

**Buynak R, Shapiro DY, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo-and active-controlled Phase III study. Expert Opin Pharmacother 2010; 11(11)1787-1804.**

Design: Randomized clinical trial

Population/sample size/setting:

- 965 patients (406 men, 559 women, mean age 50) treated for chronic low back pain at 103 sites in the US, Canada, and Australia
- Eligibility criteria were low back pain of at least 3 months duration not satisfactorily relieved by analgesics, with a numerical rating scale (NRS) of at least 5 on a scale of 0-10 after 3-7 days off all analgesics, and, for patients taking opioids, a dose equivalent to no more than 160 mg morphine
- Exclusion criteria were extensive, and included previous participation in tapentadol trials, numerous medication classes (steroids, tricyclics, anticonvulsants, antiparkinsonian drugs, SNRIs, MAOIs), back surgery within the past 3 months, substance abuse, and several medical comorbidities: stroke/TIA, seizures, HIV, Hepatitis B or C, malignancy in past 2 years, renal/hepatic impairment, or uncontrolled hypertension
- Patients were permitted to take SSRIs for depression, and could continue therapies such as TENS, acupuncture, physical therapy, and acetaminophen

Main outcome measures:

- Randomized to tapentadol extended release (ER, n=318), oxycodone controlled release (n=328) or placebo (n=319)
- Placebo tablets and capsules were used with both active treatments to maintain the double-blind, double-dummy design
- Titration began with tapentadol 50 mg bid and oxycodone 10 mg bid; doses were increased after 3 days to tapentadol 100 mg bid, and oxycodone 20 mg bid, which were the minimum doses allowed for the remainder of the study
- Additional dose increases were done at 3 day intervals up to the highest tested doses of tapentadol 250 mg bid or oxycodone 50 mg bid; patients were allowed to adjust their own doses during the 3 week titration period
- The 3 week titration period was followed by a 12 week maintenance period
- In the US, the primary efficacy measure was the change in pain intensity from baseline to week 12 of the maintenance period
- In the Canada and Australia, the primary efficacy measure was the change from baseline in mean pain intensity averaged over the entire 12 week maintenance period
- Secondary efficacy measures included the percentage of participants with 30% and 50% reductions in pain intensity, the patient global impression of change (PCIG) on a scale from 1 (very much improved) to 1 (very much worse); the SF-36 was also done

- Safety and tolerability measures included the Patient Assessment of Constipation Symptoms (PAC-SYM) and the Clinical Opiate withdrawal Scale (COWS)
- Attrition was high; the percentage of patients who completed the study was 47.6% for placebo, 52.2% for tapentadol, and 40.5% for oxycodone
- Primary reasons for attrition were adverse events (placebo, 4.7%, tapentadol, 16.7%, and oxycodone, 32.3%) and lack of efficacy (placebo, 20.7%, tapentadol, 5.7%, and oxycodone, 2.7%)
- The median total daily dose during the maintenance phase was 400 mg for tapentadol and 80 mg for oxycodone
- Average pain intensity reduction on the NRS from baseline to week 12 was 2.1 for placebo, 2.9 for tapentadol, and 2.9 for oxycodone; thus, tapentadol and oxycodone were more effective than placebo by a mean of 0.8 points on the NRS (the data from Canada and Australia, which used the change from baseline to the average over the entire 12 week maintenance period, were nearly identical)
- Responder rates (30% and 50% reduction in pain) were higher in tapentadol than in placebo groups, but oxycodone did not differ significantly from placebo: for 30% response the rates were: placebo, 27.1%, tapentadol, 39.7%, oxycodone, 30.4%; for 50% response, the rates were: placebo, 18.9%, tapentadol, 27.0%, oxycodone, 23.3%
- Treatment-emergent adverse events (TAEA) were common in all treatment groups: for placebo, 59.6%, for tapentadol, 75.5%, and for oxycodone, 84.8%
- Most TEAE were mild or moderate; GI upset, dizziness, and headache were common, but the odds of having constipation were lower in the tapentadol group than in the oxycodone group; this was reflected in the PAC-SYM scores, which were lower in placebo and tapentadol groups than with oxycodone
- COWS assessments in most patients did not demonstrate opiate withdrawal after abrupt discontinuation of treatment; mild or moderate opioid withdrawal was reported in 10.2% of placebo group, 4.8% of tapentadol, and 8.9% of oxycodone

#### Authors' conclusions:

- Tapentadol ER 100-250 mg bid was more effective than placebo for chronic low back pain over 15 weeks of administration
- Oxycodone also reduced pain scores more effectively than placebo, but the percent of 30% and 50% pain responses were not significantly different from placebo, perhaps due to the high attrition with oxycodone during titration
- Oxycodone and tapentadol provide similar analgesic efficacy, but tapentadol appears to be better tolerated with lower rates of constipation, nausea, vomiting, dizziness, and pruritus than oxycodone
- Immediate release forms of tapentadol, like the extended release form in the current study, have had analgesic efficacy similar to oxycodone, with more favorable tolerability profiles; the norepinephrine reuptake inhibiting effect may provide an opioid-sparing effect

- Extended release tapentadol may be an effective treatment option for moderate to severe pain with a neuropathic component

Comments:

- Most important threats to an unbiased comparison of treatment groups were adequately controlled; randomization, allocation concealment, and blinding were reported in a way that leads to a low risk of bias
- There was attrition in all 3 groups from “patient choice” in Figure 1; the nature of these choices is not clear, but it appears that it was classified differently from adverse effects and lack of efficacy
- The large sample size is advantageous to have in a study with generally sound safeguards against bias
- The opiate withdrawal symptoms appeared to be lower in tapentadol than in placebo; the authors imply that this is due to its low affinity for the mu receptor

Assessment: High quality for evidence that tapentadol is more effective than placebo and comparable to oxycodone (low risk of bias, large sample size)