Tapentadol for the management of cancer pain in adults: an update

Jason W. Boland

Purpose of review
Tapentadol is the first of a new class of analgesics, having synergistic μ-opioid receptor agonist and noradrenaline reuptake inhibitory actions. It has been widely researched in many areas of pain, often in noninferiority studies against potent opioids. This review describes all randomized and recent nonrandomized studies of tapentadol in adults with cancer pain.

Recent findings
Tapentadol has been shown to be at least as effective as morphine and oxycodone in five randomized (two of which were multicenter and double-blind) and a range of nonrandomized trials, although caution is needed when interpreting these results. It is effective in both opioid-naive patients and those already taking opioids. By having a lower μ-opioid receptor binding affinity, it has fewer opioid-related toxicities such as constipation and nausea. A recent randomized trial comparing tapentadol to tapentadol plus duloxetine in patients with chemotherapy-induced peripheral neuropathy shows similar improvement in both groups in a range of pain relieving and quality of life measures, with similar adverse effects.

Summary
Tapentadol has been shown in a range of studies to be an effective analgesic and thus should be considered as an alternative to morphine and oxycodone, especially when opioid toxicities are an issue.

Keywords
cancer, opioids, pain, tapentadol

INTRODUCTION

Tapentadol has been marketed in Australia, Europe, and the USA for at least 12 years [1▪▪] and it is being increasingly used [2,3]. Tapentadol was synthetized using rational drug-design to create a molecule with μ-opioid receptor (MOR) agonism and noradrenalin reuptake inhibition (NRI) (Fig. 1) [4]. It is the first of a new class of MOR-NRI drugs and the only one of this class available [4–6▪▪,7]. As well as being a MOR agonist, tapentadol blocks the reuptake of noradrenalin, potentiating the inhibitory effect of noradrenalin (which is ordinarily released by activation of the descending inhibitory pathway) [4–6▪▪,7]. It thus inhibits pain signaling by acting on both ascending and descending pathways (Fig. 1) [4,5,8]. MOR activation is particularly relevant for reducing acute nociceptive pain. As preclinical studies show inhibitory descending pathways can protect against the development of chronic pain, NRI limits central sensitization, reducing the progression of acute to chronic neuropathic pain [4,8,9].

Other opioids, such as morphine, fentanyl, and oxycodone, produce their main analgesic effects by activating MOR [10]. Tramadol also has serotonin and NRI actions leading to analgesia [1▪▪,7], although the balance of serotonin at the different 5HT receptors in the pain pathway can have variable effects on pain transmission, being facilitatory in chronic pain [4]. Tapentadol has no clinically relevant effect on serotonin, so it potentially has more predictable analgesic properties across a range of clinical pain situations.

Like many other opioids, tapentadol is available in both immediate and modified/slow-release preparations [11]. The modified release preparations are called prolonged release (PR) or extended release [11]. As per the electronic medicines compendium (emc) Summary of Product Characteristics, PR will be used

Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, Hull, UK.

Correspondence to Jason W. Boland, PhD, FRCP, SFHEA, Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, Hull, UK. Tel: +44 (0) 1482 463464; e-mail: jason.boland@hyms.ac.uk

Curr Opin Support Palliat Care 2023, 17:90–97
DOI:10.1097/SPC.0000000000000641

KEY POINTS

- Tapentadol is a centrally acting μ-opioid receptor agonist and noradrenaline reuptake inhibitor.
- Noninferiority studies show it is at least as effective as morphine and oxycodone.
- It is effective in both opioid-naive patients and those already taking opioids.
- Tapentadol has a lower incidence of nausea and constipation compared with morphine and oxycodone.
- Tapentadol could be considered an alternative to morphine and oxycodone.

for all modified or slow-release preparations in this article [12]. Dosing information in different clinical situations and cautions are also detailed here [12].

Tapentadol is approximately two to three times more potent than tramadol, two to three times less potent than morphine, and five times less potent than oxycodone [1▪▪]. As none of Tapentadol's metabolites are analgesic, and it is metabolized by hepatic glucuronidation, not cytochrome P450 enzymes, it has fewer drug–drug interactions and interindividual variability due to cytochrome P450 genetic polymorphisms compared to tramadol and other opioids; clearance is reduced by hepatic dysfunction [1▪▪,11,13]. As a low-efficacy MOR agonist [14▪], with up to a 50 times lower MOR binding affinity compared to morphine [6▪▪], tapentadol has the potential for fewer opioid adverse effects [5]. In preclinical pain models, it provides highly effective analgesia comparable to morphine and oxycodone, despite moderate MOR affinity and relatively moderate NRI activity [6▪▪,10]. These two central actions are synergistic in terms of analgesic efficacy but not toxicity [8,15].

In terms of adverse effects, the concept of μ-load of tapentadol (the % contribution of the opioid component to the adverse effect magnitude relative to a pure MOR agonist at equianalgesia) in respiratory depression and constipation has been used [8,10]. The μ-load of tapentadol is less than or equal to 40% (relative to pure MOR agonists, μ-load 100%) [10]. The reduced μ-load of tapentadol reduces opioid-related adverse events, such as endocrine and gastrointestinal (GI) adverse effects [8,16].

Pain in patients with cancer is common and often moderate or severe [4]. Over 60% of patients with advanced cancer have pain; a similar proportion of those receiving anticancer treatment have pain, and 33% of those receiving curative cancer treatment have pain [17]. Mechanisms include being due to the cancer itself (60% nociceptive, 20% neuropathic, and 20% a combination of neuropathic and nociceptive pain), as well as treatment-related causes. Pain in patients with cancer can also be caused by other comorbidities. This article will focus on reviewing the clinical literature on the efficacy and toxicity of tapentadol in patients with cancer pain.

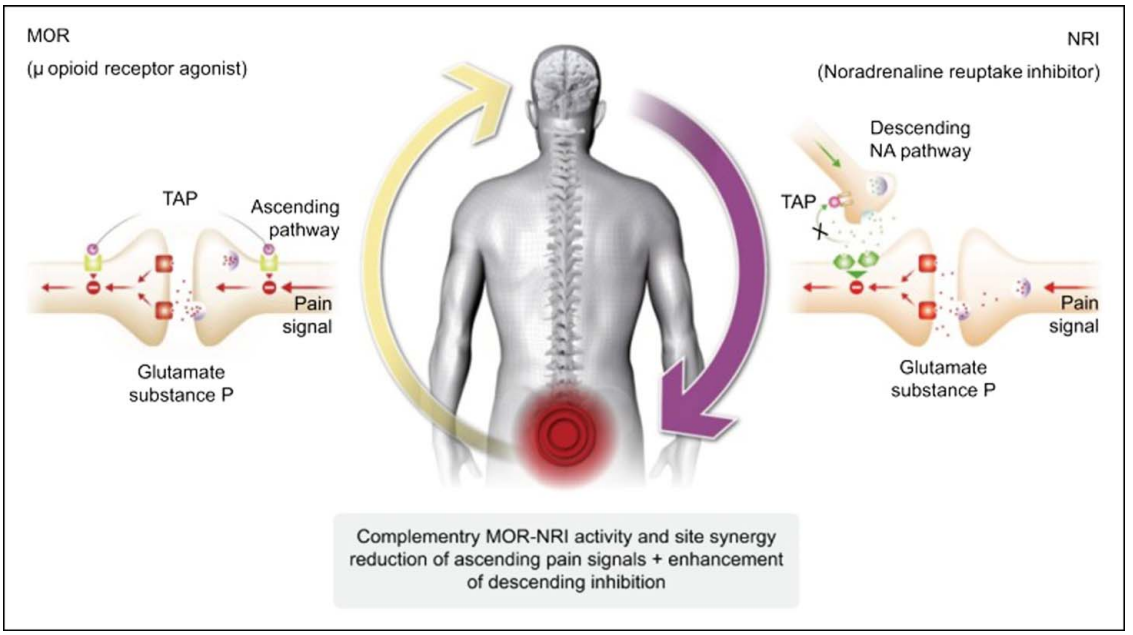

FIGURE 1. Tapentadol: mechanism of action at spinal level. MOR, μ-opioid receptor; NRI, noradrenaline reuptake inhibitor; NA, noradrenaline; TAP, tapentadol. Reproduced from Romualdi *et al.* [4].

CLINICAL STUDIES

The following sections will summarize the clinical studies of tapentadol in patients with cancer pain. Tapentadol has been tested in patients with cancer and noncancer (some of the studies in the latter population are over the longer-term and thus will be briefly covered at the end of this article). The cancer pain studies primarily include European, Japanese, and Korean patients. These include those who are opioid-naive and have been pretreated with other opioids, patients with different pain etiologies (nociceptive, neuropathic, and mixed), with pain from solid cancers or hematological malignancies; and patients experiencing pain conditions due to anticancer treatment.

There are five randomized-controlled phase III trials of tapentadol in patients with cancer pain and many other nonrandomized studies. The five randomized studies will initially be described, followed by the recent nonrandomized studies, before coming to the longer-term data from chronic noncancer pain studies.

Randomized-controlled phase III trials of tapentadol in patients with cancer pain

Previous reviews, including a Cochrane review [18], included four randomized-controlled trials (RCTs) with greater than 1000 adults with moderate to severe cancer pain [19]. Subsequent to these studies, which compared tapentadol to morphine, oxycodone, and/or placebo, there has been an RCT ($n = 114$) comparing tapentadol to tapentadol plus duloxetine in patients with chemotherapy-induced peripheral neuropathy (CIPN) [20▪]; (Table 1).

Due to heterogeneous designs, no pooling of data has been possible [18,19]. All the studies were small or medium-sized, but overall, most studies were considered to have a low (or uncertain) risk of bias in most domains in the Cochrane review [18]. One trial was open-label [22], and one trial was stopped early due to rescue medication problems, so it was underpowered and unpublished [24]; caution is thus needed in interpreting the results of these studies [18]. Other than the recent study, which was unfunded [20▪], all the other studies were funded by pharma [18,21–24].

All studies show that tapentadol generally controls pain well, similar to morphine and oxycodone. Most were noninferiority studies. In general, there was less constipation with tapentadol, with otherwise similar adverse effects between tapentadol, morphine, and oxycodone [18,19,21–24].

Two of the five RCTs that assessed tapentadol PR in moderate to severe cancer pain were multicenter, randomized, double-blind, active-controlled phase III studies [21,23]. One was conducted in Japan and Korea [23], and the other was in Europe [21].

In the Asian study, tapentadol PR was at least as effective in cancer-related pain relief as oxycodone PR in terms of response (≥ 30 or $\geq 50\%$ decrease in pain intensity compared with baseline) [23]. The Patient Global Impression of Change study showed tapentadol was at least as good as oxycodone in providing sufficient pain relief. There was significantly less constipation with tapentadol compared with oxycodone [23].

The European trial evaluated the efficacy and tolerability of tapentadol PR compared with placebo and morphine PR [21]. Differing from the Asian study, this trial included patients who were either opioid-naive or opioid-pretreated (up to a maximum dose of 160 mg morphine equivalent per day) and who were dissatisfied with their prior analgesic medication. Tapentadol was effective compared with placebo (responder rate odds ratio: 2; $P = 0.02$), and has comparable efficacy to morphine (responder rate: 76% for tapentadol vs. 83% for morphine). Tapentadol was associated with better GI tolerability. [21]. A post-hoc subgroup analysis of this RCT [21] was performed in patients who were dissatisfied with their previous tramadol treatment and who had a pain intensity greater than or equal to 5 before converting to tapentadol PR ($n = 129$) [25]. This showed patients with moderate to severe chronic cancer pain can safely be converted from tramadol to tapentadol, with 70% experiencing a pain reduction and similar tolerability [25].

A Japanese randomized, open-label, phase III study included 100 patients with moderate to severe cancer-related pain well controlled on an opioid [22]. Conversion from previous strong opioids to starting daily dose tapentadol PR (50–250 mg twice daily) was based on the dose of previous opioid treatment. Conversion to tapentadol was effective in terms of pain control and safe, with improved GI tolerability (including constipation and vomiting) versus morphine [22].

The recent RCT included 114 patients with CIPN who were randomized in a double-blind, single-center study to receive tapentadol ($n = 56$) or tapentadol plus duloxetine ($n = 58$) for 28 days [20▪]. In both arms, pain, as measured by the 11-point numerical rating scale (NRS) and Douleur Neuropathique 4 score, was equally reduced at all timepoints ($P < 0.05$ compared to baseline), with no difference between groups at any timepoint. Hospital Anxiety and Depression Scale score, Quality of Life score, Pain-Catastrophizing Scale, were all improved ($P < 0.05$) from baseline in both groups. There was no difference in overall adverse events between groups. The noninferiority

Table 1. Summary of randomized-controlled phase III trials of tapentadol in patients with cancer pain

References	Type of study Country	Objective	Participants	N	Interventions	Duration	Tools used	Outcomes
Sansone *et al.* [20▪]	Single-center, randomized, double-blind, controlled, noninferiority trial Italy	To assess analgesic and safety noninferiority of tapentadol alone compared to tapentadol plus duloxetine in patients with chemotherapy-induced peripheral neuropathy	Adult patients with chemotherapy-induced peripheral neuropathy lasting more than 1 month	114	Tapentadol versus tapentadol plus duloxetine tapentadol 50–500 mg/day ($n=56$) or tapentadol 50–500 mg/day plus duloxetine 60–120 mg/day ($n=58$)	4 weeks	NRS-11 points DN4 PCS HADS PRS EORTC QLQ-CIPN20 LEPs	Tapentadol reduced pain equivalent to tapentadol/duloxetine. At days 7, 14, 21, 28, and 42, the mean NRS score was significantly ($P<0.05$) reduced from baseline in both groups. Mean difference between initial NRS and at 28 days was −4.21 in the tapentadol group and −4.4 in the tapentadol/duloxetine group Similar improvements in quality of life, anxiety and depression ($P<0.05$) from baseline No difference between groups No difference in overall adverse effects between groups
Kress *et al.* [21]	Enriched-enrollment, randomized withdrawal, double-blind, phase III multicenter noninferiority, parallel-group, active- and placebo-controlled, efficacy trial 16 countries, Europe	To assess the efficacy and tolerability of tapentadol vs. placebo and morphine in the treatment of moderate to severe cancer pain	Chronic moderate to severe tumor-related pain (NRS ≥ 5/11) Either opioid-naive or opioid-pretreated (up to a maximum dose of 160 mg morphine equivalent per day, and who were dissatisfied with their prior analgesic medication)	496 randomized (2:1) into titration phase, 327 re-randomized (1:1) entered maintenance phase, 217 completed protocol	Tapentadol vs. placebo Titration: tapentadol ($n=338$) vs. morphine ($n=158$) Maintenance: tapentadol PR 100–250 mg twice daily ($n=106$) Morphine PR 40–100 mg twice daily ($n=109$) Placebo ($n=112$) Rescue medication: morphine IR 10 mg	Screening: 1 weeks Titration: 2 weeks (tapentadol or morphine) Maintenance: 4 weeks (tapentadol or morphine or placebo)	NRS-11 points AEs were monitored throughout the study period	Maintenance period responder rates were 50% (placebo), 62% (tapentadol) and 69% (morphine). Tapentadol was superior to placebo (responder rate odds ratio: 2; $P=0.02$) and not inferior to morphine (end of titration responder rates: 76% tapentadol vs. 83% morphine). Most widely used mean dose of tapentadol 300 mg/day. Tapentadol exhibited better GI tolerability profile than morphine (titration stage)
Imanaka *et al.* [22]	Randomized, open-label, parallel-group, multicenter phase III noninferiority clinical trial Japan	To appraise the effectiveness and tolerability of Tapentadol in patients with chronic, moderate to severe oncological pain, in patients who rotated from another opiate and whose pain was well controlled (to assess maintenance of efficacy)	Adults with chronic moderate-to-severe cancer pain controlled with strong opioids, NRS ≤ 4/11	100	Tapentadol PR titrated to equivalent of previous total daily opioid dose (100–500 mg/day), $n=50$ Morphine PR titrated to equivalent of previous total daily opioid dose (20–140 mg/day), $n=50$ Rescue medication: IR oral morphine or oxycodone Duration of treatment: 4 weeks	Screening: 1–2 weeks (on previous opioid) 8 weeks treatment	NRS-11 points PGIC AEs and withdrawals were monitored throughout the study period	Successful conversion from previous opiate to tapentadol (maintenance of analgesia in 84% of the sample). Mean dose Tapentadol (SD) at 8 weeks 173.5 (101.51) mg/day. Overall safety profile similar. Better GI safety profile (including constipation and vomiting) than MOR

Table 1. (*continued*)

References	Type of study Country	Objective	Participants	*N*	Interventions	Duration	Tools used	Outcomes
Imanaka *et al.* [23]	Randomized, double-blind, multicenter, parallel-group, active control phase III noninferiority trial Japan and Korea	To evaluate the efficacy and safety of prolonged-release tapentadol vs. OXY in the treatment of moderate to severe chronic cancer-related pain noninferiority analgesic effect of tapentadol efficacy versus oxycodone	Chronic moderate to severe cancer-related pain (NRS $\geq$4/11), requiring opioid treatment (investigator assessment) opioid naive	343 randomized 236 completed treatment	Tapentadol PR (25–200 mg twice daily), n=168 Oxycodone PR (5–40 mg twice daily), n=172 Rescue medication: oral morphine IR 5 mg	4 weeks treatment 1-week post-treatment	NRS-11 points PGIC AEs and Withdrawals were monitored throughout the study period	Tapentadol efficacy was not inferior to oxycodone both treatments reduced average pain intensities by 2.6–2.7 points on the 11-point NRS no difference in rescue medication Tapentadol had better GI tolerability profile
Grünenthal [24] (unpublished)	Enriched-enrollment, randomized-withdrawal, parallel-group, active- and placebo-controlled, double-blind efficacy multicenter phase III trial	To evaluate the effectiveness and safety of tapentadol in the treatment of chronic tumor-related pain compared with placebo and morphine	Chronic tumor-related pain. Opioid naive or previously treated (up to 160 mg/day oral morphine equivalent), without satisfactory pain control ($\geq$5 on 11-point NRS)	93 Early termination, due to a recall of the morphine rescue medication and issues regarding supply of an alternative. Planned enrollment was 573 participants. 93 (16%) available for analysis	Tapentadol PR 100–250 mg twice daily (titration and maintenance) Morphine PR 45–90 mg twice daily (titration and maintenance) Placebo (maintenance) Rescue medication: morphine IR	Two-week titration phase (morphine or tapentadol) Four-week maintenance phase (morphine or tapentadol or placebo)	NRS-11 points PGIC	PGIC improved at end of maintenance phase. Treatment-related adverse events reported in 80% of the morphine arm and 63% of the tapentadol group. Underrecruited, so caution with interpretation

DN4, douleur neuropathique 4; EORTC QLQ-CIPN20, European Organization for the Research and Treatment of Cancer Quality of Life Chemotherapy-Induced Peripheral Neuropathy Questionnaire; GI, gastrointestinal; HADS; Hospital Anxiety and Depression Scale; IR, immediate release; LEPs, laser-evoked potentials; NRS, numerical rating scale; PCS, Pain-Catastrophizing Scale; PGIC, Patient Global Impression of Change; PR, prolonged release; PRS, Pain Relief Scale.

of tapentadol in terms of efficacy was shown. The mean total daily dose of tapentadol was higher in the monotherapy arm (104.5 vs. 51.6 mg) [20▪]. Ideally, a duloxetine monotherapy arm (or a standard treatment for CIPN) would have also been included for comparison. This study, however, shows that tapentadol at higher doses is similar to tapentadol plus duloxetine (both at lower doses). This study included patients with CIPN of only greater than 1 month duration; it might thus be more likely to spontaneously resolve (there was no placebo control arm to account for the natural history); this might partly account for the large effect sizes seen in both study arms.

In summary, there are five randomized-controlled phase III trials assessing the analgesic effect and adverse effects of tapentadol versus placebo, morphine, oxycodone, or tapentadol plus duloxetine in adults with moderate to severe cancer pain. These are mostly noninferiority trials, and they show tapentadol is at least as effective as morphine or oxycodone and more effective than a placebo. Tapentadol had fewer GI adverse events (Table 1).

Nonrandomized studies of tapentadol in patients with cancer pain

In addition to the aforementioned randomized-controlled phase III trials, there have been several recent nonrandomized studies of tapentadol, including two prospective and four retrospective studies, which are detailed in this section.

A total of 650 patients (including 349 with moderate to severe chronic cancer pain) completed a prospective, open-label, 13 center trial in Korea [26]. They could be either using other analgesics or not. In the patients with cancer, at week 4, tapentadol significantly reduced pain by 2.1 points (from a mean of 7 to 4.9) on an 11-point NRS; this was maintained during the 6-month observation period. Over 90% of the patients reported an improvement in their pain from the clinical global impression change tool; this was statistically significant [26].

A small prospective open-label Italian study included 31 patients with CIPN [27]. Seven patients (23%) discontinued tapentadol after 1 week due to nonserious adverse events, and another patient withdrew. After 3 months of tapentadol, 19/22 (86%) had analgesic efficacy with tapentadol ($\geq$30% reduction of pain intensity on the NRS); 15/22 (68%) had greater than or equal to 50% decrease. Compared to baseline, at 3 months, tapentadol significantly reduced the NRS and Douleur Neuropathique 4 ($P<0.001$) and improved global health status ($P=0.046$) [27].

In a retrospective comparison study, 127 Japanese cancer patients with neuropathic pain were administered tapentadol ($n=29$), methadone ($n=32$), oxycodone ($n=20$), fentanyl ($n=26$), or hydromorphone ($n=20$) [28]. The mean pain reduction was significantly greater in the tapentadol group than in the oxycodone group at all timepoints (day 7 $P=0.0024$). There was a nonsignificant trend for greater pain reduction in the tapentadol group, compared to the methadone, fentanyl, and hydromorphone groups. No patients were discontinued in the tapentadol group versus methadone 6.3% versus oxycodone 5.0% versus fentanyl 3.8% versus hydromorphone, 10.0% [28].

A retrospective single-center study in 84 Japanese patients with moderate to severe cancer pain evaluated the effectiveness, safety, and tolerability of tapentadol [29]. 93% greater than or equal to 50% reduction in NRS score from baseline. Median NRS score decreased from 7 at baseline to 2 at initial pain relief, further decreasing to 1 at the end of the maintenance period ($P<0.0001$). Tapentadol was effective in opioid-naive and tolerant patients (>90% had $\geq$50% reduction in NRS) within a median of 3 days. Effectiveness was seen in patients with nociceptive, neuropathic, or mixed pain. At baseline, 22 of 84 (26%) had nausea and 19 were opioid-tolerant; the nausea resolved in nine of these (47%). However, three opioid-tolerant patients experienced tapentadol-related nausea. There were no discontinuations due to serious adverse events [29].

In a retrospective multicenter study in Japan, the safety and discontinuation of tapentadol were assessed [30]. Nine hundred and six patients with cancer were included, and 685 (76%) patients were followed up until tapentadol was stopped. In 119 cases (17%) this was due to adverse events. These were most commonly nausea (5%), drowsiness (2%), delirium, and cardiovascular symptoms (1%); most of these occurred within 28 days of starting tapentadol [30].

A single-center Japanese retrospective study evaluated how tapentadol was used in clinical practice [31]. One hundred seventy-five cancer patients were included; of these, 45 (26%) in whom tapentadol was started were opioid-naive. It was most often started by the palliative care team ($n=121$; 69%), especially in patients with neuropathic pain or with a history of nausea. In 14 (8%) cases, it was stopped due to adverse effects [31].

In summary, all these recent prospective and retrospective nonrandomized studies of tapentadol indicate that tapentadol is safe and effective in the management of cancer pain. They are, however,

uncontrolled and most were retrospective, and thus, although they may potentially give some clinical practice data, they are prone to bias, do not account for the natural history of the disease and pain, and thus must be interpreted with caution.

Chronic noncancer pain studies

Two recent systematic reviews and three observational studies in patients with noncancer pain are detailed below. In a systematic review of tapentadol for the treatment of neuropathic pain, four out of the five included studies show tapentadol monotherapy to be effective for the treatment of diabetic peripheral neuropathy or chronic low back pain [32]. A systematic review of RCTs and network meta-analysis showed a lower incidence of nausea and constipation with tapentadol compared with other strong opioids in moderate or severe chronic pain [33]. A multicenter, open-label, uncontrolled, observational 72-week extension Spanish study recruited patients with severe knee osteoarthritis pain or low back pain who responded to tapentadol in phase IIIb clinical trials [34]. In the 81 patients included, the mean pain intensity was unchanged over this time. Tapentadol doses remained relatively stable at the end of treatment; 90% of patients reported at least good treatment satisfaction. Pain relief and quality of life were sustained for the 72 treatment weeks. Tapentadol-related adverse events occurred in 18%, constipation (7%) was the most common [34]. In an observational study of tapentadol and other opioids in patients with chronic noncancer pain, tapentadol had better pain relief and tolerability compared to traditional opioids (fentanyl, oxycodone, morphine, buprenorphine, and hydromorphone) [35,36]. A 12-week retrospective German database study in 2331 patients with low back pain reported more responders and better tolerability and safety for tapentadol PR ($P < 0.001$) [37]. Chronic noncancer pain studies confirm the efficacy and tolerability of tapentadol compared to other opioids, with the same caveats as above for the nonrandomized, uncontrolled studies. They give longer-term data on tapentadol in musculoskeletal and diabetic peripheral neuropathy pain conditions and indicate continued effectiveness for up to 2 years' treatment with no evidence of tolerance [11].

CONCLUSION

Tapentadol, a novel MOR agonist and NRI, has been widely studied in many areas of pain. This review outlines all randomized and recent nonrandomized studies of tapentadol in adults with cancer pain. The five randomized-controlled phase III trials (including two multicenter, double-blind trials) show tapentadol is at least as effective as morphine or oxycodone, with fewer GI adverse events. Similar findings are noted in the recent prospective and retrospective nonrandomized studies of tapentadol, which indicate that tapentadol is safe and effective. Chronic noncancer pain studies give longer-term efficacy and tolerability data on tapentadol, indicating continued effectiveness for up to 2 years' treatment with no evidence of tolerance. An area for future research, in view of its MOR and NRI properties, would be how tapentadol would compare to morphine or oxycodone plus amitriptyline. Tapentadol has been shown in a range of studies to be an effective analgesic and thus should be considered as an alternative to morphine and oxycodone, especially when opioid GI toxicities are an issue, when conventional opioids are intolerable, or when long-term analgesic treatment is needed.

Acknowledgements

The author thanks Dr Elaine Boland, Hull University Teaching Hospitals NHS Trust, for her detailed input into this manuscript. Kirsty Morrison, Library and Evidence Support Information Specialist, BMA Library, for conducting the literature searches.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. ■■ Roulet L, Rollason V, Desmeules J, *et al.* Tapentadol versus tramadol: a narrative and comparative review of their pharmacological, efficacy and safety profiles in adult patients. Drugs 2021; 81:1257–1272.

Excellent review of tapentadol's pharmacology, efficacy and adverse effects.

2. Xie J, Strauss VY, Collins GS, *et al.* Trends of dispensed opioids in Catalonia, Spain, 2007-19: a population-based Cohort study of over 5 million individuals. Front Pharmacol 2022; 13:912361.
3. Perello-Bratescu A, Dursteler C, Alvarez-Carrera MA, *et al.* Trends in the prescription of strong opioids for chronic non-cancer pain in primary care in Catalonia: Opicat-Padris-Project. Pharmaceutics 2022; 14:237.
4. Romualdi P, Grilli M, Canonico PL, *et al.* Pharmacological rationale for tapentadol therapy: a review of new evidence. J Pain Res 2019; 12: 1513–1520.
5. Kress HG, Coluzzi F. Tapentadol in the management of cancer pain: current evidence and future perspectives. J Pain Res 2019; 12:1553–1560.
6. ■■ Coluzzi F, Rullo L, Scerpa MS, *et al.* Current and future therapeutic options in pain management: multi-mechanistic opioids involving both MOR and NOP receptor activation. CNS Drugs 2022; 36:617–632.

Excellent overview of Tapentadol actions and binding affinity.

7. Pergolizzi J, Magnusson P, Coluzzi F, *et al.* Multimechanistic single-entity combinations for chronic pain control: a narrative review. Cureus 2022; 14: e26000.
8. Caraci F, Coluzzi F, Marinangeli F, *et al.* Modulation of sensitization processes in the management of pain and the importance of descending pathways: a role for tapentadol? Curr Med Res Opin 2020; 36: 1015–1024.

9. Coluzzi F, Fornasari D, Pergolizzi J, *et al*. From acute to chronic pain: tapentadol in the progressive stages of this disease entity. Eur Rev Med Pharmacol Sci 2017; 21:1672–1683.

10. Raffa RB, Elling C, Tzschentke TM. Does 'strong analgesic' equal 'strong opioid'? Tapentadol and the concept of 'micro-Load'. Adv Ther 2018; 35: 1471–1484.

11. Deeks ED. Tapentadol prolonged release: a review in pain management. Drugs 2018; 78:1805–1816.

12. Electronic medicines compendium (emc): summary of Product Characteristics (SmPC); Palexia SR 100 mg prolonged-release tablets. 2021. https://www.medicines.org.uk/emc/product/11410/smpc. [Accessed: March 1 2023].

13. Homma M, Kokubun H, Okuwaki K, *et al*. Pharmacokinetic analysis, analgesic effects, and adverse effects of tapentadol in cancer patients with pain. Biol Pharm Bull 2020; 43:1000–1006.

14. ■ Manandhar P, Connor M, Santiago M. Tapentadol shows lower intrinsic efficacy at micro receptor than morphine and oxycodone. Pharmacol Res Perspect 2022; 10:e00921.

Evaluated the intrinsic efficacy of tapentadol and other opioids at the MOR.

15. Schroder W, Tzschentke TM, Terlinden R, *et al*. Synergistic interaction between the two mechanisms of action of tapentadol in analgesia. J Pharmacol Exp Ther 2011; 337:312–320.

16. Coluzzi F, Billeci D, Maggi M, *et al*. Testosterone deficiency in non-cancer opioid-treated patients. J Endocrinol Invest 2018; 41:1377–1388.

17. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, *et al*. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage 2016; 51:1070–1090. e1079.

18. Wiffen PJ, Derry S, Naessens K, *et al*. Oral tapentadol for cancer pain. Cochrane Database Syst Rev 2015; 2015:CD011460.

19. Carmona-Bayonas A, Jimenez Fonseca P, Virizuela Echaburu J. Tapentadol for cancer pain management: a narrative review. Pain Pract 2017; 17: 1075–1088.

20. ■ Sansone P, Giaccari LG, Aurilio C, *et al*. Comparative efficacy of tapentadol versus tapentadol plus duloxetine in patients with chemotherapy-induced peripheral neuropathy (CIPN): a randomized non-inferiority clinical trial. Cancers (Basel) 2022;14:4002.

Only recent RCT of tapentadol which compares it against tapentadol plus duloxetine in CIPN.

21. Kress HG, Koch ED, Kosturski H, *et al*. Tapentadol prolonged release for managing moderate to severe, chronic malignant tumor-related pain. Pain Physician 2014; 17:329–343.

22. Imanaka K, Tominaga Y, Etropolski M, *et al*. Ready conversion of patients with well-controlled, moderate to severe, chronic malignant tumor-related pain on other opioids to tapentadol extended release. Clin Drug Investig 2014; 34:501–511.

23. Imanaka K, Tominaga Y, Etropolski M, *et al*. Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain. Curr Med Res Opin 2013; 29:1399–1409.

24. Grünenthal. A study to evaluate the effectiveness and safety of CG5503 (tapentadol) in the treatment of chronic tumor related pain compared with placebo and morphine. clinicaltrials.gov; 2010 NCT00505414. https://clinicaltrials.gov/ct2/show/NCT00505414. [Accessed March 1 2023].

25. Kress HG, Koch ED, Kosturski H, *et al*. Direct conversion from tramadol to tapentadol prolonged release for moderate to severe, chronic malignant tumour-related pain. Eur J Pain 2016; 20:1513–1518.

26. Jung JY, Chon HJ, Choi YJ, *et al*. A prospective, multicenter, open-label study of the clinical efficacy of tapentadol extended-release in the treatment of cancer-related pain and improvement in the quality of life of opioid-naive or opioid-resistant patients. Support Care Cancer 2022; 30:6103–6112.

27. Galie E, Villani V, Terrenato I, *et al*. Tapentadol in neuropathic pain cancer patients: a prospective open label study. Neurol Sci 2017; 38: 1747–1752.

28. Takemura M, Niki K, Okamoto Y, *et al*. Tapentadol in cancer patients with neuropathic pain: a comparison of methadone, oxycodone, fentanyl, and hydromorphone. Biol Pharm Bull 2021; 44:1286–1293.

29. Sazuka S, Koitabashi T. Tapentadol is effective in the management of moderate-to-severe cancer-related pain in opioid-naive and opioid-tolerant patients: a retrospective study. J Anesth 2020; 34:834–840.

30. Iwaki M, Kessoku T, Kanamori T, *et al*. Tapentadol safety and patient characteristics associated with treatment discontinuation in cancer therapy: a retrospective multicentre study in Japan. Pain Ther 2021; 10: 1635–1648.

31. Kubo E, Ishiki H, Abe K, *et al*. Clinical role and safety of tapentadol in patients with cancer: a single-center experience. J Opioid Manag 2022; 18:273–280.

32. Erosa SC, Haffey PR, Mehta N, *et al*. Tapentadol, buprenorphine, and levorphanol for the treatment of neuropathic pain: a systematic review. Curr Pain Headache Rep 2021; 25:18.

33. Freynhagen R, Elling C, Radic T, *et al*. Safety of tapentadol compared with other opioids in chronic pain treatment: network meta-analysis of randomized controlled and withdrawal trials. Curr Med Res Opin 2021; 37:89–100.

34. Mateos RG, Bernal DS, Morera LMT, *et al*. Long-term effectiveness and tolerability of pain treatment with tapentadol prolonged release. Pain Physician 2021; 24:E75–E85.

35. Barrachina J, Margarit C, Muriel J, *et al*. Oxycodone/naloxone versus tapentadol in real-world chronic non-cancer pain management: an observational and pharmacogenetic study. Sci Rep 2022a; 12:10126.

36. Barrachina J, Margarit C, Muriel J, *et al*. Sex differences in oxycodone/naloxone vs. tapentadol in chronic non-cancer pain: an observational real-world study. Biomedicines 2022;10:2468.

37. Uberall MA, Elling C, Eibl C, *et al*. Tapentadol prolonged release in patients with chronic low back pain: real-world data from the German Pain eRegistry. Pain Manag 2022; 12:211–227.