Nurmikko TJ, Serpell MG, et al. Sativex successfully treats neuropathic pain characterized by allodynia: A randomized, double-blind, placebo-controlled trial. Pain 2007;133:210-220.

Design: Randomized clinical trial

Population/sample size/setting:

- 125 patients (51 men, 74 women, mean age 52) treated for neuropathic pain at 5 centers in the UK and 1 in Belgium
- Eligibility criteria were unilateral peripheral neuropathic pain with allodynia, lasting at least 6 months with an identifiable nerve lesion (CRPS patients were eligible if they had CRPS-II), pain severity at least 4 on a scale of 0-10 for at least 4 days in previous week, taking a stable regimen of medication for at least 2 weeks, willing to abstain from cannabis during the study
- Allodynia was determined by the investigator at baseline and the end of the study; mechanical allodynia was assessed with a standardized brush and punctate allodynia by a metal filament and a strain gauge
- Exclusion criteria were use of any cannabinoid at least 7 days before randomization, major psychiatric diagnoses, coexisting severe non-neuropathic pain (from cancer, diabetes, etc). known history of alcohol or substance abuse, and severe medical comorbidity (heart, renal, hepatic)

Main outcome measures:

- Primary outcome measure was change from baseline in pain numerical rating scale (NRS) on a scale from 0-10
- Randomization was to sativex, a spray preparation of two cannabinoid agonists (n=63) or a placebo spray (n=62), with both sprays supplemented with peppermint extract to mask the presence of the cannabinoids
- Several secondary measures were assessed, including mechanical allodynia, sleep disturbance, pain disability index, patient global impression of change, and the General Heath Questionnaire (GHQ-12)
- Baseline NRS was defined as the mean of all patient diary entries for the 7 days prior to treatment, and endpoint NRS was the mean of all diary entries in the last 7 days of the study
- The trial lasted 5 weeks, with initial dosing done under clinical supervision at the study site; a maximum of 8 sprays were administered, with signs of intoxication and vital signs monitored by the investigator
- At baseline, one third of each group was taking an antiepileptic drug; the groups were similar with respect to strong opioid use (11% of sativex and 13% of placebo) and weak opioid use (52% of sativex and 61% of placebo)
- After the initial dose, patients were allowed to self-administer sativex at home, with a maximum of 8 sprays per 3 hour interval and a maximum of 48 sprays in 24 hours, keeping a diary of pain scores, sleep, and adverse events
- At baseline, both groups had severe pain (mean NRS 7.3 for sativex and 7.2 for placebo); at the end of 5 weeks, the sativex group had a 22% reduction (1.48 points), while the placebo group had an 8% reduction (0.52 points)

- The proportion of patients with a 30% pain reduction was 26% for sativex and 15% for placebo; for a 50% pain reduction, the rates were 20% and 8%
- Mechanical allodynia decreased by 20% in the sativex group and by 5% in the placebo group
- Adverse effects were reported by more sativex patients than placebo patients: 91% of sativex patients and 77% of placebo patients
- Most adverse effects were mild gastrointestinal symptoms which occurred at the onset of treatment, but more withdrawals due to adverse effects occurred with sativex (18%) than with placebo (3%)
- Baseline and follow-up neuropsychological testing showed no group differences in cognitive function
- At the end of the 5 week trial, all 125 patients were invited to participate in an extended open-label study; 89 patients (71%) accepted
- The extension open-label study lasted from 1 day to 871 days; during the extension period, 63% of patients withdrew: 18 for adverse effects, 16 for lack of efficacy, 15 due to withdrawal of consent, and 7 for other reasons

Authors' conclusions:

- Sativex is effective in the relief of peripheral neuropathic pain when combined with existing pain medication)
- Considering the refractory nature of the pain at entry, the percentage of patients with 30% and 50% pain relief is encouraging
- Tolerance seems not to have developed during the study, since the number of sprays taken daily by sativex patients remained stable
- Although no formal assessment of unblinding took place, the psychometric and intoxication tests during the trial, and the study medication returned by the patients, make it unlikely that sativex patients concluded that they were taking the active drug

Comments:

- Threats to selection bias appear to be adequately controlled: randomization and concealment of allocation are clearly described
- Blinding was not assessed by direct questioning; however, the authors may be justified in inferring from their behavior that significant unblinding was not likely
- The use of other medications at baseline is clearly described, but the use of these during the course of the trial is not further elaborated, and this is an outcome of practical interest
- The clinical tests of allodynia at baseline and follow-up are difficult to interpret as outcomes of practical interest
- Five weeks is a short time to assess the effects of the study drug with continued use; the fact that the majority of patients discontinued using sativex during the extended open-label trial suggests that there may be barriers to long-term use

- Although the effect size appears to be modest, and the success rate is less than half of the patients, most of the participants may have been refractory to other interventions, and a moderate contribution to pain relief can be important

Assessment: Adequate for evidence that oral-mucosal spray of THC and cannabidiol may provide additional analgesia in chronic neuropathic pain