Sei Secoli di Storia

Ospedale San Giovanni di Dio
di Firenze
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Trial clinici vs real world data in neurologia: Effetto placebo e nocebo

Gaetano Zaccara
Ospedale S. Giovanni di Dio
Firenze

Firenze, 7 aprile 2018

St Jerome writing. *Circa* 1604 (oil on canvas)
Michelangelo Merisi da Caravaggio (1571–1610). Galleria Borghese, Rome, Italy

Salmo 116

Placebo effect can benefit organ functioning and the overall health of the individual, though the healing power of belief, positive expectations and conditioning processes (Pacheco-Lopez et al, 2006)

Placebo, placebo effect and answer to placebo

- …When a drug is administered to a patient a clinical improvement may take place. This may be due to the specific effect of the drug or due to other factors, such as the spontaneous remission of the disease, statistical artefacts such as regression to the mean, subjective reporting bias, and the psychosocial context surrounding the therapeutic act (Fabrizio Benedetti).
- To isolate and measure the various components of the therapeutic ritual, researchers need to replace the active drug with an inactive substance (placebo) in controlled experiments.

Placebo effect in diseases other than epilepsy

- **Pain is the area that has been most investigated in placebo studies**. Expectation about therapeutic benefit, can produce a real analgesic effect via different neurochemical systems. There is a selective activation of either endogenous oppioid or cannabinoid receptors.
- **Parkinson's disease is another model for understanding neurobiology of placebo responses.**

- **Neuroimaging studies** demonstrate that placebo responses activate the same brain regions (ventromedial prefrontal cortex, and orbitofrontal cortex) across different conditions.

Benedetti et al., Lancet Neurol. 2016 pii: S1474-4422(16)00066-1.

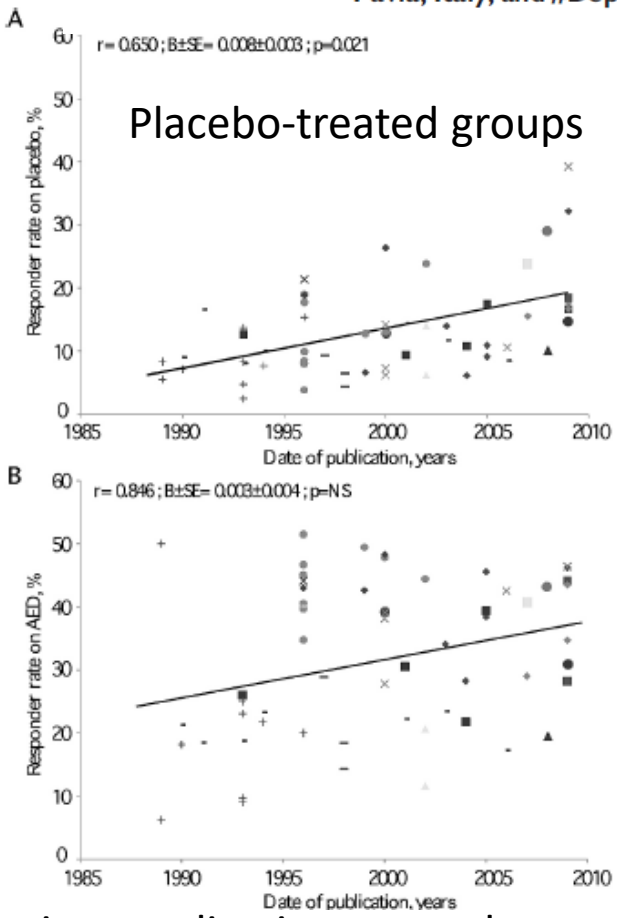
Extent of placebo response in epilepsy patients	
Author	**Magnitudo of placebo response**
Meta-analyses of randomized clinical trials	
Rehims et al., 2011	**9.9% ± 4.6%**
Gueckt et al., 2010	**12.5% 95CI=10.3-14.9%**
Zaccara et al., 2015	**15.2 95% CI= 13.3-17.1%; range 0-39%**
Patients exposed to medical devices	
Vagus et al., 1995	**13%**
Bae et al., 2011	**15.8%**
Morrell et al., 2011	**27%**
De Giorgio et al., 2013	**21%**
Placebo in surgery	
Penfield and Steelman, 1947	**31% (5 out 16)**

Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis

Epilepsia. 2011 ;52(2):219-33

*†‡§Sylvain Rheims, ¶Emilio Perucca, #Michel Cucherat, and *†‡§Philippe Ryvlin

*Hospices Civils de Lyon, Department of Functional Neurology and Epileptology, Institute for Children and Adolescents with Epilepsy (IDEE), Lyon, France; †INSERM, U1012, Centre de Recherche en Neurosciences de Lyon, TIGER, Lyon, France; ‡CNRS, UMR5292, Centre de Recherche en Neurosciences de Lyon, TIGER, Lyon, France; §Université de Lyon, Lyon, France; ¶Clinical Pharmacology Unit, Institute of Neurology IRCCS C. Mondino Foundation, Clinical Trial Center, University of Pavia, Pavia, Italy; and #Department of Clinical Pharmacology, Université Lyon 1, Lyon, France

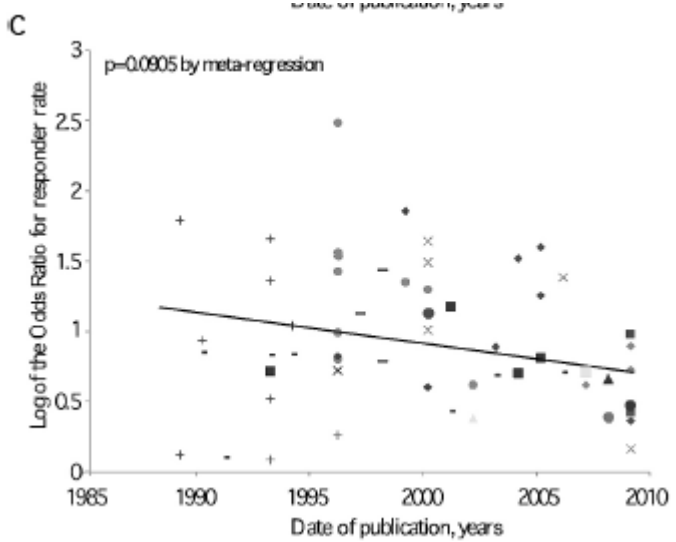


Placebo-treated groups

Active medication-treated groups

- Brivaracetam
- Carisbamate
- Divalproex sodium
- Eslicarbazepine acetate
- Gabapentin
- Lamotrigine
- Lamotrigine-XR
- Levetiracetam
- Levetiracetam-XR
- Losigamone
- Oxcarbazepine
- Pregabalin
- Remacemide
- Retigabine
- Rufinamide
- Tiagabine
- Topiramate
- Vigabatrin
- Zonisamide

Treatment effect



Relationships between responder rates and year of trial publication.

Which factors may influence placebo effect in clinical studies in epilepsy patients?

- **Characteristics of recruited patients**
  - Four clinical features significantly associated , in multivariate analyses, with **lower** placebo response: history of 7 or more prior lifetime AEDs, a high baseline seizure frequency, prior epilepsy surgery, and higher age at diagnosis
- **Characteristics of RCTs**
  - Inclusion of patients from different geographical areas
  - Methods of assessment (responder rate assessed for all duration of double-blind phase or restricted to maintenance phase only)
  - Number of arms of included studies

Rheims et al., 2011; Schmidt et al., 2013; Zaccara et al., 2015

Which mechanisms of placebo effects may be at work in epilepsy patients?

- Neurobiological studies on the placebo response in epilepsy are not available. Suggested neurochemical mechanisms include activation of endogenous opioid pathways. Neuropeptides have an important role in modulating seizures and epilepsy
- Regression to the mean
- Spontaneous fluctuations of seizure frequency as part of the patterns of epilepsy observed in several studies
- Positive expectations of patients which may generate a subjective feeling of improvement which do not correspond to a real seizure reduction
- Unrecognized psychogenic nonepileptic seizures.
- Intentional or unintentional false reporting by patients or caregivers eager to please the investigator.
- Expectations from investigators which may influence a patient's reporting of seizures.

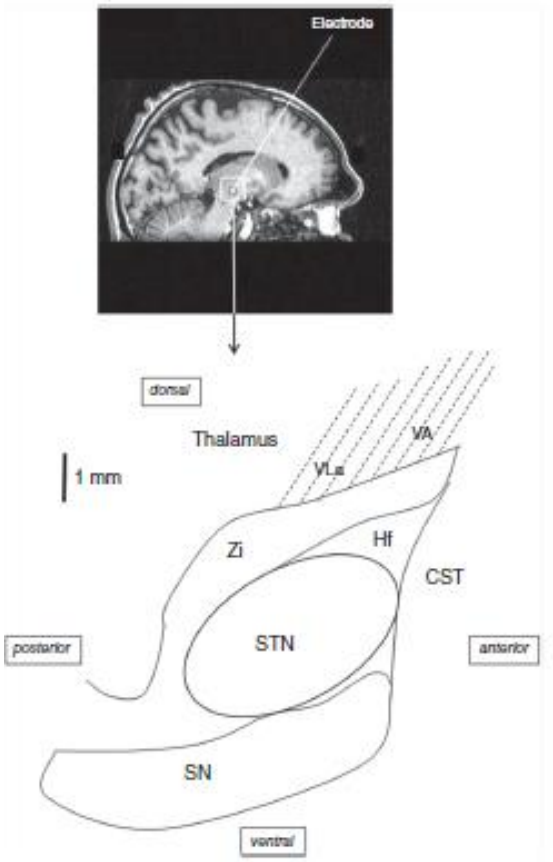
Particolare della *Scuola di Atene* di Raffaello
Platone che indica con il dito proteso verso l'alto la realtà del mondo delle idee e Aristotele invece tende la mano sulle realtà materiali.

Placebo effects are interpretable as the results of the brain processing information.

Teaching neurons to respond to placebos

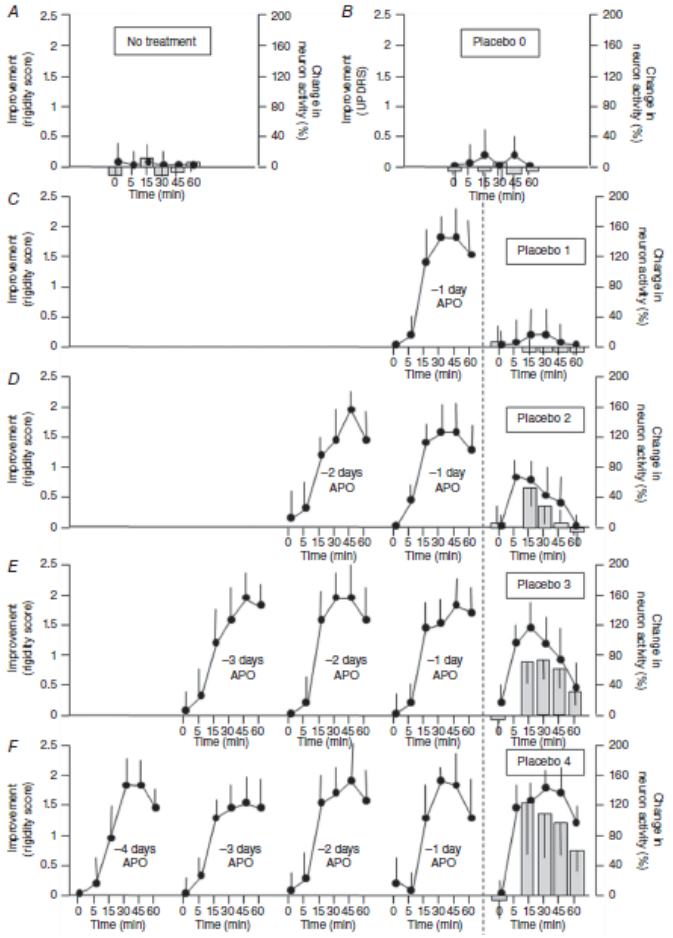
Fabrizio Benedetti[1,2], Elisa Frisaldi[1], Elisa Carlino[1], Lucia Giudetti[3], Alan Pampallona[3], Maurizio Zibetti[1], Michele Lanotte[1] and Leonardo Lopiano[1]

J Physiol 594.19 (2016) pp 5647–5660



Arm rigidity (black circles) is expressed as clinical improvement of rigidity score

Thalamic neuron activity (grey columns) is expressed as the percentage increase in firing rate after placebo administration

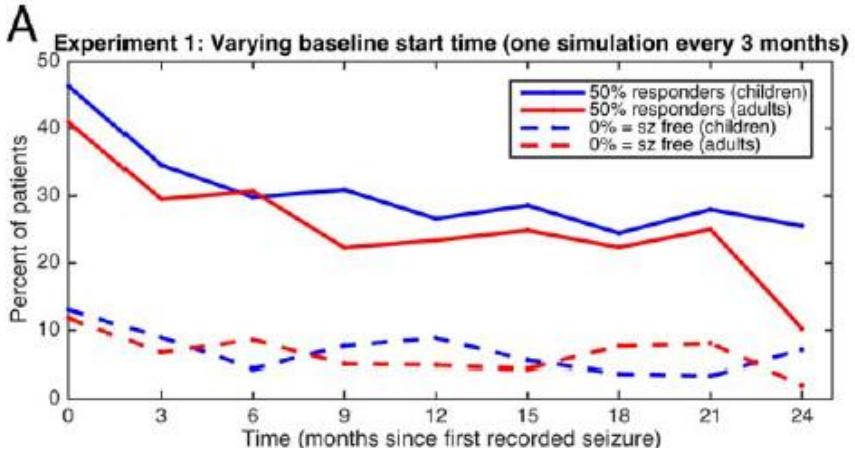


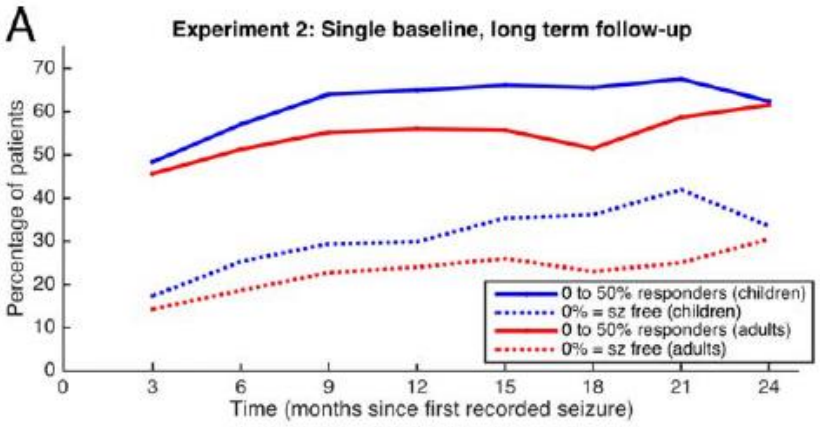
Comparisons across six groups of patients for both clinical and electrophysiological data

Confusing Placebo Effect with Natural History in Epilepsy: A Big Data Approach

Daniel M. Goldenholz, MD, PhD,[1] Robert Moss, BS,[2] Jonathan Scott, BS,[3]
Sungyoung Auh, PhD,[4] and William H. Theodore, MD[1]

ANN NEUROL 2015;78:329–336



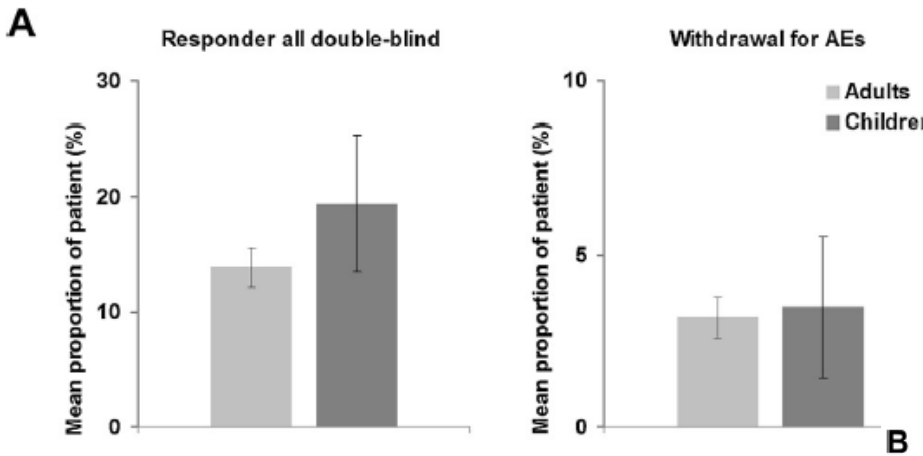


Although prior studies attribute placebo arm improvement to various factors, we found evidence of persistent ongoing improvement, even in the absence of a true placebo. This may reflect underlying disease processes, inadequate outcome measures, or both.

Adverse events, placebo and nocebo effects in placebo-treated paediatric patients with refractory focal epilepsies. Analysis of double-blind studies

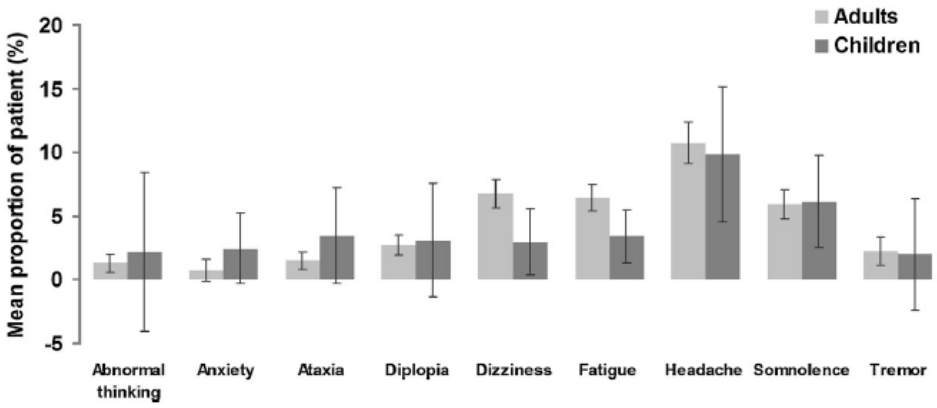
Epilepsy Res. 2014;108:1685-93.

Gaetano Zaccara[a,*], Fabio Giovannelli[a,b], Valentina Franco[c,d], Massimo Cincotta[a], Luciana Tramacere[a], Alberto Verrotti[e]



Comparison between pediatric and adult patients: Proportion of responders (patients with a ≥ 50% reduction of their total seizure frequency during all double-blind phase compared to baseline), proportion of patients withdrawing due to adverse effects

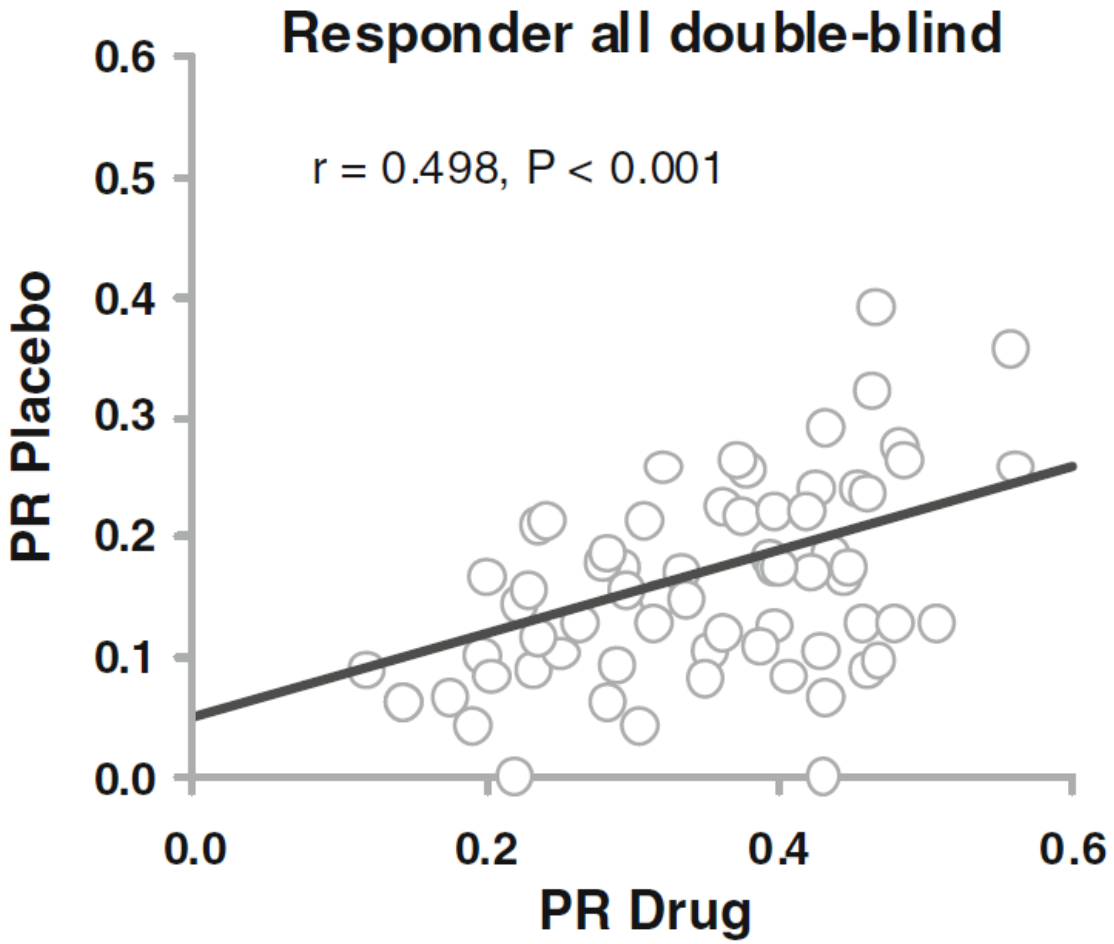
Proportion of patients who had specific predefined AEs.



Adverse events of placebo-treated, drug-resistant, focal epileptic patients in randomized controlled trials: a systematic review

Gaetano Zaccara · Fabio Giovannelli · Massimo Cincotta · Giulia Loiacono · Alberto Verrotti

J Neurol (2015) 262:501-515



Relationships between placebo and active treatment for all outcome measures analyzed

The Need for Randomization in Animal Trials: An Overview of Systematic Reviews

Jennifer A. Hirst[1*], Jeremy Howick[1*], Jeffrey K. Aronson[1], Nia Roberts[2], Rafael Perera[1], Constantinos Koshiaris, Carl Heneghan[1]

PLOS | ONE June 2014 | Volume 9 | Issue 6 | e98856

Double-Masked, Placebo-Controlled Study of Intravenous Levetiracetam for the Treatment of Status Epilepticus and Acute Repetitive Seizures in Dogs

B.T. Hardy, E. E. Patterson, J.M. Cloyd, R.M. Hardy, and I.E. Leppik

J Vet Intern Med 2012;26:334–340

Nocebo effect

- ✓ The nocebo effect is explained by patient-related psychological factors such as negative expectations, conditioning of adverse reactions on medication, and personality traits (eg, somatization, anxiety) and contextual factors such as negative suggestions of the physician.
- ✓ Moreover, the ascertainment strategy of adverse effects influences the tolerability profile of drugs.

Contents lists available at ScienceDirect

Epilepsy & Behavior

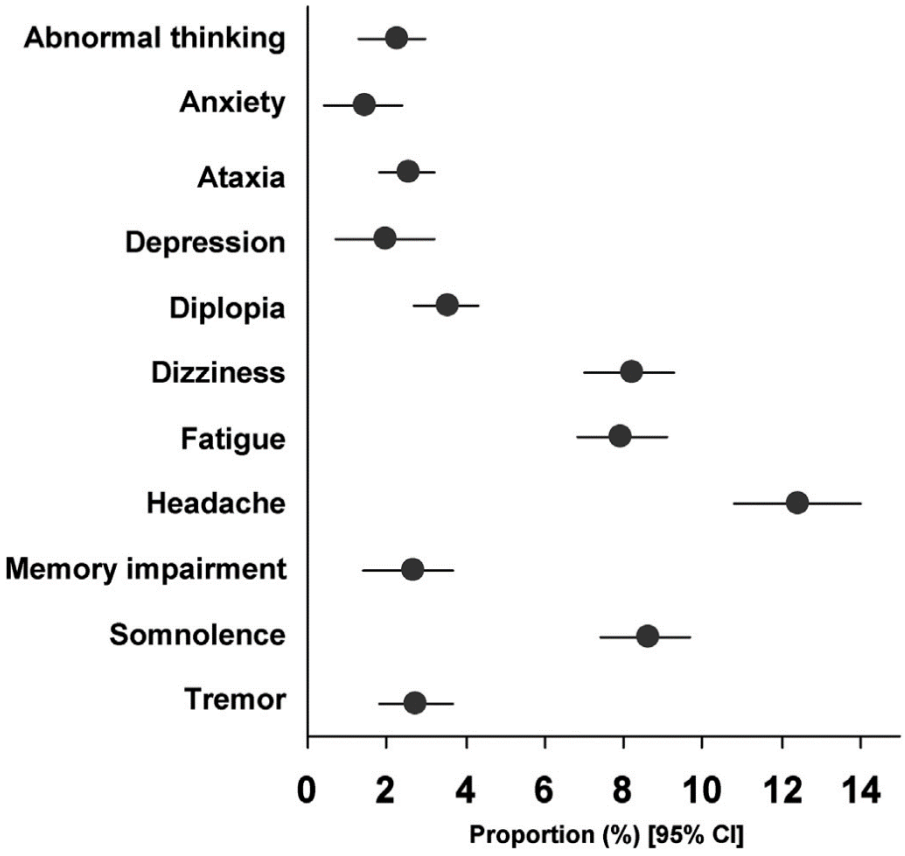
journal homepage: www.elsevier.com/locate/yebeh

Review

Placebo and nocebo responses in drug trials of epilepsy

Gaetano Zaccara [a,*], Fabio Giovannelli [a,b], Dieter Schmidt [c]

Epilepsy Behav. 2015 Feb;43:128-34



Proportion of placebo-treated patients with some selected adverse events (from a meta-analysis of 79 studies with a total number of 6793 patients treated with placebo)

Proportion of **patients withdrawing because of intolerable AEs was 3.9%,** while 60.3% complained of some AEs during the study.

Adverse events of placebo-treated, drug-resistant, focal epileptic patients in randomized controlled trials: a systematic review

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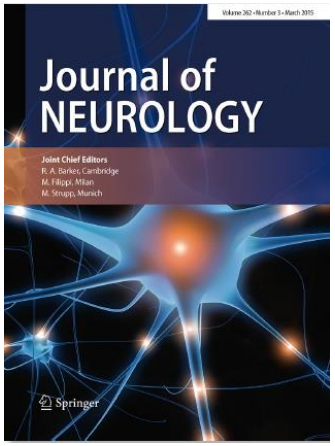

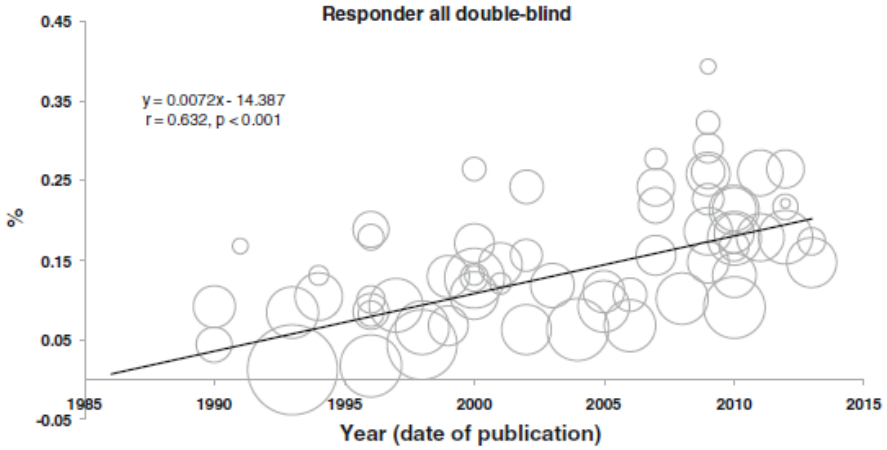

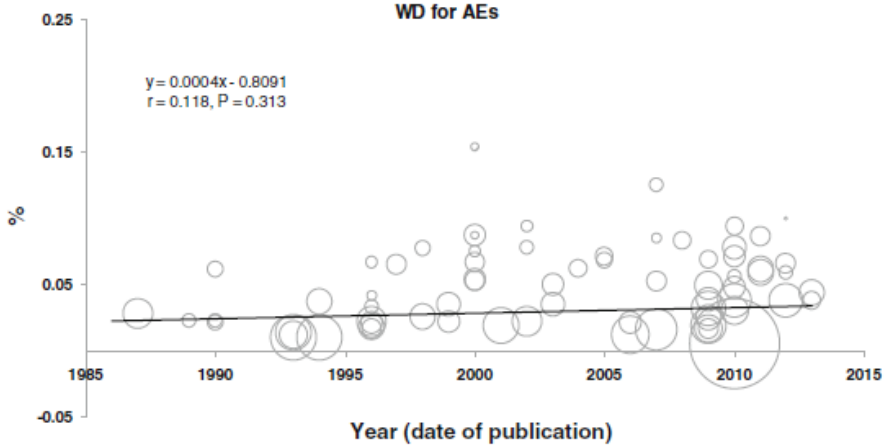

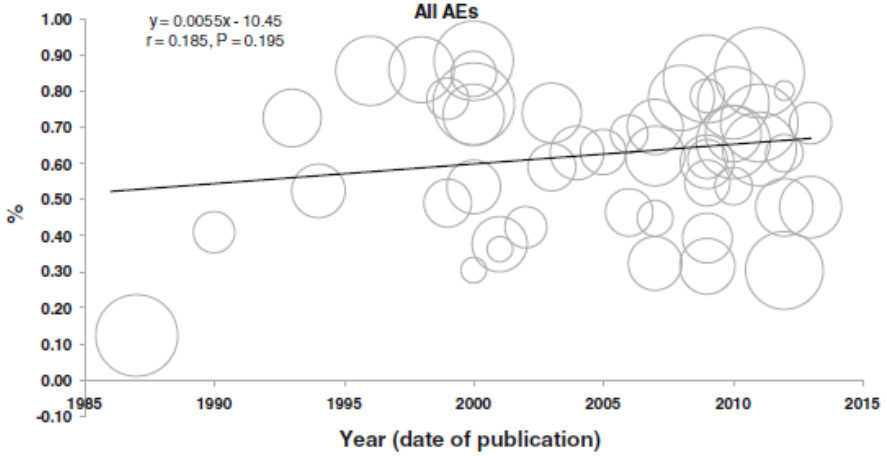

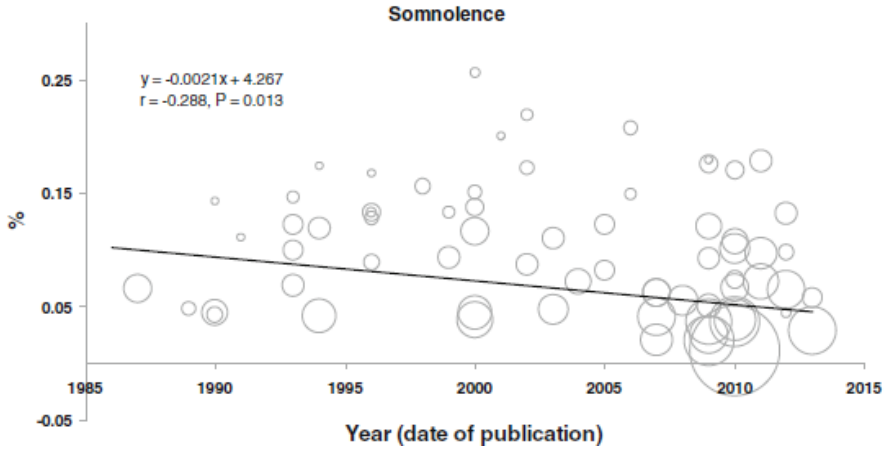

Adverse events of placebo-treated, drug-resistant, focal epileptic patients in randomized controlled trials: a systematic review

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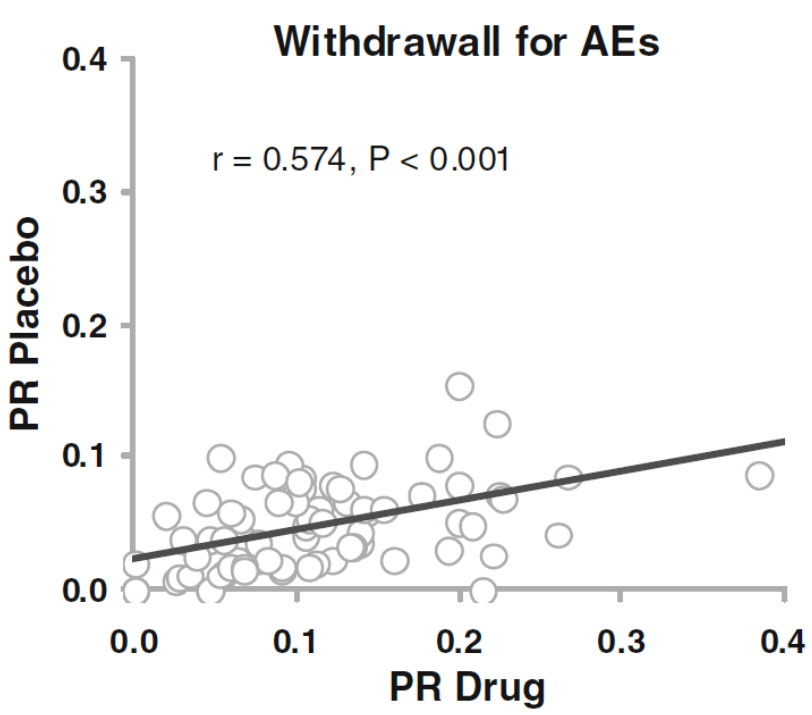
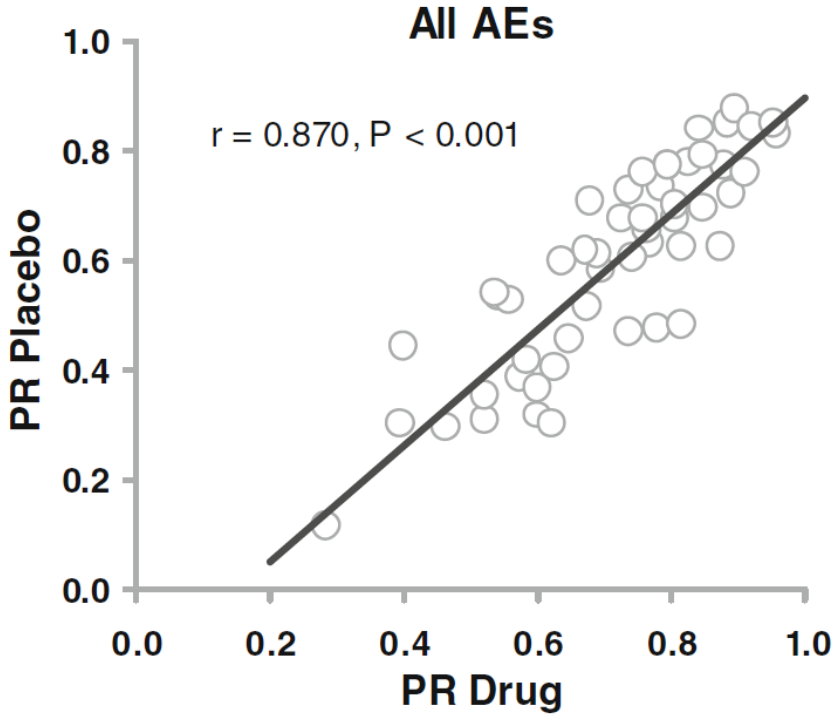
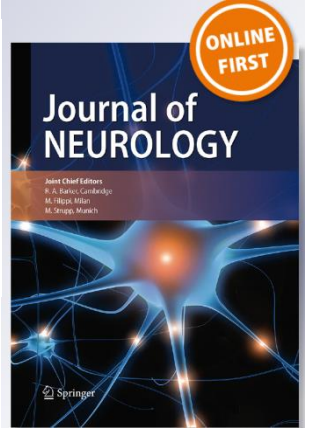




Relationships between placebo and active treatment for all outcome measures analyzed

Analysis of nocebo effects of antiepileptic drugs across different conditions

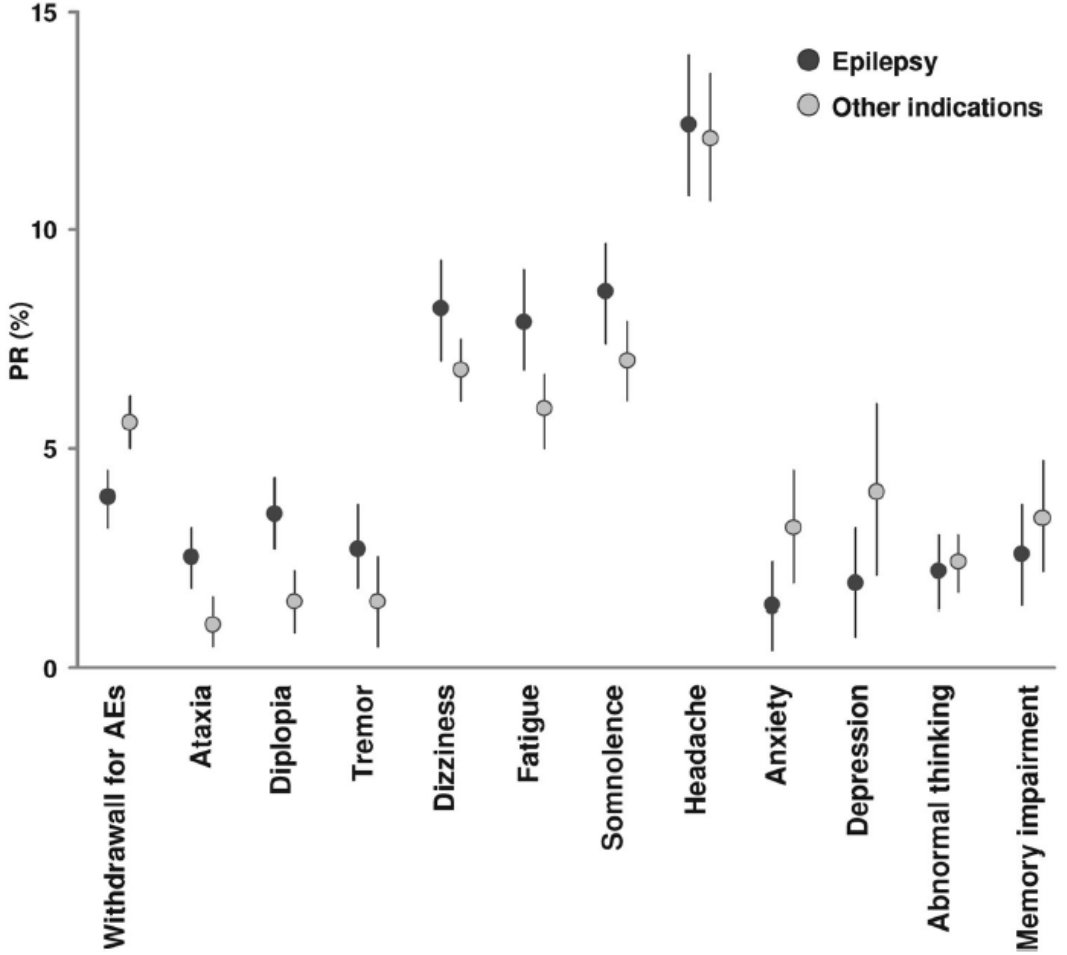
Gaetano Zaccara[1] · Fabio Giovannelli[1,2] · Filippo Sean Giorgi[3] · Valentina Franco[4] · Sara Gasparini[5]



One hundred-fifty-seven RCTs studying 13 AEDs.
A total of 13.500 patients randomized to placebo and 20.752 to active drug.

Proportion of placebo-treated patients reporting each of selected adverse events in the various conditions for which RCTs exploring efficacy of AEDs have been performed.

All conditions except epilepsy have been pooled



A systematic review of adverse events in placebo groups of anti-migraine clinical trials

Martina Amanzio [a,b,*], Luca Latini Corazzini [a,b], Lene Vase [c], Fabrizio Benedetti [d,e]

PAIN® 146 (2009) 261–269

Bar chart plots of the percentage of adverse effects in the placebo arms

1) NSAID (white bars)
2) Triptan grey bars,
3) Anticonvulsant trials (black bars)

Cosa è speculare rispetto all'effetto placebo (o nocebo) ?

- La proiezione temporale non ci fa riconoscere come conseguenti al farmaco effetti che invece sono probabilmente da questo causati
- L'esempio dell'induzione enzimatica

Potential drug interactions of enzyme-inducer antiepileptic drugs in patients with epilepsy

At the date 1/1/2016, of the 25.996 patients identified as affected by epilepsy in Tuscany (prevalence of 6.9/1.000), 9221(35.5%) were treated with at least one traditional EIAEDs.

Enzyme inducer AED	Number of patients identified as affected by epilepsy and treated with at least one enzyme inducer (%)
Carbamazepine	5.341 (51,4)
Phenobarbital/ Primidone	3.961 (38,1)
Phenytoin	1.098 (10,6)
Total number of treatments	10.400 (100) §

Zaccara et al., 2018

Most frequent associations between traditional EIAEDs and the identified inducible NON-AEDs,

ATC classification	Level of interaction: 1, Major		Level of interaction: 2, Moderate	
	Number of patients	Percentage	Number of patients	Percentage
A - Alimentary tract and metabolism	440	4.8%	1.081	11,7%
B Blood and blood forming organs	720	7.81%	417	4.5%
C – Cardiovascular sysytem	1.108	12,02%	1.008	10,9%
H - Systemic hormonal preparations	192	2.08%	67	0.6 %
N - Nervous system (AEDs excluded)	270	2.93 %	811	8.8%
Total	2730	29.6 %	3384	36.7%

Grazie per l’attenzione