

ENDGAMES

STATISTICAL QUESTION

The placebo effect

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Varenicline is used as a smoking cessation aid. Its efficacy and safety were assessed by a double blind, placebo controlled, randomised controlled trial. In total, 213 participants were randomised to varenicline and 218 to placebo. Treatment was for 12 weeks, and participants were followed up for 14 weeks after treatment.¹

The primary end point was continuous abstinence from smoking for the final four weeks of treatment (weeks 9 to 12). The observed treatment effect—the rate of continuous abstinence—was 59% in the varenicline group and 39% in the placebo group. The difference between the varenicline and placebo treatment groups in continued absence between weeks 9 and 12 was significant (relative risk 1.6 (95% confidence interval 1.32 to 1.87); $P < 0.001$).

Which one of the following statements best quantifies the placebo effect?

- The observed treatment effect in the placebo group.
- The difference in observed treatment effect between the varenicline and placebo groups.
- The difference in treatment effect between the placebo group and a conceptual natural history control group.
- The difference in treatment effect between the varenicline group and a conceptual natural history control group.

Answers

Answer *c* best quantifies the placebo effect.

The observed treatment effect in the varenicline group is made up of two components: the direct response to provision of the active therapeutic drug and non-specific treatment effects not directly ascribed to the active treatment. These non-specific effects include the placebo effect and the natural history of abstinence in users of smokeless tobacco (those users of smokeless tobacco who would have ordinarily achieved abstinence in the absence of any intervention). It is generally accepted that the placebo effect represents the patient's response to intervention, including the patient's response to a therapeutic ritual, subsequent response to observation and assessment, and

response to the patient-doctor interaction. No doubt there is a complex relation between these three components.

The placebo group acted as a control group, providing an estimate of the non-specific treatment effects—that is, the placebo effect together with the natural history of abstinence (*a* is false). The natural history of abstinence could be quantified by the proportion of users of smokeless tobacco who would achieve abstinence if randomised to a conceptual control group that received no intervention. Therefore, the difference in observed treatment effects between the placebo group and a conceptual natural history control group would estimate the placebo effect (*c* is true).

The absolute therapeutic benefit of varenicline is estimated by the observed treatment effect in the varenicline group over and above that in the placebo effect (*b* is false). The difference in observed treatment effects between the varenicline group and a conceptual natural history control group would represent the combined absolute therapeutic benefit of varenicline and the placebo effect (*d* is false).

The placebo effect can be observed in any medical encounter and not solely in clinical trials that incorporate a placebo treatment group. It is possible that the provision of any therapeutic regimen will elicit a placebo effect. The placebo effect may, however, be enhanced in clinical trials, when compared with routine clinical practice, because trial participants typically receive additional care and attention, and they may have increased expectations and feel privileged to have been invited to take part in clinical research. Although the placebo effect is generally held to exist, debate exists as to the magnitude of the treatment effect it represents.

Competing interests: None declared.

¹ Fagerström K, Gilljam H, Metcalfe M, Tonstad S, Messig M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. *BMJ* 2010;341:c6549.

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