The Placebo Effect in Epilepsy Trials: Where Does it Come From?

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Outline

✓ Definitions
✓ Magnitude of the improvement on placebo in epilepsy trials
✓ Causes, correlates and predictors
Definitions

Placebo effect
Any effect attributable to a pill, potion or procedure, but not to its pharmacodynamic and specific properties

Placebo-associated improvement
Any clinical improvement which occurs during administration of placebo (for example, in the placebo arm compared with baseline)

1Wolf S, Pharmacol Rev 1959;11:689-704
"This is a 'placebo' line. It serves no purpose but it makes us feel good."
How Large is Placebo-Associated Improvement? Responders Rates on Placebo in Recent RCTs in Adults with Refractory Partial Seizures

Trials published in 2008-2009

Placebo responder rate (%)

- Elger (RUF)
- Ben-Menachem (ESL)
- Biton (RUF)
- French (BRV)
- Sperling (CRS)
- Chung (LCM)
- Brodie (RTG)
- Brodie (RUF)
- Elger (ESL)
- Baulac (PGB,LTG)
- Sperling (CRS)
- Gil Nagel (ESL)
- Halasz (LCS)
- Wu (LEV)
- Peltola (LEV)
- Lee (PGB)
- Lu (ZNS)
- Xiao (LEV)
How Large is Placebo-Associated Improvement?

Responder Rates on Placebo in Recent RCTs in Adults with Primarily Generalized Tonic Clonic Seizures

Placebo responder rate (%)

- Biton 1999 (TPM): 17%
- Biton 2010 (LTG XR): 32%
- Berkovic 2007 (LEV): 45%
- Biton 2005 (LTG): 49%*

* calculated over maintenance phase
How Large is Placebo-Associated Improvement? An Analysis of Three Epilepsy Trials in 28 Dogs

Decrease in Seizure counts vs Baseline

50% Seizure Reduction Rates

Munana et al, J Vet Int Med 2010;24:166-70
Possible Causes of Placebo-Associated Improvement in Epilepsy

- Chance
- Regression to the mean, natural history
- Patient’s bias (tendency to “please” caregivers, desire to enter or to remain in the trial)
- Observer’s bias (unconscious tendency to find what one expects, or hopes for)
- Higher level of care during the trial
- Emotional / psychological influences on seizure susceptibility
Changes in Seizure Frequency on Placebo Occur in Both Directions

Percentage of Patients with Increased Seizures in the Placebo Arm (Trials in Partial Epilepsy)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiagabine trials (n=275)</td>
<td>49%</td>
</tr>
<tr>
<td>Topiramate trials (n=216)</td>
<td>48%</td>
</tr>
<tr>
<td>Levetiracetam trials (n=310)</td>
<td>45%</td>
</tr>
</tbody>
</table>

Between 3 and 9% of patients overall showed a greater than 100% increase in seizure frequency (vs baseline)

Factors Reported to Influence Placebo-associated Improvement in Epilepsy Trials

- ✓ Seizure type (generalized tonic-clonic vs partial) or frequency
- ✓ Age
- ✓ Number of underlying AEDs
- ✓ Duration of the assessment period
- ✓ Method used to calculate response
- ✓ Year in which trial was conducted
- ✓ Location where trial was conducted
PlaceboResponderRatesinPartialEpilepsyareGreaterinChildrenThaninAdults:AMetanalysisof32RCTs

Rheims et al, PLoS Medicine 2008;5:e166
Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis

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Factors Correlating with Placebo-Associated Responder Rates: A Metanalysis of 63 Trials in >14,000 Adults with Partial Epilepsy

Responder rates on placebo:

✓ Tend to increase with increasing duration of treatment (p=0.059)

✓ Are higher during maintenance than during entire treatment period (p=0.005)

✓ Increased over the years (p=0.001).

✓ Are higher with LOCF than with completer’s analysis (p<0.001)

✓ Seem to show geographical variation

Rheims et al, Epilepsia 2011;52:219-233
Time Course of Seizure-Free Days in Active and Placebo Arms from a Pooled Analysis of Pregabalin Trials in Partial Epilepsy

Ramsay et al, Epilepsia 2009;50:1891-8
Placebo trials: \( n = 75, r = 0.45, p < 0.001 \)

Has Placebo Response in Epilepsy Trials Increased over the Years?

Rheims et al, Epilepsia Epilepsia 2011;52:219-233
Has Effect Size in Active Treatment Arms of Epilepsy Trials Decreased over the Years?

Rheims et al, Epilepsia 2011;52:219-233
Is Increase In Placebo Responder Rates Over Time Related to Increase in Number of Study Sites?
An Analysis of Trials in Pediatric Depression

Bridge et al, Am J Psychiatry 2009; 166:42–49
Does Geographical Variation Contribute?
Observations from a Recent Add-on Trial comparing Pregabalin, Lamotrigine and Placebo

“…trial sites in one country enrolled many patients (91 out of the 433 total population) new to this level of medical care and showed an unusually enhanced response in the placebo group. … their responses to placebo were nearly three times that seen in patients from other countries (53% vs 19% seizure reduction...)”

“…The factoring of this unusually large placebo effect with regression to mean effect and Hawthorne effect has undoubtedly contributed to lack of efficacy versus placebo for these two established AEDs…”

Baulac et al, Epilepsy Res. 2010; 91:10-9
How Large is Placebo-Associated Improvement? Responder Rates on Placebo in Recent RCTs in Adults with Refractory Partial Seizures

Trials published in 2008-2009
Does a true placebo effect exist in epilepsy?
"We found little evidence in general that placebos had powerful clinical effects. Although placebo had no significant effects on objective or binary outcomes, they had possible small benefits in studies with continuous subjective outcomes and for the treatment of pain."

Some Neurotransmitters Associated with Placebo Responses Based on Data from Imaging Studies

- Opioid transmitters (pain studies)
- Dopamine (studies in Parkinson’s disease)
- Serotonin (studies in depression)

Diederich and Goetz, Neurology 2008;71:677-684
Behavioral/Systems/Cognitive

A Link between Serotonin-Related Gene Polymorphisms, Amygdala Activity, and Placebo-Induced Relief from Social Anxiety

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Conclusions

- The causes underlying placebo-associated improvement in epilepsy trials are multifactorial.
- Available evidence does not allow to disentangle the relative contribution of individual factors.
- No reliable predictors exist of being responder on placebo at individual level – some correlates identified at population level are intriguing.
- Better understanding of factors influencing placebo-associated improvement is important to improve the design of epilepsy trials.
Sagital view of cingulate increases during placebo administration in hemodynamic imaging studies in analgesics studies (■), acupuncture analgesia (■), emotional processing/anxiolysis (■).

Faria et al, Eur Neuropsychopharmacology 2008; 18:473-85
Relative Risks for Being a Responder (Drug vs Placebo) for 5 AEDs: Partial Epilepsy Trials, Children vs Adults

Rheims et al, PloS Medicine 2008; 5:e166
Has Placebo Response Increased over the Years?
Trials in Schizophrenia

All trials (U.S. trials in black)
n = 31.  p<0.0018

U.S. trials only
n = 23.  p=0.0018

Chen et al, Pharm Statistics 2010;9:217-29
Time Course of Seizure-Free Days in Active and Placebo Arms from a Pooled Analysis of Levetiracetam Trials in Partial Epilepsy

French et al, Epilepsia 2005;46:1304-7
Comparison between Responders and Non-responders in the Placebo Arms of Levetiracetam Trials in Adults with Partial Seizures (n=904)

- Age of epilepsy onset was higher in responders than in non-responders (20.8 vs 15.2 years, p = 0.019)

- Responder rates were higher when there was one baseline AED compared with ≥2 or more (69.0% vs 45.6%, p=0.056)
Has Placebo Response Increased over the Years?
Trials in Major Depression

Placebo trials: n=75, r=0.45, p<0.001

Walsh et al, JAMA 2002:287:1840-7