Lynch ME, Clark AJ et al. Topical 2% Amitriptyline and 1% Ketamine in Neuropathic Pain Syndromes. Anesthesiology 2005;103:140-6.

Revised, no change to conclusions, November 2016

Design: Randomized clinical trial

Population/sample size/setting:

- 92 patients (47 men, 45 women, mean age 52) treated for chronic neuropathic pain at three outpatient pain clinics in eastern Canada
- Inclusion criteria were established diagnosis of either postherpetic neuralgia, diabetic neuropathy, or postsurgical/posttraumatic pain, symptoms lasting 3 months or longer, tactile allodynia or pinprick hyperalgesia in the area of pain, and normal cognitive ability
- Exclusion criteria were evidence of another type of pain as severe as the neuropathic pain, major depression, use of a MAO inhibitor, or allergy to the study medicine

Main outcome measures:

- Randomized to one of four treatments: placebo cream (n=25), 2% amitriptyline cream (n=22), 1% ketamine cream (n=22), or a combination of 2% amitriptyline and 1% ketamine (n=23)
- Application of cream was to be 4 ml tid to the site of maximal pain for 3 weeks
- Main outcome was pain intensity on a numerical rating scale (0-10)
- McGill Pain Questionnaire was included as a secondary outcome
- Pain Disability Index (home, social, recreational, occupational, sexual, self-care, and life support), and Patient Satisfaction (0-10) were also included
- Results were analyzed after 3 weeks of treatment; the pain intensity scores decreased in all groups, but did not differ between treatment groups; reduction in pain was 50% or more for 10% of amitriptyline, 10% of ketamine, 20% for combination, and 18% for placebo
- Similarly, McGill Pain Questionnaire showed a 27% reduction in affective pain for the whole study population, with no inter-group differences
- There were no differences in perceived disability; all groups had moderate patient satisfaction
- Adverse events were reported in 30% of participants; these were evenly distributed across treatment groups, and were most commonly related to minor skin irritation at the application site
- Plasma was analyzed for the presence of ketamine and amitriptyline, but systemic absorption appeared not to have occurred

Authors' conclusions:

- At a dose of 2% amitriptyline and 1% ketamine, topical administration of the drugs separately or in combination does not appear to be more effective than placebo at relieving neuropathic pain

- Other studies have used higher concentrations (4% amitriptyline and 2% ketamine) of the drugs, and may represent optimum doses

Comments:

- Threats to bias were well controlled and well reported; randomization, concealment allocation, blinding, and follow-up were all done at a high level
- The period of follow-up was fairly short, but would be expected to show an acute effect if a large one were present, since the study was adequately powered to detect a 1 point difference on the pain scale
- The study with the higher dose referred to by the authors in the discussion section was done on 250 patients with postherpetic neuralgia; it was presented as an abstract in a journal supplement, but never published

Assessment: High quality; will support an evidence statement that amitriptyline and ketamine at a concentration of 2% and 1%, or a combination of both, does not differ from placebo for the treatment of neuropathic pain.