

**Frank B, Serpell MG, et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomized, crossover, double blind study. BMJ 2008; 336:199-201
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Design: Randomized crossover trial

Brief summary of results:

- 96 patients (46 women, 50 men, mean age 50) treated for neuropathic pain at 3 outpatient facilities in the UK
- Eligibility criteria were chronic neuropathic pain of at least 40 mm on a 100 mm scale (characterized by allodynia, sensory abnormality, sympathetic dysfunction, burning/lancinating pain), taking a stable dose of analgesic except for dihydrocodeine (duration of symptoms for eligibility was not reported, but both groups had mean duration of years)
- Exclusion criteria were epilepsy, liver disease, psychosis or bipolar disorder, substance misuse, renal failure, of adverse responses to dihydrocodeine or nabilone; taking any cannabinoid preparation, or having ongoing legal action associated with the clinical condition
- Commonest syndrome was after injury or surgery (n=22), demyelination (n=11), and CRPS (n=9)
- A crossover trial was conducted, with a screening period of 1 week, a 6 week treatment period on one drug, a 2 week washout period, and a second 6 week treatment period on the other drug
- Randomization was to dihydrocodeine first, followed by nabilone (n=48) or to nabilone first, followed by dihydrocodeine (n=48)
- Primary outcome was pain score; several secondary outcomes were also measured: sleep, mood, and quality of life (SF-36)
- Trial drugs were titrated (from starting dose of 30 mg to a final dose of 240 mg for dihydrocodeine, and from starting dose of 250 mcg to final dose of 2 mg for nabilone); if side effects developed during dose titration, the dose was reduced to the previous level for the duration of the trial
- The mean baseline pain VAS was 69.6 mm
- Of the 96 patients who were randomized and began the trial, 73 were available for analysis at the end of the trial, and 64 had adhered to the protocol and were available for a per protocol analysis
- The available case analysis showed that dihydrocodeine was a better analgesic than nabilone (treatment effect of 6.0 mm on the VAS);
- A decrease of 10 mm was considered clinically relevant; this was achieved by 3 of the 64 patients in the per protocol analysis for nabilone and by 12 of the 64 patients for dihydrocodeine; however, 49 patients had no clinically relevant decrease on either treatment
- No major side effects occurred, and both drugs were equally well tolerated; nabilone was associated with more sickness than dihydrocodeine (46 vs. 10), but dihydrocodeine was associated with more tiredness than nabilone (102 vs. 79)

Authors' conclusions:

- For chronic neuropathic pain, dihydrocodeine was statistically better than nabilone
- The study was weakened by the fact that 33 patients failed to complete the trial, and by the fact that they had a variety of neuropathic pain conditions

Comments:

- The study data are presented in a way which is confusing and unclear
- For example, the treatment effect is not clear; the mean baseline VAS is reported in the text as 69.6 mm, which is greater than the baseline VAS for either the dihydrocodeine first group (68.0) or the nabilone first group (66.4)
- Further, the text reports that the mean VAS was 59.93 for patients taking nabilone and was 58.58 for patients taking dihydrocodeine; this is a difference of only 1.35 mm; it is not clear whether these scores were those averaged over the weekly means for all six weeks of each treatment period, or if they are taken closer to the end of each treatment period
- It appears that there were secondary outcomes (sleep, SF-36 scales) which were collected at the end of each period; Table 3 compares the treatment effects of nabilone and dihydrocodeine, giving the number of points by which the scores differed; however, it is not clear whether these effects represent any change from the baseline values for the reported effects (for example, the treatment effect for sleep is 0.2, but the actual changes from baseline are not reported; there may have been large and equal improvements under both treatments, or there may have been no changes from baseline for either treatment)
- Presumably, the 11 patients with demyelination included some with multiple sclerosis, but it is not clear if all 11 of these patients had MS
- Table 4 reports side effects, but the units are not clear; for tiredness, the reported effect is 79 for nabilone and 102 for dihydrocodeine; in addition, "sickness" is a very vague term, and its occurrence in the nabilone group cannot be interpreted without further information
- Table 4 might be expected to report on the frequency of constipation for dihydrocodeine but does not; it is possible that constipation could unblind the patients to their treatment during the dihydrocodeine period
- Since there were only 96 patients randomized, the 102 for dihydrocodeine is greater than the number of patients in the study; if Table 4 is reporting percents, 102% is greater than 100%; neither interpretation of Table 4 makes sense
- The study is reported as blinded, and the code breaking envelopes were kept in the hospital pharmacy; however, the code was disclosed to the requesting doctor who "was not involved in the study;" if the patient saw the requesting doctor at any time during the trial, the code may have become unblinded

Assessment: Inadequate for evidence of effectiveness of nabilone or dihydrocodeine (results are reported in a way that cannot be clearly interpreted)