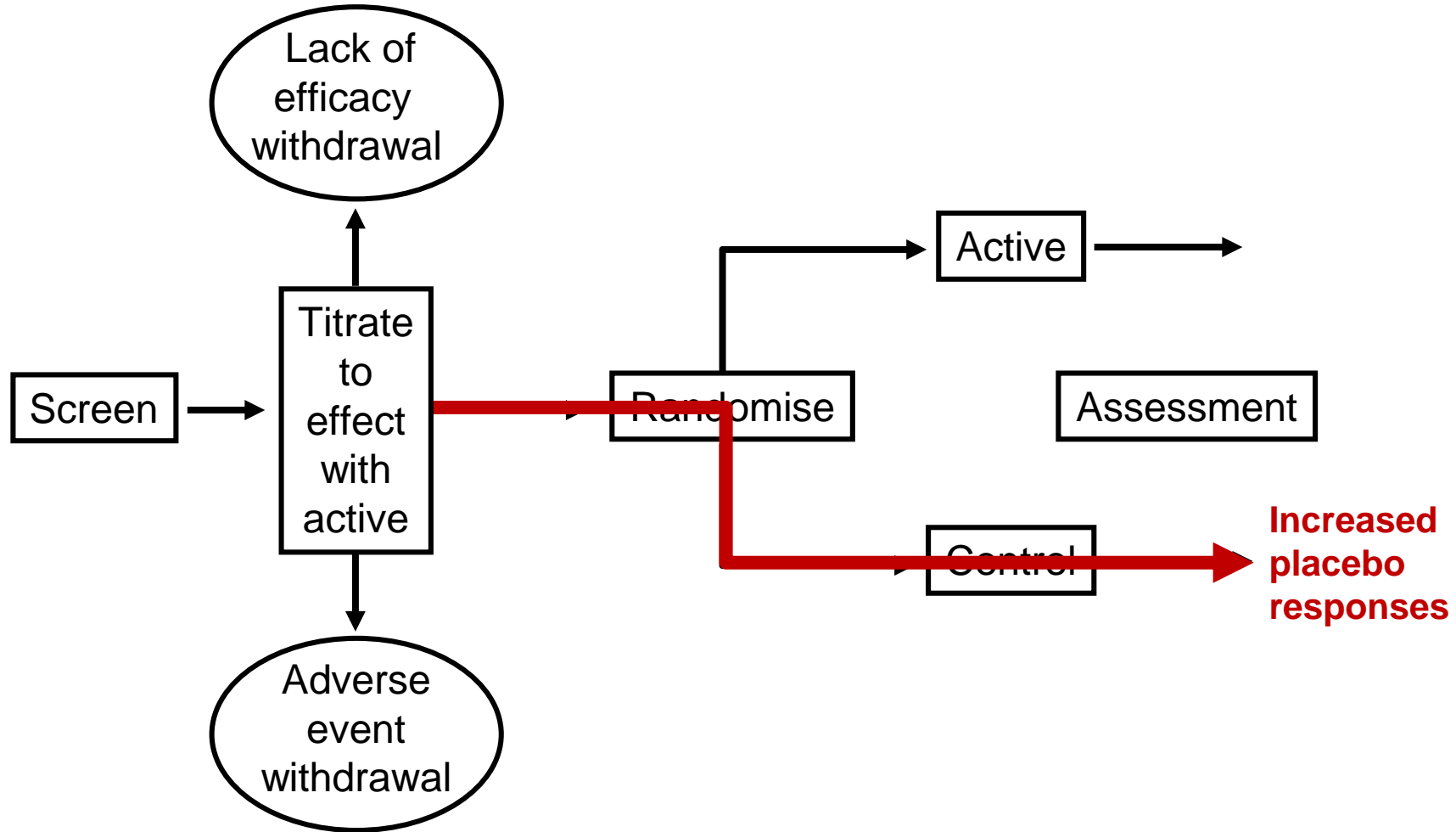
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Placebo responders and nonresponders can be identified *a priori*

# Activation likelihood estimation (ALE) meta-analysis



# Enriched Enrolment with Randomized Withdrawal



# Evidence from basic and clinical research

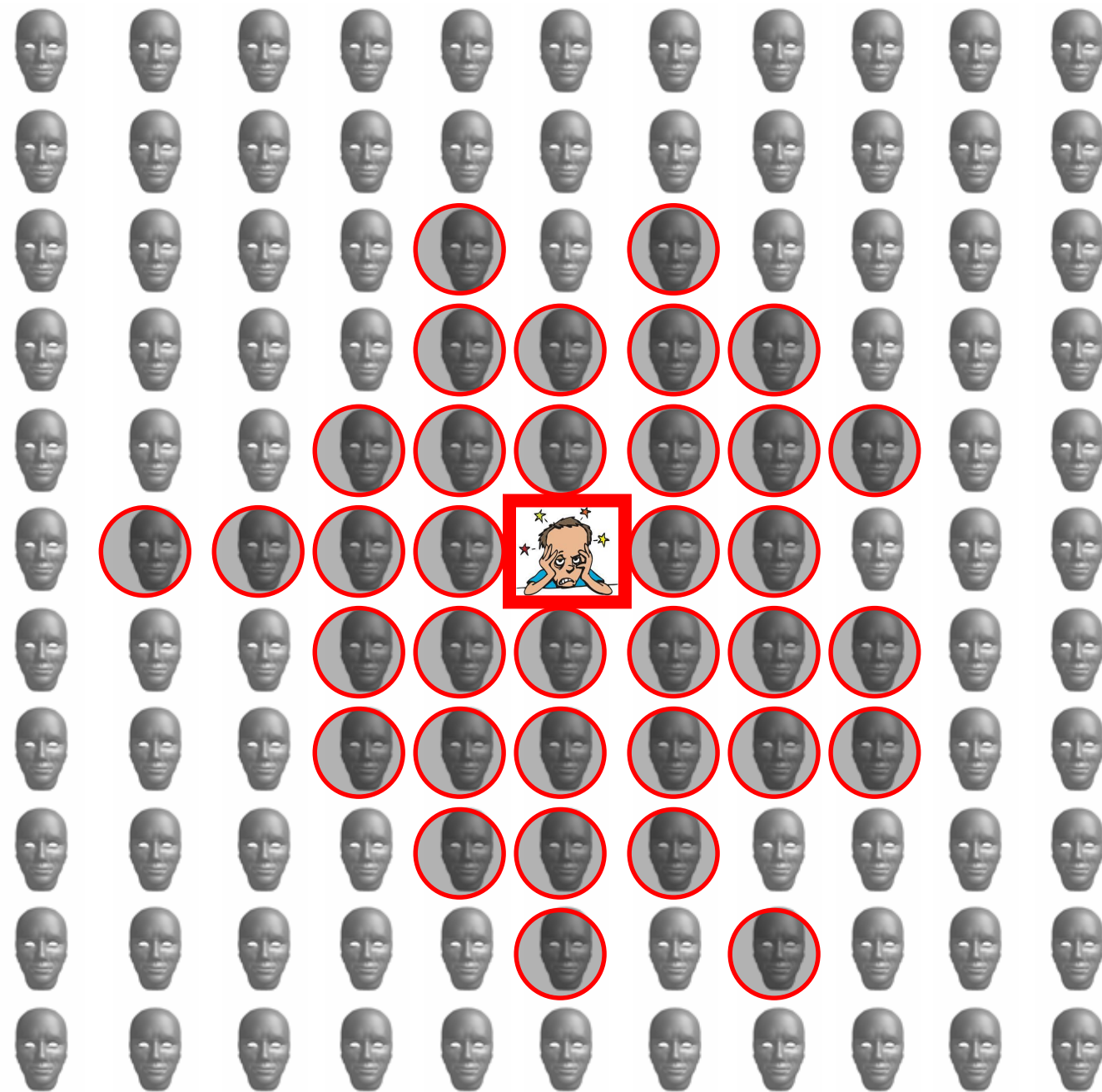
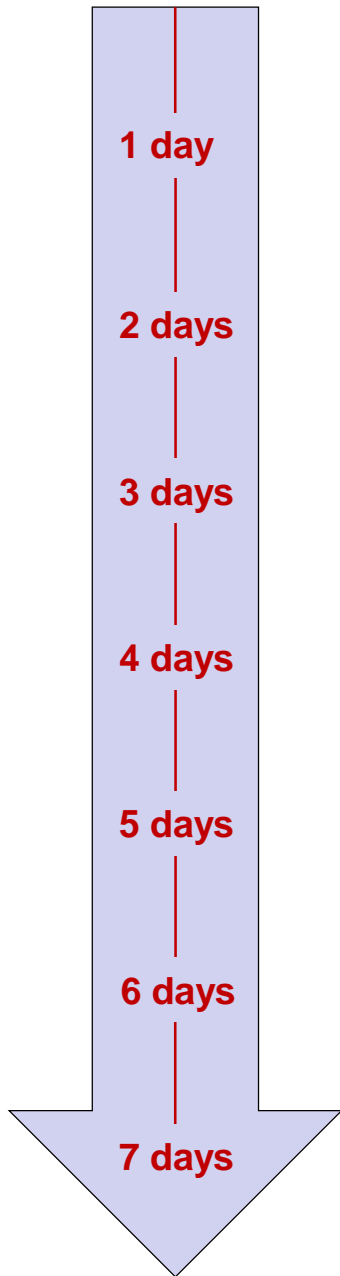
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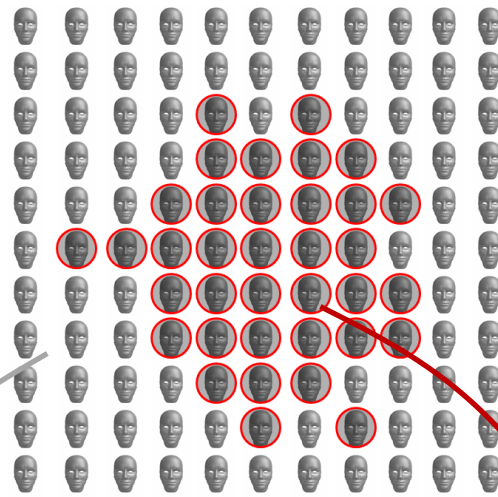
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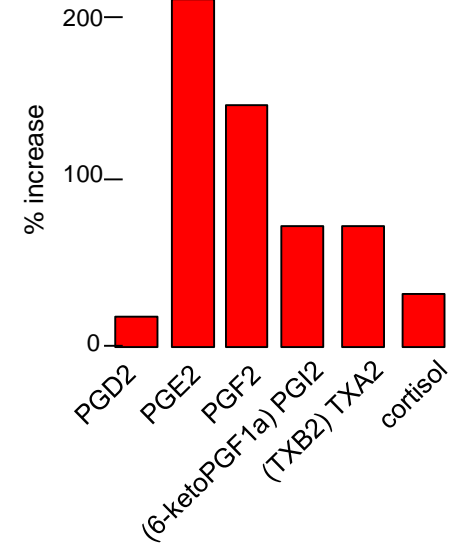
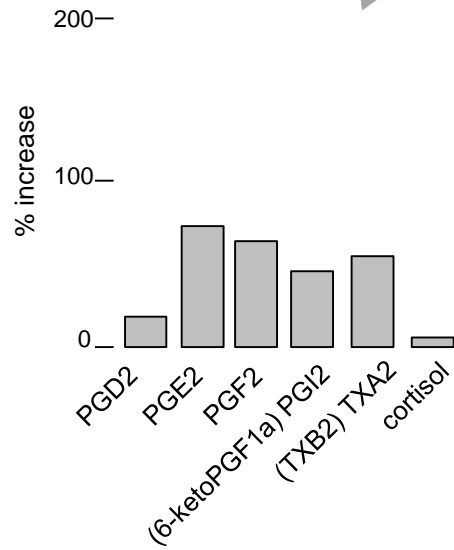


Benedetti et al (2014) *Pain*

 **52%**  
**Not informed**  
(no expectations)



**86%**   
**Socially infected**  
(negative expectations)



Benedetti et al (2014) *Pain*  
Benedetti (2014) *Neuron*  
Benedetti et al (2016) *Lancet Neurol*

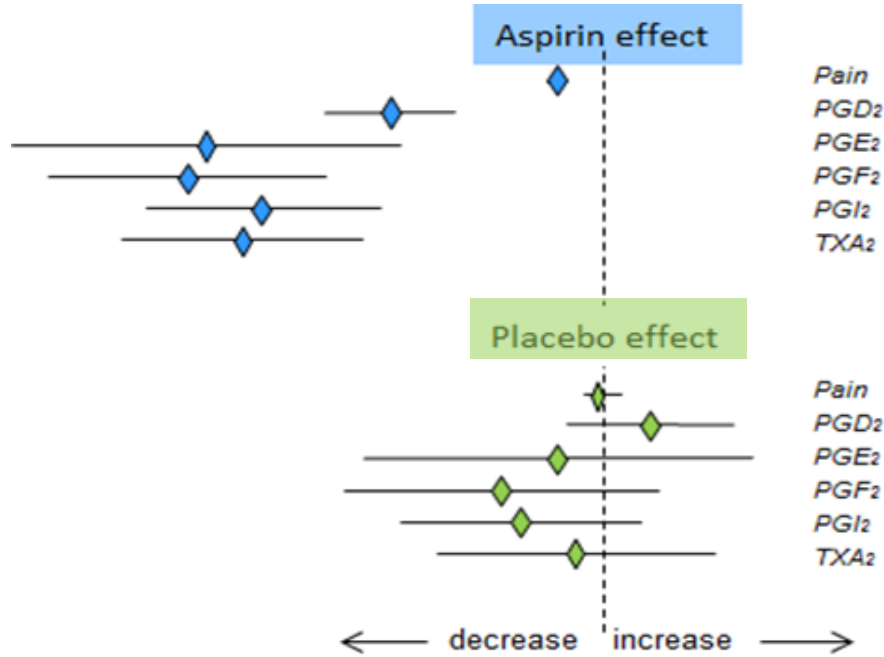


**52%**  
**Not informed**  
(no expectations)

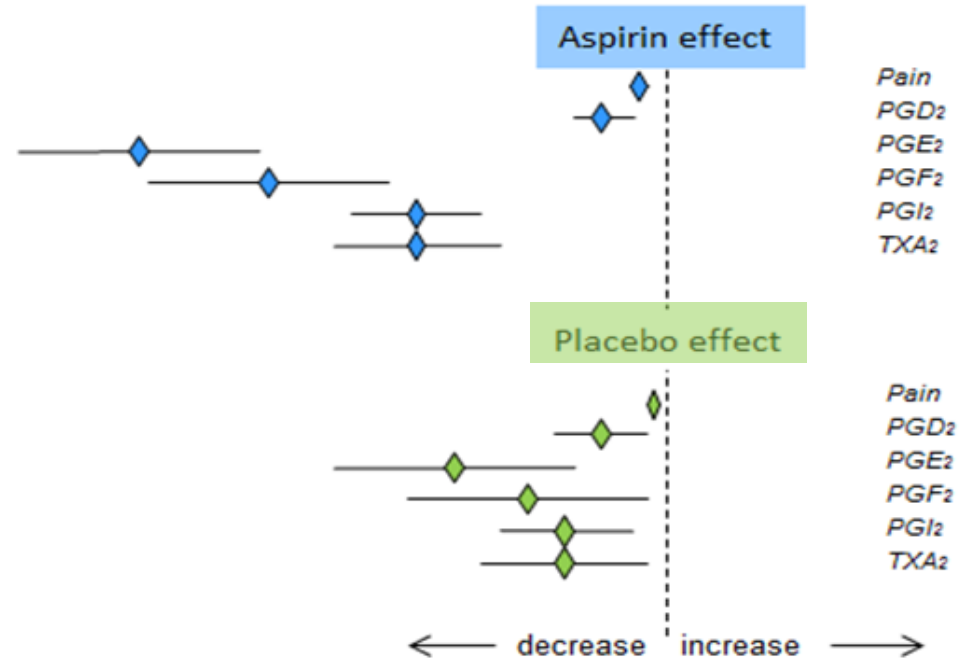


**86%**  
**Socially infected**  
(negative expectations)

**aspirin vs placebo**



**aspirin vs placebo**  
**with a pre-existing nocebo effect**





# Evidence from basic and clinical research

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Placebo non-responder



Placebo responder



## Personality



**Suggestibility**  
**Hypnotic susceptibility**  
*De Pascalis et al 2002*  
*Derbyshire and Oakley 2013*  
*Huber et al 2013*

**Optimism**  
**Pessimism**  
*Geers et al 2005, 2007, 2010*

**Dopamine-related  
personality traits  
(sensitivity to incentives  
and rewards)**  
*Schweinhardt et al 2009*

**Ego-resiliency**  
**Altruism**  
**Angry hostility**  
*Pecina et al 2013*

## Placebo non-responder



25 -

Pain tolerance (minutes)

15 -



DAY1 DAY2

**PLA**

## Learning...

← ...can create placebo responders and non responders in the lab →

Matching or mismatching what patients expect and what they get

## Placebo responder

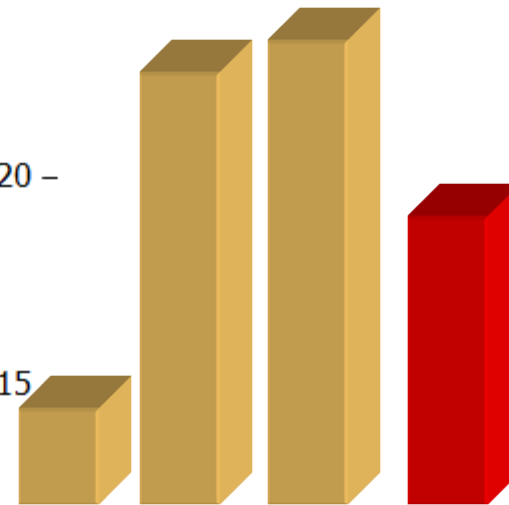


25 -

25 -

20 -

15 -



DAY1 DAY2 DAY3 DAY4

**Exp ANA** **Exp ANA** **PLA**  
**Get ANA** **Get ANA**

20 -

15 -



DAY1 DAY2 DAY3 DAY4

**Exp ANA** **Exp ANA** **PLA**  
**Get No ef** **Get No ef**

# **Evidence from basic and clinical research**

## **CONCLUSIONS**

**Patients' expectations should be assessed in all clinical trials**

**Drug history should be assessed carefully to ascertain possible learning effects**

**Communication across participants should be avoided**

**Future research should be aimed at better identifying placebo (non)responders**

# Thanks to:

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