Tapentadol modified release

Introduction
Tapentadol is a strong opioid drug combining μ-opioid agonist action and noradrenaline reuptake inhibitor activity. The immediate release preparation is licensed for use in moderate to severe acute pain which can be managed only with opioid analgesics. Tapentadol modified release (MR) is indicated for use in severe chronic pain which can only be adequately managed with opioid analgesics and was approved by the FDA in 2008 and by the EMA in 2011.

Pharmacology
Figure 1 outlines the pharmacological action of tapentadol. It is a centrally-acting drug with a dual mode of action affecting both the ascending (excitatory) and the descending (inhibitory) pain pathways. Its pharmacological actions are mediated in two ways: it is a highly selective potent agonist at the μ-opioid receptor and, by inhibition of noradrenaline reuptake in the ascending pathways to the dorsal horn, enhances inhibitory painful impulses. These mechanisms act synergistically to produce analgesia. Tapentadol MR is given orally and reaches maximum serum concentrations in 3–6 hours. It undergoes extensive first-pass metabolism and is almost exclusively renally excreted.1

Trials of efficacy and safety
The safety and efficacy of tapentadol MR in chronic pain have been investigated in several clinical trials. Tapentadol MR was compared with oxycodone controlled release (CR) in randomised, double-blind, placebo-controlled trials in patients with osteoarthritis (OA) and lower back pain (LBP). There was a three-week titration and a 12-week maintenance period. The primary efficacy endpoints were change from baseline in mean pain intensity (11-point numerical rating scale; 0=no pain, 11=pain as bad you can imagine) at week 12 of the maintenance period (in the US) and change from baseline over the entire 12-week maintenance period (EU). Safety and tolerability evaluations were

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**Figure 1.** Tapentadol has a dual mechanism of action. It acts as a potent agonist at the μ-opioid receptor on the pre-synaptic neurones to block neurotransmitter release (SP and GLU) in the ascending excitatory pathway, but also through noradrenaline reuptake activity enhancing the effect of the descending inhibitory pathway.

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**Drug notes**
made primarily by adverse event reporting and clinical opiate withdrawal scale (COWS) questionnaires.

The LBP trial demonstrated significant differences between both tapentadol MR and oxycodone CR to placebo (p<0.001) in the reduction of mean pain intensity from baseline to week 12 and from baseline over the entire maintenance period. The proportion of patients achieving ≥30% and a ≥50% reduction in pain was significantly different between tapentadol MR and placebo at week 12 (39% vs 27.1%, p<0.001, number needed to treat [NNT] 8; and 27% vs 18.9%, p=0.016, NNT 13, respectively). There was no difference between oxycodone CR and placebo. The clinical significance of these improvements must be considered as the actual reduction in pain intensity was small when placebo-corrected at 0.8 at 12 weeks (least squares mean difference [LSMD] vs placebo -0.8 [95% CI -1.22 to -0.47]), and 0.7 from baseline over the entire maintenance period (LSMD vs placebo -0.7 [95% CI -1.06 to -0.35]).

The most commonly-reported adverse effects included nausea, vomiting, constipation, headache, dizziness, pruritus and somnolence, and were reported by 59.6%, 75.5% and 84.8% of participants in the placebo, tapentadol MR and oxycodone CR groups, respectively. The oxycodone CR group reported almost double the incidence of vomiting, dizziness and pruritus compared to tapentadol MR. Most patients experienced no opioid withdrawal after abrupt discontinuation, and there was no significant difference in mean COWS in either group compared to placebo.

The OA study reported significant reduction in pain with tapentadol MR compared to placebo. The LSMD vs placebo was -0.7 (95% CI -1.04 to -0.33) at week 12 from baseline, and -0.7 (95% CI -1.00 to -0.35) for the overall maintenance period. Oxycodone CR also showed significant reduction in pain intensity for the overall maintenance period but not at week 12 compared to placebo. There was no significant difference in the proportion of patients achieving ≥30% reduction in pain intensity from baseline, at week 12 with tapentadol MR compared to placebo (43% vs 35.9%, p=0.058); however, it was significantly lower for oxycodone than placebo (24.9% vs 35.9%, p=0.002). Compared to placebo, significantly more patients attained ≥50% reduction in pain intensity under tapentadol (32% vs 24.3%, p=0.027) but not under oxycodone (17.3% vs 24.3%). There were higher discontinuation rates in the oxycodone group, mostly due to higher gastrointestinal side effects (67.3% vs 43% for tapentadol MR) which affected the latter analysis. The safety assessments were consistent with the LBP trial, with greater adverse effects and discontinuation rates with oxycodone CR and mainly no or only mild opioid withdrawal in all groups.

Specific evidence for use in diabetes

Tapentadol MR has been approved for use in diabetic painful neuropathy (DPN) by the FDA and the EMA. The evidence for its safety and efficacy in patients with DPN comes primarily from two similarly designed randomised withdrawal, placebo-controlled trials, the results of which were pooled in an analysis published in 2014.

In each trial, patients with type 1 or 2 diabetes with a minimum six-month history of painful DPN who were taking opioid or non-opioid analgesia with a mean pain intensity score ≥5 (moderate) were included. The primary efficacy endpoint was the mean change in average pain intensity from baseline to week 12. Tapentadol MR was titrated to optimum dose (maximum 250mg b.d.) over three weeks. Those treated with tapentadol MR and who had a reduction in pain intensity by ≥1 were randomised 1:1 (n=703) to receive tapentadol MR or placebo for the 12-week, double-blind, placebo-controlled maintenance period.

The pooled analysis found mean changes in pain intensity from baseline to week 12 of maintenance of 1.28 (SD 2.41) and 0.08 (SD 1.87) in the tapentadol MR and placebo groups, respectively (LSMD -1.14 [95% CI -1.435 to -0.838], p<0.001, in favour of tapentadol MR). Adverse events were reported in 56% and 74.7% of the placebo and tapentadol MR groups respectively, the most common being constipation, nausea, vomiting, dizziness and somnolence.

Two important limitations of these trials are that only patients who responded to tapentadol MR in the open-label phase were randomised, and the trials were not actively controlled. More rigorous trials of tapentadol MR in painful DPN that show non-inferiority are required. Currently, there are no studies comparing tapentadol MR with other opioids.

Conclusion

Tapentadol MR has been shown to be non-inferior to oxycodone in efficacy and to have improved gastrointestinal tolerability in patients with chronic pain, including painful DPN. It may be an alternative in patients with painful DPN who are unable to tolerate other opioids, but further efficacy studies are required to establish its role for this indication.

Declaration of interests

There are no conflicts of interest declared.

References


Key points

- Tapentadol has combined μ-opioid agonist action and noradrenaline reuptake inhibitor activity working synergistically to lower the opioid load and generate efficacious analgesia
- Its effect is comparable to that of oxycodone but with a more favourable side effect profile
- Clinical trials in patients with diabetic painful neuropathy show efficacy and safety for use in both type 1 and type 2 diabetes, but further studies are required

Drug notes

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