

ENDGAMES

STATISTICAL QUESTION

Crossover trials

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Researchers investigated the efficacy and side effects of the synthetic cannabinoid nabilone in comparison with those of the weak opioid dihydrocodeine for treating chronic neuropathic pain. A randomised, double blind, crossover trial was used. In total 96 participants with chronic neuropathic pain aged 23-84 years were recruited. Treatments were delivered in an escalating manner so that by the end of a six week treatment period the participants were receiving a maximum daily dose of 240 mg dihydrocodeine or 2 mg nabilone. The trial lasted for 14 weeks, comprising two treatment periods each of six weeks' duration, separated by a two week washout period.¹

The main outcome measure was pain as measured on a visual analogue scale over the final two weeks of each treatment period. The researchers reported that dihydrocodeine provided better pain relief than nabilone and had slightly fewer side effects.

Which one of the following statements best describes how trial participants were allocated to treatment group?

- Participants were randomised to nabilone or dihydrocodeine and received the same drug for both treatment periods.
- Participants received both drugs—nabilone and dihydrocodeine—with treatment order for each participant decided at random.
- All participants received both drugs in the same order, with the treatment order determined at random (either they all received nabilone in the first treatment period and dihydrocodeine in the second or vice versa)

Answers

Statement *b* best describes the allocation of participants to treatment.

In the above trial participants received both treatments. The order in which participants received treatment was determined at random for each patient: nabilone followed by dihydrocodeine or vice versa (answer *b*). The researchers reported that 48 participants received nabilone followed by dihydrocodeine, with the remaining participants receiving treatment in the opposite order. The main outcome measure—pain as measured on a visual analogue scale—was averaged across the last two weeks

of each six week treatment period. The difference in outcome between treatments was obtained for each patient. Even though the trial was double blind, the treatment order had to be random for each patient. This therefore ensured that if treatment order affected outcome it would be averaged out across the sample and therefore would not bias the results. Crossover trials are only appropriate where the condition is chronic and any treatment effects are reversible or not permanent.

Because patients received both interventions they acted as their own controls, permitting a comparison of the efficacy and side effects of nabilone with dihydrocodeine on a “within-subject” basis. As a within-subject design, the crossover trial removes natural patient variation and therefore provides a more precise comparison of treatments than a between-subject study design. The within-subject design also requires fewer patients than a between-subject trial. In a between-subject trial patients are randomly allocated to a single treatment and receive the same treatment for the entire study period. Treatment outcomes are then compared between participants—that is, between independent groups of patients.

Each treatment period lasted six weeks, separated by a two week washout period. The purpose of the washout period was to allow the dissipation of effects of the treatment administered first, both pharmacologically and psychologically, before the second treatment was delivered. The researchers reported that during the washout period participants were weaned off the drug they were first allocated by halving the dose every three days. For the last six days of the washout period participants were not allowed to take the drug they had been initially allocated. As it was not acceptable to expect participants to tolerate intervals when no analgesia was available, they were allowed a maximum of eight tablets of analgesia a day (paracetamol 500 mg or codeine 30 mg per tablet).

Competing interests: None declared.

¹ Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ* 2008;336:199.

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