

ENDGAMES

Placebo controlled trials

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Researchers assessed the efficacy of varenicline (a licensed cigarette smoking cessation aid) in helping users of smokeless tobacco to quit. A double blind placebo controlled parallel group randomised controlled trial study design was used. The intervention was varenicline 1 mg twice daily. Treatment was delivered for 12 weeks, with 14 weeks' follow-up afterwards. Participants were aged 18 years or more. They were also users of smokeless tobacco who wished to quit and had no abstinence period longer than three months during the year before recruitment. In total, 431 participants were recruited and randomised to varenicline (n=213) or placebo (n=218). All participants were offered brief behavioural support or counselling at the discretion of the investigators.¹

The primary endpoint was continuous abstinence for four weeks at the end of treatment (weeks 9-12) confirmed by cotinine concentration. A significantly higher rate of abstinence was reported in the varenicline group compared with placebo (59% v 39%; relative risk 1.6, 95% confidence interval 1.32 to 1.87; P<0.001).

Which of the following statements, if any, are true?

- a) The placebo is referred to as an active control
- b) The use of a concurrent control group minimised confounding
- c) The rate of abstinence in the placebo group (39%) is termed the placebo effect
- d) The most recent version (2013) of the Declaration of Helsinki precludes the use of placebos in randomised controlled trials

Answers

Statement *b* is true, whereas *a*, *c*, and *d* are false.

Smokeless tobacco is often used by smokers trying to quit because it is considered less harmful than smoking. The aim of the above trial was to assess the efficacy of varenicline (a licensed cigarette smoking cessation aid) in helping users of smokeless tobacco to quit. It was essential that a control group was included. Control treatments in trials are typically the standard treatment, placebo, or no intervention. A control group acts as a comparator against which the efficacy of the intervention is compared. The inclusion of a control treatment

means that the trial is described as controlled. A placebo was chosen as the control in the above trial, so the trial is referred to as placebo controlled. A placebo is called a negative control because it is pharmacologically inert (*a* is false). A control treatment is described as active or positive if it has known therapeutic benefits—for example, the standard treatment would be an active control treatment.

Participants were randomised to the intervention or placebo. The randomisation of participants in the trial eliminated allocation bias and therefore minimised confounding. Allocation bias is the systematic difference between participants in how they are allocated to treatment. Confounding is a difference between treatment groups in those factors that affect treatment and outcome measures. In general, if the sample size for a trial is large enough then randomisation of participants will result in groups of patients who are similar in baseline characteristics. Such factors include demographics, prognostic factors, and other characteristics that influence someone to participate in or withdraw from a trial. If confounding is minimised then differences between treatment groups in outcome will be the result of differences in treatment received, not differences in characteristics at baseline. In such cases, a causal association can be inferred between treatment and outcome. Confounding in clinical trials has been described in a previous question.² The treatment groups were then followed prospectively and the effects of treatment compared between groups. The treatment groups are described as concurrent or parallel, and the trial as parallel.

It was important that the treatment groups were concurrent rather than historical. A historical group would be patients who had already received treatment and been assessed. Many factors may affect the progress of smoking cessation for users of smokeless tobacco. In particular, the characteristics of patients and those of the healthcare staff, and their approach to counselling patients for cessation of smokeless tobacco, may change with time. Therefore, concurrent treatment groups minimised confounding at baseline (*b* is true) by ensuring similarity between treatment groups in those characteristics that might vary with time.

A randomised controlled trial is the most rigorous way to determine whether a causal association exists between a

treatment and the outcome. An important feature of the study design is how the participants are allocated to treatment. In the above trial, participants were randomised to varenicline or placebo as described to eliminate allocation bias and minimise confounding at baseline. When the trial was conducted, no effective drug treatment was available to help users of smokeless tobacco to quit. A placebo was chosen as the control rather than no treatment. The placebo was a pharmacologically inert substance, indistinguishable from varenicline in taste and appearance. By using a placebo and randomisation, the participants and researchers would not be aware of the treatment allocation. This ensured that the trial was double blind.

The above trial was undertaken as a superiority trial,³ the aim being to establish whether varenicline was superior to placebo in the primary outcome. Varenicline was shown to be significantly superior to placebo, and it could therefore be inferred that it was an effective intervention. The choice of control in a trial influences the inferences that can subsequently be made. The comparison of varenicline against placebo permitted the therapeutic benefit of the intervention to be evaluated. If the control in the above trial had been a standard treatment, then the demonstration of superiority would have indicated which treatment was the most effective.

The rate of abstinence in the varenicline group was significantly higher than in the placebo group (59% v 39%; relative risk 1.6, 1.32 to 1.87). The placebo group's response was the result of non-specific treatment effects. These non-specific effects included the placebo effect and the natural course of abstinence in users of smokeless tobacco who wanted to quit (*c* is false). The placebo effect represents the patient's response to investigation, including the response to a therapeutic ritual, subsequent response to observation and assessment, and response to the patient-researcher interaction. The association between these components is probably complex. The response by the intervention group included the direct therapeutic benefit of varenicline plus the non-specific treatment effects described

above. The therapeutic benefit of the intervention was estimated by the difference between the treatment groups in continuous abstinence for four weeks at the end of treatment (weeks 9-12).

The use of placebos in clinical trials has generated much ethical debate. This is especially true where standard treatment exists and when research is conducted among vulnerable groups. In October 2013 the World Medical Association updated the Declaration of Helsinki. The 2013 version is arguably more liberal than the previous (2008) version with regard to the use of placebos in research. However, the newest version continues to proscribe the use of placebos in research except in certain circumstances. Specifically, placebos should not be used unless no proved intervention exists, or there are compelling and scientifically sound reasons why a placebo should be used to determine the efficacy or safety of an intervention (*d* is false). Furthermore, the patients who receive the placebo should not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proved intervention. The new version of the Declaration of Helsinki also clearly states that, although placebos can be used in research, "extreme care must be taken to avoid abuse of this option." When the trial above was conducted no effective drug treatments were available to help users of smokeless tobacco to quit, although behavioural interventions had been found to be of some benefit. Nonetheless, the use of a placebo in the trial above would probably be deemed ethical from the perspective of the current Declaration of Helsinki.

Competing interests: None declared.

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