Barton DL, Wos EJ et al. A Double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy [CIPN]: NCCTG trial N06CA Support Care Cancer 2011; 19:833-841.

Reviewed, no chang to conclusions January 2017

Design: Randomized clinical trial

Population/sample size/setting:

- 203 cancer patients (126 women, 76 men, mean age 61) treated for chemotherapy-induced peripheral neuropathy in several states under the auspices of the Mayo Clinic
- Eligible patients had received, or were currently receiving neurotoxic chemotherapy with numbness, tingling, or pain limited to the hands and/or feet for at least one month, had a numbness/tingling/pain VAS score of at least 4 on a scale from 0 to 10, and a life expectancy of at least 4 months
- Exclusion criteria were any history of peripheral neuropathy from other causes, current treatment for neuropathy with tricyclics or anticonvulsants, history of coronary artery disease, creatinine more than 1.5 times upper limit of normal, and allergy to ketamine, baclofen, or amitriptyline

Main outcome measures:

- All participants applied topical gel twice per day, once on awakening and again at bedtime, to each symptomatic area (not more than 4 areas)
- Randomized to placebo gel (n=102) or to gel with 10 mg baclofen, 40 mg amitriptyline, and 20 mg of ketamine (BAK, n=101)
- Primary end point was change in the sensory neuropathy subscale of the CIPN20, a questionnaire evaluating sensory (9 items), motor (8 items), and autonomic (3 items) symptoms associated with chemotherapy neuropathy
- Majority of patients had taken either taxanes or platinum-based drugs; a small number took vinca alkaloids or other drugs
- Gel was to be applied twice per day for four weeks
- CIPN20 assessments were done at baseline and at the end of 4 weeks
    - Sensory, motor, and autonomic subscales were all scaled to score from 0 to 100
    - BAK sensory subscale improved by 8.1 points compared to 3.8 for placebo (p=0.053)
    - BAK motor subscale improved by 7.1 points compared to 1.8 for placebo (p=0.021)
    - BAK autonomic subscale improved by 3.3 points compared to 1.7 for placebo (p=0.58)
- Individual items on the sensory and motor subscales which showed most improvement in BAK group were tingling in fingers/hands, burning or shooting pain in fingers/hands, and ability to hold a pen
- Attrition was large in both groups; 26 patients in BAK group and 27 in placebo group did not provide 4 week follow-up CIPN20 scores

    - In BAK group, 11 refused follow-up data due to an adverse event, and 15 for unspecified reasons
    - In placebo group, 8 refused for adverse event, 1 died, and 18 refused for unspecified reasons
- Brief Pain Inventory and Profile of Mood States were also done; there were no differences between groups on either scale
- Blood was drawn on 8 participants and there were no measurable levels of the study drugs or their metabolites

Authors' conclusions:

- The BAK gel showed a trend toward improvement in sensory and motor neuropathy scores compared to placebo, but the effect was not large
- When the CIPN20 scores were analyzed on their original scales, which are graded from 1 to 4, rather than from 0 to 100, there were no differences between treatments for motor or sensory scales (p=0/195)
- While there is some support for the hypothesis that BAK can improve symptoms of CIPN, the data fall short of convincingly proving this hypothesis
- Because the FDA was concerned about the possibility of systemic absorption, it required lower doses for this trial than the investigators had originally proposed to study; the lower dose may account for the lack of large benefit
- The lecithin gel vehicle presented difficulty for some patients getting it to absorb into their skin; future studies may wish to try Lipoderm, which could be easier for patients to rub into the skin
- The 25% attrition is consistent with a situation involving patients with advanced disease, who could go in and out of treatment and experience other health problems

Comments:

- The high attrition rate is commented on but not explained; it should be possible to characterize which patients tended to drop out—those receiving ongoing neurotoxic chemotherapy, for example, versus those who had completed chemotherapy
- Table 1 presents baseline comparisons of some variables, but none for the main outcomes of interest—the CIPN20 scores
    - This interferes with interpreting the reported declines in the subscale scores from baseline
- The authors are justified in declining to interpret their data as evidence that BAK gel effectively treats CIPN
    - The trend in the data are suggestive of a therapeutic effect of BAK, and warrant further investigation of its clinical use

Assessment: Inadequate for evidence that BAK gel alleviates symptoms of chemotherapy-induced neuropathy (small effect size; high attrition, authors' statement that the study dose may have been to low to show a therapeutic effect)