Norrbrink C, Lundeberg T. Tramadol in Neuropathic Pain After Spinal Cord Injury. Clin J Pain 2009;'25(3):177-184.

Design: Randomized clinical trial

Population/sample size/setting:

- 35 patients (28 women, 7 men, mean age 51) treated for neuropathic pain at 3 regional hospitals in Stockholm
- Inclusion criteria included spinal cord injury (SCI) of at least 12 months duration, pain classified as neuropathic at or below the level of the cord lesion for at least 6 months, no known cognitive impairment, and a pain intensity of 3 or more on a 10 point scale
- Exclusion criteria were pregnancy, lactation, previous use of tramadol, or intolerance to opioid in the past

Main outcome measures:

- Randomized to 50 mg tramadol (n=23) or placebo (n=12)
- Identical appearing tablets were dispensed with instructions to start dose at 1 tablet tid, increasing the dose every days by 1 tablet until a maximum of 8 tablets were being used—400 mg tramadol for those in that group
- Pain intensity (present, general, and worst in last week) and patient global impression of change (PGIC) were primary outcomes; secondary outcomes included anxiety, life satisfaction, and sleep quality
- There were baseline imbalances in the treatment groups on pain scores; for present, general, and worst pain intensity, the placebo group had higher pain scores than the tramadol group (e.g., tramadol group had general pain intensity average of 4 at baseline, while the placebo group had a mean score of 7)
- Treatment efficacy was evaluated 4 weeks after trial entry at the spinal unit of the referring hospitals
- The proportion of patients reporting pain relief was greater for tramadol than for placebo; the results are reported graphically rather than numerically in a table
- For PGIC, 7 tramadol patients reported pain as minimally or much improved; 1 placebo patient was minimally improved
- For PGIC, only 4 tramadol patients and no placebo patients reported being "much improved"
- No patient in either group was "very much improved"
- Most secondary outcomes did not differ greatly between groups
- Adverse effects leading to withdrawal from the study were common; 11 patients in the tramadol group and 2 in the placebo group withdrew because of adverse effects
- The most common adverse effects were tiredness, dry mouth, and dizziness

Authors' conclusions:

- Patients with SCI and neuropathic pain have significantly better pain improvement with tramadol than with placebo
- However, the occurrence of adverse effects with tramadol is very high, and this limits its usefulness; it should be used only after other agents like gabapentin/pregabalin, tricyclics, and SSRI drugs have been used; tramadol can then be considered as an adjuvant or solitary drug

Comments:

- Randomization sequence generation and allocation concealment are not explicitly described, but the trial tablets were provided in sealed, coded envelopes whose code was not broken until the end of the trial; this may be inferred to be evidence of allocation concealment
- Blinding and co-intervention bias appear to have been well controlled
- Overall risk of bias: low
- The primary outcome was not reported in terms of percent change from baseline; however, it is reasonable to infer that "much improved" is approximately equivalent to 50% improved or more
- The baseline imbalance is a potential source of bias, since the baseline pain score in the tramadol group was probably too low to allow for a demonstration of the efficacy of the trial drug, while the higher pain score in the placebo group could allow for a demonstrable change due to a placebo effect, if any
- The effect of the baseline imbalance is therefore in the direction of making tramadol appear less effective than it might really be
- The attrition rate is very high and may limit the clinical usefulness of tramadol; as the authors note, dose titration should be carefully done

Assessment: Adequate for evidence that tramadol may alleviate neuropathic pain due to spinal cord injury (lack of reporting of percent improvement, and proportion of patients with 30% and 50% improvement, precludes a high quality rating)