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Review article

Response to placebo in clinical epilepsy trials—Old ideas and new insights

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SUMMARY

Randomized placebo-controlled trials are a mainstay of modern clinical epilepsy research; the success or failure of innovative therapies depends on proving superiority to a placebo. Consequently, understanding what drives response to placebo (including the "placebo effect") may facilitate evaluation of new therapies. In this review, part one will explore observations about placebos specific to epilepsy, including the relatively higher placebo response in children, apparent increase in placebo response over the past several decades, geographic variation in placebo effect, relationship to baseline epilepsy characteristics, influence of nocebo on clinical trials, the possible increase in (SUDEP) in placebo arms of trials, and patterns that placebo responses appear to follow in individual patients. Part two will discuss the principal causes of placebo responses, including regression to the mean, anticipation, classical conditioning, the Hawthorne effect, expectations from symbols, and the natural history of disease. Included in part two will be a brief overview of recent advances using simulations from large datasets that have afforded new insights into causes of epilepsy-related placebo responses. In part three, new developments in study design will be explored, including sequential parallel comparison, two-way enriched design, time to pre-randomization, delayed start, and cohort reduction techniques.

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Abbreviations: RCT, randomized clinical trial; TNS, trigeminal nerve stimulation; TMS, transcranial magnetic stimulation; VNS, vagal nerve stimulation; RNS, responsive neuro-stimulation; DBS, deep brain stimulation; LOCF, last observation carried forward; AED, anti-epileptic drug; SUDEP, sudden unexplained death in epilepsy; SPCD, sequential parallel comparison design; TED, two-way enriched design.

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1. Introduction

Epilepsy affects at least 2.2 million Americans, costs $9.5–$12.5 billion annually, and it has a 10-fold increased risk of sudden death compared to the general public (Institute of Medicine US, 2012). Approximately 30% of patients remain uncontrolled by anti-seizure drugs (Kwan and Brodie, 2000). Surgery for uncontrolled patients results in 13.5–92.5% seizure freedom (West et al., 2015), but only 44–45% achieve long-term seizure freedom (Englot et al., 2012; Schmidt and Stavem, 2009). In the face of these challenges, modern clinical epilepsy trials frequently employed a comparison of therapy to placebo as a control. Strangely, the effects of the placebo arm often are quite positive, making an efficacious therapy difficult to validate.

The term placebo had been in use since 1785 or earlier; however, the modern redefinition came with Beecher(Kaptchuk, 1998). He implied it to mean a non-therapeutic intervention of any kind (Beecher, 1961). The term "placebo effect", in turn, was popularized in part by Beecher's influential 1955 paper (Beecher, 1955). At the time, his review of 15 studies concluded that placebos possessed, on average, 35.2% effectiveness. Interestingly, decades later, a re-interpretation of Beecher's original work suggested that the effectiveness he believed was related directly to the placebo was not a placebo effect at all (Kienle and Kiene, 1997). In fact, other effects accounted for all of the placebo improvements, such as added treatments, natural improvements, misquotations, and scaling bias. A notable omission from Beecher's original study – and many randomized controlled trials since then – is the percentage of patients who *worsen* with placebo treatment (Kaptchuk, 1998). A few years before Beecher's paper, a study was published on motion sickness remedies that showed no evidence of a placebo effect at all (Tyler, 1946). The study randomly assigned subjects on a boat to drug treatment, placebo, or no treatment. Interestingly, the no treatment arm (35%) and placebo arm (34%) had essentially equivalent levels of severe motion sickness. Such "no-treatment" arms are rarely used, but they can highlight effects of study design, such as regression to the mean and natural history of disease.

Within the last 60 years, varying definitions of placebo effects have been suggested (Beecher, 1961). In this review, we will adopt the approach of Kienle and Keine: "(1) A *placebo* had to be given. (2) The event had to be an *effect* of the placebo treatment, i.e., the event would not have happened without placebo administration. (3) The event had to be relevant for the disease or symptom, i.e., it had to be a *therapeutic* event (Kienle and Kiene, 1997)." Additionally, we define here the "placebo response" as any response observed during the trial in the placebo arm, regardless of cause. It is noteworthy that with these definitions, one must be careful not to mis-attribute "placebo effect" when one observes a "placebo response".

This review will provide the reader with an overview of important observations about placebos in epilepsy trials, the causes believed to influence placebo response, and new trial designs crafted to better control the placebo response.

2. Part 1: Observations about placebos in epilepsy

2.1. Magnitude of effect

Several meta-analyses of randomized controlled trials (RCTs) report on the responses to placebo in epilepsy. Estimates of the placebo response magnitude (for 50% responders) in drug trials range from 4 to 19% (Burneo et al., 2002; Cramer et al., 1999; Guekht et al., 2010; Rheims et al., 2008; Zaccara et al., 2015).

In device studies, a similar range exists for 50% responders. In a review of trials in transcranial magnetic stimulation (TMS), placebo responder rates were 16–20% (Bae et al., 2011). In trigeminal nerve stimulation (TNS), a phase II RCT found the 25 placebo-arm patients to respond at a rate of 21.1% (DeGiorgio et al., 2013). A trial of responsive neuro-stimulation (RNS) found 27% response rate in the 93 patients assigned to sham stimulation (Morrell, 2011). The large vagal nerve stimulation (VNS) trial found that the 60 patients assigned to placebo (in this case "low stimulation") had a 13% responder rate (Vagus et al., 1995). In a deep brain stimulation (DBS) RCT of 109 patients (54 stimulated, 55 control), the authors found no "statistically significant treatment group difference" for 50% responders during the blinded phase, but did not actually report the number (Fisher et al., 2010).

Seizure freedom rates in RCTs are much lower than the 50% responder rates: 8.2% for drug and 2.1% for placebo in one meta-analysis (Beyenburg et al., 2010). In another study, drug-treated seizure-free rates were 4.5% and 2.8% in children and adults, respectively; placebo-treated children and adults achieved rates of 0.6% and 0.4%, respectively (Rheims et al., 2008). Several studies raised the point that use of the last observation carried forward (LOCF) method (rather than using full completers) artificially increase seizure freedom rates and responder rates in both placebo and active drug-treated patients (Gazzola et al., 2007; Rheims et al., 2011).

Device trials reported 0% "placebo" seizure-free responders for TMS (Bae et al., 2011), TNS (DeGiorgio et al., 2013), RNS (Morrell, 2011), and VNS (Vagus et al., 1995). A randomized trial of DBS reported 1.8% (1 out of 55) "placebo" patients and 0% "active treatment" patients became seizure-free during the blinded phase (Fisher et al., 2010).

Taken altogether across drugs and devices, seizure freedom rates on placebo are quite low (0–2.8%), while 50% responder rates on placebo are quite a bit larger (4–27%).