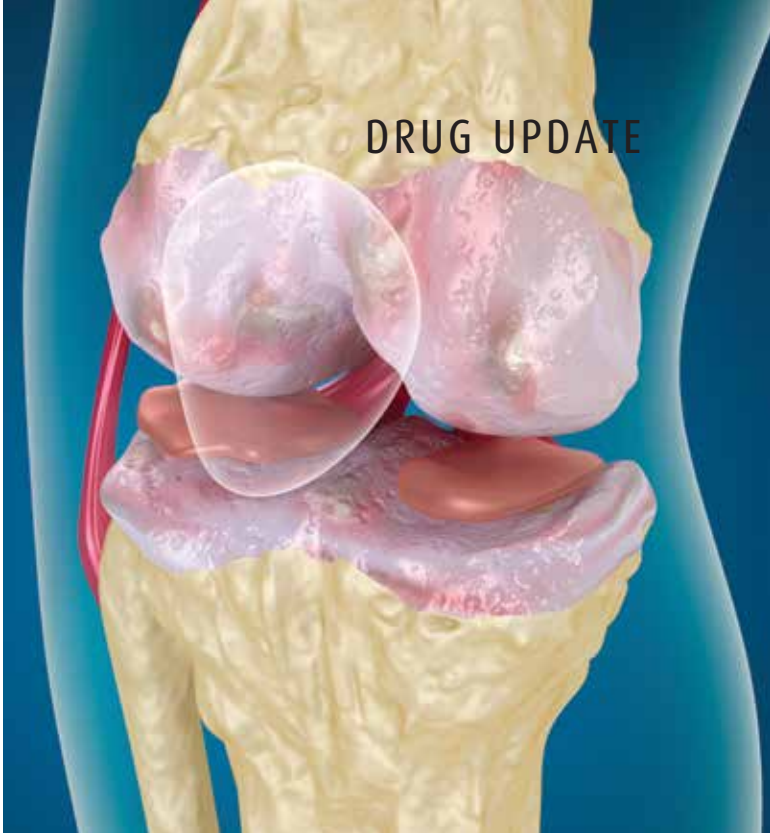

Tapentadol
A new analgesic among the opioids

STEPHAN A. SCHUG MD, FANZCA, FFPMANZCA

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Tapentadol offers equianalgesic effects to conventional opioids with reduced gastrointestinal adverse effects and possibly a lower abuse potential. It is a representative of a new class of analgesics relying on the analgesic synergy between mu-receptor agonism and noradrenaline reuptake inhibition.

Tapentadol is a recently registered analgesic for the treatment of chronic moderate to severe pain that relies on the synergy between mu-receptor agonism and noradrenaline reuptake inhibition to provide pain relief. It is not really a new opioid but a representative of a new class of analgesics relying on this analgesic synergy.

WHAT IS THE MEDICATION?

A slow-release preparation of tapentadol has been recently approved by the TGA for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesics. However, tapentadol is not yet listed on the PBS.

Tapentadol represents a novel analgesic drug in so far as it relies on a dual mode of action. On the one hand, it is a mu-opioid receptor (MOR) agonist, although with much lower affinity for this opioid receptor than, for example, morphine. In addition, tapentadol is a noradrenaline reuptake inhibitor (NRI), thereby amplifying descending inhibitory pathways of pain control. The two mechanisms of action have been shown to be synergistic in animal models; the proposal for a class name is MOR–NRI.

Theoretically, this synergy would suggest reduced adverse effects in comparison to equianalgesic doses of pure mu-agonists, a reduced abuse potential and possibly an increased efficacy in neuropathic and dysfunctional pain states. The informed reader might recognise similarities to tramadol; however, there are several relevant differences.[1] Tapentadol relies neither on the racemic mixture of two stereoisomers with different effects nor on metabolism to achieve the mu-agonist effect. It also has a greater intrinsic activity at the mu-receptor than the tramadol metabolite, and only minimal and possibly clinically irrelevant serotonin reuptake inhibition.

WHEN IS IT USED?

Tapentadol has been in clinical use for several years in the USA and Europe for the treatment of various acute and chronic pain states. The extended-release formulation of tapentadol has been studied in clinical trials for the management of chronic nonmalignant pain in conditions such as osteoarthritis, low back pain and diabetic polyneuropathy. Only limited data are available at present on the use of tapentadol in the management of malignant pain.

A systematic review based on 42 clinical trials compared tapentadol directly with oxycodone and indirectly with other strong opioids.[2] The findings were a comparable efficacy in moderate to severe pain with reduced gastrointestinal adverse events compared with fentanyl, hydromorphone, morphine, oxymorphone and oxycodone, leading to a significant reduction of treatment discontinuation. These results have been confirmed by several more recent meta-analyses.

Professor Schug is Chair of Anaesthesiology in the School of Medicine and Pharmacology – Pharmacology, Pharmacy and Anaesthesiology Unit, University of Western Australia, and Director of Pain Medicine at the Royal Perth Hospital, Perth, WA.

HOW IS IT USED?

Current treatment recommendations suggest that opioid-naïve patients should be started on tapentadol 50 mg twice daily, with subsequent titration to pain relief up to a currently recommended maximum daily dose of 500 mg.

For patients who are already taking an opioid, opioid switching is possible and has been performed successfully in several clinical trials. These identified a conversion ratio between oral morphine equivalents and tapentadol of 1:3.3 in both directions.[3] This is confirmed by a ratio of 1:5 when switching from oxycodone to tapentadol, i.e. 1 mg of oxycodone can be replaced by 5 mg of tapentadol.[4]

The lack of an immediate-release preparation of tapentadol on the Australian market makes this analgesic not suitable for the management of acute pain states.

ADVERSE EFFECTS

Adverse effects

A meta-analysis of nine trials involving almost 8000 patients showed that tapentadol in comparison with oxycodone reduces the risk of typical opioid-based adverse effects such as nausea, vomiting, constipation, dizziness, somnolence and pruritus, but increases the risk of dry mouth (and dyspepsia in one trial).[5] A comparison between tapentadol and the oxycodone–naloxone combination with regard to constipation has not yet been published.

PRECAUTIONS

Use in patients with renal or hepatic impairment

Tapentadol is primarily metabolised by glucuronidation, and subsequent excretion of the glucuronides is via the kidneys. None of the metabolites have a relevant analgesic effect and, therefore, neither renal impairment nor hepatic impairment requires dose adjustment, as long as these impairments are not severe.

Drug interactions

Similar to other opioids, interactions of tapentadol with CNS depressants are of relevance. Also, its use in patients taking monoamine oxidase inhibitors is contraindicated.

The risk of a serotonin syndrome when tapentadol is used in combination with serotonergic drugs is only theoretical and has not been established in clinical trials.

Potential for abuse

Due to its opioid-receptor affinity, tapentadol has been scheduled as a S8 drug in Australia (a Controlled Drug). Although there were significant concerns about the risk of abuse of tapentadol, the limited data from experience in the USA suggest that immediate-release tapentadol had very low population-based rates of abuse and diversion. These rates were similar to rates for tramadol and lower than rates for conventional opioids such as oxycodone and hydrocodone (not TGA approved or available in Australia).[6]

In addition, it was found that the risk of 'opioid doctor shopping' (i.e. the obtaining of opioid prescriptions from multiple prescribers) was lower with tapentadol than with oxycodone.[7]

If these findings can be confirmed in further studies and clinical practice, tapentadol will offer an interesting alternative to conventional opioids in the setting of chronic pain.

CONCLUSION

Tapentadol is a representative of a new class of analgesics relying on the analgesic synergy between mu-receptor agonism and noradrenaline reuptake inhibition. It offers equianalgesic effects to conventional opioids with reduced gastrointestinal adverse effects leading to better compliance. It might also have a lower abuse potential and may play a role in the management of neuropathic pain, but further studies are needed to support these assumptions. MT

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COMPETING INTERESTS: Professor Schug is a member of the International and the Australian Advisory Boards on tapentadol. The Anaesthesiology Unit of the University of Western Australia, but not the author personally, receives honoraria and consulting fees from Grünenthal, the manufacturer of tapentadol.