Systematic review of tapentadol in chronic severe pain

CRD summary
The review concluded that the benefit-risk ratio of tapentadol appeared to be improved compared to step three opioids. This was a well conducted review but good quality head-to-head evidence largely pertains to one step three opioid, oxycodone.

Authors' objectives
To determine the evidence base for current recommendations on opioids and to determine the relative efficacy and safety of tapentadol and strong opioids (step three WHO pain ladder) for the treatment of chronic severe pain in adults.

Searching
Thirteen databases, including MEDLINE, EMBASE, PsycINFO, DARE, HTA and LILACS were searched from 1980 to November 2010. There were no restrictions in terms of language or publication type. Search terms were reported. Websites of licensing bodies and HTA agencies, as well as the references of retrieved articles and systematic reviews, were checked for additional studies.

Study selection
Randomised controlled trials (RCTs) that evaluated the safety and efficacy of step three opioids in adults above 18 years old who suffered from cancer or non-cancer related chronic pain (defined as pain lasting at least three months). Any dose or duration of treatment were considered but only oral and transdermal routes of administration were included. The primary endpoint was pain intensity. Enriched design studies were excluded.

Tapentadol doses ranged from 100 to 250mg prolonged release twice a day and 50 to 100mg every four to six hours immediate release and oxycodone doses ranged from 20 to 50mg prolonged release and 10 to 15mg every four to six hours immediate release; formulations and doses of other opioids were also reported. Most participants were described as having non-cancer related chronic pain; 13 trials included patients with cancer related chronic pain. Where reported, mean age ranged from 42.6 to 66 years, the percentage of women ranged from 35.1 to 73.7%, and the proportion of participants who were opioid naive ranged from 0 to 94.2%. Length of follow-up varied across trials, ranging from seven days to 24 months.

Two reviewers independently selected trials for inclusion in the review; any disagreements were resolved through discussion and consensus.

Assessment of study quality
Quality of the included trials was assessed using the Cochrane risk of bias tool which considered the following domains: random sequence generation, allocation concealment, blinding of participants, personnel and outcome, incomplete outcome data, selective reporting and other sources of bias.

Trial quality was assessed independently by two reviewers. Any disagreements were resolved by consensus.

Data extraction
For continuous outcomes, means and standard deviations were extracted or, where necessary, the standard error was estimated to calculate the mean difference. For dichotomous outcomes, data allowing the calculation of relative risks (RRs) were extracted. Where the standard deviation or mean was missing and not able to be determined it was imputed from a representative value from other trials. For cross-over trials, only data from the first-phase before cross-over was used.

One reviewer extracted data from the included trials which were checked by a second reviewer; any disagreements were resolved by consensus.

Methods of synthesis
Risk ratios and mean differences (MDs), or standardised mean differences where different outcome measures were used, were pooled using a random-effects model and summary estimates with 95% confidence intervals (CIs) calculated. Heterogeneity was assessed by a visual inspection of the forest plots as well as by measuring the degree of inconsistency in the trial results ($I^2$). Network meta-analyses were used to compare more than two treatments in the same analysis; where several doses were included in the same trial all doses were included in the analyses and treated as one intervention.

**Results of the review**

Forty-two studies met the inclusion criteria; 12 RCTs reported data on chronic severe pain and 42 RCTs reported data on chronic moderate-to-severe pain.

**Severe chronic pain**: Overall, the methodological quality of these trials was considered to be good.

Compared to oxycodone, tapentadol was found to significantly reduce pain intensity (MD -2.64, 95% CI -4.84 to -0.44; four RCTs). A significant difference in pain relief of 30% and 50% at the end of treatment in favour of tapentadol was also found. No significant between group difference was found for the incidence of serious adverse events (four RCTs), but tapentadol was found to significantly reduce the risk of constipation, nausea, and vomiting (seven RCTs).

Compared to placebo, tapentadol was found to significantly reduce pain intensity (MD -6.33, 95% CI -8.55 to -4.11; five RCTs). A significant difference in favour of tapentadol in pain relief of 30% and 50% was also found. No significant between group difference was found for the incidence of serious adverse events (three RCTs), but tapentadol was found to significantly increase the risk of constipation, nausea, vomiting, somnolence, and dizziness (six RCTs).

**Moderate-to-severe chronic pain**: Overall, the methodological quality of these trials was considered to be poor, although the tapentadol trials were of good quality.

Compared with oxycodone, a significant difference in favour of tapentadol was found for pain intensity (MD -2.45, 95% CI -4.04 to -0.86; seven RCTs), and incidence of serious adverse events (RR 0.53, 95% CI 0.28 to 1.00). A significant difference was also found for pain relief 30% and 50%. Tapentadol was also found to increase quality of life (five RCTs) and reduce the incidence of constipation, nausea, and vomiting (seven RCTs).

Compared with placebo, tapentadol reduced pain intensity (MD -6.91, 95% CI -9.80 to -4.02; six RCTs). A significant difference in favour of tapentadol in pain relief 30% and 50% was also found. No significant between group difference was found for the incidence of serious adverse events (six RCTs). Tapentadol was found to improve quality of sleep (four RCTs), quality of life (five RCTs), and scores on the Patients’ Global Impression of Change scale (six RCTs), but increase the incidence of constipation, nausea, vomiting, somnolence, dizziness, and discontinuation rates for all causes and serious adverse events (six RCTs).

Indirect comparisons were also reported (see paper for more complete details); in general these results supported the head-to-head trials.

**Authors’ conclusions**
The benefit-risk ratio of tapentadol appeared to be improved compared to step three opioids.

**CRD commentary**
The review question was supported by clearly defined inclusion criteria and several sources were searched without restrictions to language or publication type. Steps were taken to minimise the possibility of reviewer error or bias in the selection of trials, data extraction and assessment of trial quality. Appropriate criteria were used to assess study quality and individual trial results were reported. With exception of the tapentadol trials, the overall methodological quality was considered to be poor. Only ten of the forty-two trials included were eligible for analysis of patients with severe chronic pain. The pooling of trials appeared appropriate, and heterogeneity was assessed but not reported. It should be considered that most evidence between tapentadol and step three opioids, other than oxycodone, is based on indirect evidence of largely poorer quality trials, but the authors’ conclusion appears suitably cautious.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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