Role of tapentadol in pain management

This article reviews tapentadol, a novel centrally-acting opioid analgesic that exerts its analgesic effects through mu-opioid receptor agonism and additionally via noradrenaline reuptake inhibition. This potentially gives it a role in the treatment of both nociceptive and neuropathic pain.

Appropriate management of acute, chronic and cancer pain remains a considerable challenge for health-care providers. The physiological and psychological effects of uncontrolled pain lead to unnecessary suffering and financial loss, not only to the individual concerned but to the family and society. Current pharmacological treatment options for the management of pain are limited by significant side effects affecting the CNS, cardiovascular system, gastrointestinal system and the respiratory system.

Mechanism of action

Tapentadol is a novel centrally-acting synthetic analgesic licensed in the UK for the management of severe chronic pain (Palexia SR; tapentadol prolonged release) and moderate to severe acute pain (Palexia; tapentadol immediate release) in adults, which can be adequately managed only with opioid analgesics (Grunenthal Ltd, 2011a,b). Its analgesic efficacy is thought to be the result of mu-opioid receptor agonist activity and noradrenaline reuptake inhibition, with both mechanisms residing in a single molecule. Combining mu-opioid receptor agonism with monoamine reuptake inhibition is useful to improve the therapeutic range of opioids. The different, complementary mechanisms of action may additively or even synergistically increase the analgesic efficacy and/or attenuate the side effects of mu-opioid receptor agonists by reducing the requirement for mu-opioid receptor activation. The facilitation of monoaminergic transmission in descending pain inhibitory pathways in the spinal cord seems to be an important mechanism because compounds that block the reuptake of noradrenaline and/or serotonin (5-hydroxytryptamine; 5-HT) are efficacious in the treatment of chronic pain conditions (Carter and Sullivan, 2002; Tzschentke, 2002) and can enhance the analgesic effect of morphine (Ossipov et al, 1982). This is fairly important because neuropathic pain is generally considered to be relatively unresponsive to opioids (Mao et al, 2000) and/or difficult to treat effectively because of mu-opioid receptor-related side effects (Martin and Eisenach, 2001).

The pharmacological profile of tapentadol confers potential advantages over other agents such as tramadol that also combine mu-opioid receptor agonism and noradrenaline reuptake inhibition. Tramadol is an atypical, racemic opioid that combines weak mu-opioid receptor activation with noradrenaline reuptake inhibition and inhibition of 5-HT (Raffa et al, 1992). Tramadol is metabolized to an active O-desmethyl-metabolite (Lintz et al, 1981). As the parent molecule is metabolized, the contribution of 5-HT and noradrenaline reuptake inhibition is reduced, whereas the contribution of mu-opioid receptor agonism increases, resulting in a complex time- and metabolism-dependent pattern of pharmacological activities. Because tramadol is mainly metabolized via cytochrome P450 2D6 (CYP2D6), which is polymorphic in humans, approximately 5–15% of the white population are 'poor metabolizers' of tramadol and do not experience satisfactory analgesia with standard doses (Poulsen et al, 1996). The analgesic effects of tapentadol on the other hand are independent of metabolic activation, and it has no active metabolites (Terlinden et al, 2010) (*Table 1*).

As the analgesic actions reside in a single enantiomer without requiring metabolic activation, the relative contributions of mu-opioid receptor agonism and noradrenaline reuptake inhibition remain constant. These complementary mechanisms of action may explain the broad clinical efficacy reported in nociceptive and neuropathic pain (Daniels et al, 2009a,b; Hartrick et al, 2009; Afilalo et al, 2010; Buynak et al, 2010; Lange et al, 2010; Schwartz et al, 2011).

Table 1. Comparison of tapentadol and tramadol

	Tapentadol	Tramadol
Molecule	Single enantiomer	Racemic mixture
Mechanism	Mu opioid receptor agonist and noradrenaline reuptake inhibitor	Mu opioid receptor agonist, noradrenaline reuptake inhibitor and 5-hydroxytryptamine inhibitor
Metabolism	Does not require metabolic activation. Metabolized by conjugation with glucuronidic acid	Requires metabolic activation via cytochrome P450 which is polymorphic in humans
Side effects	No serotonin syndrome	Serotonin syndrome
Active metabolites	None	Accumulation can lead to side effects and may need dose adjustments
Drug interactions	Less common	More common as a result of dependence of liver enzymes that also metabolize other drugs

Dr Victor Mendis *is Consultant in Pain Medicine and Anaesthesia, Mid Essex Hospitals NHS Trust, Broomfield Hospital, Chelmsford, Essex CM1 7ET (victor.mendis@meht.nhs.uk)*

Pharmacodynamics

Tapentadol is 18 times less potent than morphine in binding to the human mu-opioid receptor and is 2–3 times less potent in producing analgesia in animal models. In-vitro radioligand binding assays in rat brain membrane preparations have shown tapentadol to have only a modest affinity for the mu-opioid receptor relative to pure mu-opioid receptor agonists such as oxycodone or morphine (Monory et al, 1999), while in-vivo intracerebral microdialysis studies in rats have shown that tapentadol, in contrast to morphine, produces large increases in extracellular levels of noradrenaline (Tzschentke et al, 2007). It has been suggested that the potential for lower reliance on mu-opioid receptor agonism to produce its analgesic effects, because of the contribution of the noradrenaline reuptake inhibition component, may account for the significantly lower level of opioid-associated side effects compared to equi-analgesic doses of oxycodone in clinical trials of tapentadol prolonged release (Lange et al, 2010). Furthermore, because of the lack of significant clinical serotonergic activity with tapentadol, pain facilitation via the descending transmission system is not enhanced, and the side effects caused by increased serotonin in the CNS and the enteric nervous system are avoided (Kress, 2010).

Pharmacokinetics

Absorption

The mean absolute bioavailability after single-dose administration is approximately 32% because of the extensive first pass metabolism of tapentadol. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after dosing with tapentadol immediate release (Grunenthal Ltd, 2011a) and at around 3–6 hours after dosing with tapentadol prolonged release (Grunenthal Ltd, 2011b).

Metabolism and excretion

In humans, the metabolism of tapentadol is extensive with about 97% of the parent compound being metabolized. As discussed previously, the major pathway for metabolism is glucoronidation with 55% of orally administered tapentadol being metabolized to tapentadol-O-glucoronide. Only a small amount is metabolized by phase 1 oxidative pathways; 13% of orally administered tapentadol is metabolized by CYP2C9 and CYP2C19 to inactive N-desmethyltapentadol and 2% is converted to inactive hydroxyltapentadol by CYP2D6 (Tzschentke et al, 2007).

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life is on average 4 hours after oral administration and the total clearance is 1530 +/- 177 ml/min (Grunenthal Ltd, 2011a,b).

Structure

The structure of tapentadol hydrochloride is shown in *Figure 1*.

Current indications for use of tapentadol

Tapentadol is licensed in the UK for the management of severe chronic pain (tapentadol prolonged release) and moderate to severe acute pain (tapentadol immediate release) in adults, which can be adequately managed only with opioid analgesics (Grunenthal Ltd, 2011a,b). These conditions are:

1. Moderate to severe acute pain (post-surgical)
2. Moderate to severe chronic low back pain
3. Severe chronic pain caused by osteoarthritis of the knee
4. Painful diabetic neuropathy.

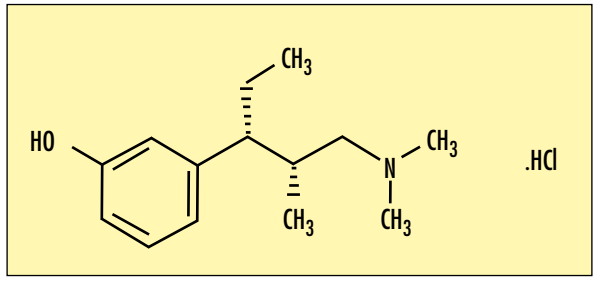
Clinical studies

Tapentadol immediate release for moderate to severe acute pain

The efficacy of tapentadol immediate release for the relief of moderate to severe acute pain has been evaluated in phase III studies in patients with postoperative (bunionectomy) pain (Daniels et al, 2009a,b) and patients with pain related to end stage degenerative joint disease awaiting primary joint replacement surgery (Hartrick et al, 2009). Efficacy of tapentadol immediate release has also been assessed as a secondary end point in a phase III 90-day safety study in patients with lower back pain or osteoarthritis of the hip or knee (Hale et al, 2009).

In a randomized, double-blind, placebo- and active-controlled, parallel group, multi-centre phase III study in 603 patients with postoperative (bunionectomy) pain, treatment with tapentadol immediate release 50 mg, 75 mg and 100 mg over a 72-hour period provided statistically significantly superior analgesia compared with placebo (Daniels et al, 2009a). The most common adverse events, occurring in ≥5% of patients in any group, were nausea, vomiting, constipation, dizziness and somnolence. Post-hoc analyses revealed that tapentadol immediate release 100 mg provided comparable analgesia to oxycodone HCl immediate release 15 mg with a significantly lower incidence of nausea and/or vomiting. In a similarly designed study in 901 patients with postoperative (bunionectomy) pain assessing tapentadol immediate release 50 mg and 75 mg *vs* placebo and oxycodone HCl immediate release 10 mg, analgesic efficacy of both doses of tapentadol was statistically superior to placebo and non-inferior to oxycodone HCl immediate release 10 mg (Daniels et al, 2009b). In this study,

Figure 1. Structure of tapentadol hydrochloride. Adapted from Tzschentke et al (2007).



tapentadol immediate release 50 mg resulted in a numerically lower incidence of nausea, and tapentadol immediate release 75 mg in a statistically lower incidence of nausea and/or vomiting compared with oxycodone HCl immediate release 10 mg.

Hartrick et al (2009) also reported non-inferior analgesic efficacy and superior gastrointestinal tolerability of tapentadol immediate release (50 or 75 mg) compared with oxycodone immediate release (10 mg) in a 10-day phase III, randomized, double-blind, active- and placebo-controlled study in 666 patients with pain related to degenerative joint disease awaiting primary joint replacement.

In the phase III, randomized, double-blind, active-controlled, parallel group, multi-centre, 90-day safety study in 849 patients with lower back pain or osteoarthritis of the hip or knee, tapentadol immediate release was associated with substantially better gastrointestinal tolerability while achieving similar analgesic efficacy compared with oxycodone HCl immediate release (Hale et al, 2009); the mean total daily dose was 284 mg in the tapentadol immediate release group and 42 mg in the oxycodone immediate release group. The percentage of patients discontinuing as a result of adverse events was lower in the tapentadol immediate release group (20.8%) compared to the oxycodone immediate release group (30.6%) with a significant difference in the distribution of times to discontinuation as a result of adverse events, patients in the oxycodone immediate release group consistently discontinuing earlier than patients in the tapentadol immediate release group.

Tapentadol prolonged release for the management of chronic low back pain

In a prospective, randomized, double blind, active- and placebo-controlled, multicentre, phase III study in 981 patients with moderate to severe chronic low back pain, tapentadol prolonged release (100–250 mg twice daily) and oxycodone controlled release (20–50 mg twice daily) significantly reduced mean pain intensity compared with placebo over the treatment period (3-week titration followed by 12-week maintenance period) (Buynak et al, 2010). This study did not directly compare the analgesic efficacy of tapentadol prolonged release and oxycodone controlled release, but the data suggest similar efficacy and a dose equivalency of approximately 5:1 for tapentadol prolonged release to oxycodone controlled release. The most common treatment emergent adverse events (reported by ≥10% patients in any group) were nausea, constipation, headache, vomiting, dizziness, pruritus and somnolence. The incidence of vomiting, constipation and pruritus in the tapentadol prolonged release group was reported to be approximately half of that in the oxycodone controlled release group, and the odds of experiencing constipation or the composite of nausea and/or vomiting were significantly lower for tapentadol prolonged release compared to oxycodone controlled release.

A randomized, open-label phase III study assessed the long-term safety and tolerability of tapentadol prolonged release in 1121 patients with chronic knee or hip osteoarthritis pain, or lower back pain (Wild et al, 2010). Patients received controlled, adjustable, oral, twice daily doses of tapentadol prolonged release (100–250 mg twice daily) or oxycodone HCl controlled release (20–50 mg twice daily) for up to 1 year.

The median duration of treatment for the safety population was more than four times longer in the tapentadol prolonged release group (268.0 days; range 1–385 days) than in the oxycodone controlled release group (59.0 days; range 1–384 days) and the most common reason for treatment continuation in both groups was adverse events (22.7% for tapentadol prolonged release and 36.8% for oxycodone controlled release). The most common treatment emergent adverse events (≥10% of patients in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue and pruritus. The incidence of gastrointestinal treatment emergent adverse events, including nausea, vomiting or constipation, that led to study discontinuation was lower in the tapentadol prolonged release group (8.6%) than in the oxycodone controlled release group (21.5%). For patients completing the study, the mean total daily dose of both tapentadol prolonged release and oxycodone controlled release increased sharply during the first 4 weeks of the treatment period (dose titration), then remained approximately stable at tapentadol prolonged release 390 mg and oxycodone HCl controlled release 74 mg for the remainder of the study giving the same approximate dose equivalency of 5:1 as reported by Buynak et al (2010).

Tapentadol prolonged release and oxycodone controlled release showed similar analgesic efficacy; baseline mean (standard error) pain intensity scores in the tapentadol prolonged release and oxycodone controlled release groups respectively were 7.6 (0.05) and 7.6 (0.11); at end point the mean (standard error) pain intensity scores were decreased to 4.4 (0.09) and 4.5 (0.17) with the scores remaining stable for the maintenance period. The authors suggest that the stability of the mean total daily dose and of the analgesic effect over the maintenance period (week 4 to week 52) support that there was no acquired tolerance at the dose range tested over the 1-year period.

Tapentadol prolonged release in severe chronic pain related to osteoarthritis

In a randomized, double-blind, placebo and active-controlled, parallel-arm, multi-centre study, involving a total of 1030 patients with chronic osteoarthritis-related knee pain, patients received twice-daily doses of tapentadol prolonged release 100–250 mg, oxycodone controlled release 20–50 mg or placebo for a total of 15 weeks (3-week titration and 12-week maintenance period) (Afilalo et al, 2010). Both tapentadol prolonged

release and oxycodone controlled release significantly reduced mean pain intensity scores throughout the treatment period (3-week titration, 12-week maintenance period) with reported mean total daily doses of approximately 350 mg for tapentadol prolonged release and 70 mg for oxycodone controlled release remaining stable during the maintenance period, again yielding a dose equivalency of 5:1. The most common treatment emergent adverse events (≥10% patients) in the active treatment groups were nausea, vomiting, constipation, dizziness, headache, somnolence, fatigue and pruritus. Incidences of constipation and the composite of nausea and/or vomiting were significantly lower in the tapentadol prolonged release group (constipation 18.9%, nausea and/or vomiting 22.7%) compared to the oxycodone controlled release group (constipation 36.8%, nausea and/or vomiting 40.6%).

The improved overall and gastrointestinal tolerability of tapentadol prolonged release are clinically important findings, as tapentadol prolonged release provided more consistent pain relief with better tolerability than oxycodone controlled release, thus allowing patients to adhere to treatment for longer periods of time.

Tapentadol prolonged release in painful diabetic peripheral neuropathy

Painful diabetic peripheral neuropathy affects 10–20% of patients with diabetes and is often difficult to treat. Because of its complex pathophysiology involving both central and peripheral mechanisms, these patients usually require treatment with multiple agents.

In a randomized withdrawal (enriched enrolment), placebo-controlled, double-blind, parallel-group trial in a total of 591 patients with moderate to severe pain from diabetic peripheral neuropathy, tapentadol prolonged release 100–250 mg twice daily provided a statistically significant difference in maintenance of a clinically important improvement in pain compared with placebo and was well tolerated (Schwartz et al, 2011). The most common treatment emergent adverse events that occurred during the double-blind period with tapentadol prolonged release included nausea (13.8%), anxiety (9.2%), diarrhoea (8.2%) and dizziness (7.7%).

The demonstrated safety and efficacy of tapentadol prolonged release in multiple chronic pain populations suggest that it may be particularly useful in pain states with both nociceptive and neuropathic components.

Guidance

The National Institute for Health and Clinical Excellence has not carried out an appraisal of either Palexia or Palexia SR. The Scottish Medicines Consortium (2011) recommended Palexia SR for use in NHS Scotland for the treatment of patients with severe chronic pain, for whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated.

Dosage and administration

As with many centrally acting analgesic medications, the dosing regimen should be individualized according to the severity of pain being treated.

Tapentadol prolonged release 100–250 mg twice daily has demonstrated efficacy and tolerability in the management of moderate to severe chronic osteoarthritis of the knee (Afilalo et al, 2010), moderate to severe chronic low back pain (Buynak et al, 2010), and painful diabetic peripheral neuropathy (Schwartz et al, 2011).

Tapentadol 50–75 mg (4–6-hourly) has demonstrated efficacy and tolerability in the management of moderate to severe postoperative (bunionectomy) pain (Daniels et al, 2009a,b), of moderate to severe pain related to degenerative joint disease (Hartrick et al, 2009) and moderate to severe lower back pain and pain from osteoarthritis of the hip or knee (Hale et al, 2009).

Contraindications

Impaired pulmonary function

Like any other drug with mu-opioid agonist activity, tapentadol immediate or prolonged release is contraindicated in patients with significant respiratory depression in unmonitored settings or the absence of resuscitative equipment.

Monoamine oxidase inhibitors

Tapentadol immediate or prolonged release is contraindicated in patients who are receiving monoamine oxidase inhibitors or who have taken them within the last 14 days because of potential additive effects on noradrenaline levels which may result in adverse cardiovascular events.

Paralytic ileus

Like any drugs with mu-opioid agonist activity, tapentadol immediate or prolonged release is contraindicated in any patient who has or is suspected of having paralytic ileus.

Adverse events

The adverse drug reactions that were experienced by patients in the aforementioned trials were predominantly of mild to moderate severity. The very common adverse events reported were gastrointestinal and CNS events such as nausea, dizziness, constipation, headache and somnolence. However, tapentadol prolonged release demonstrates significant reductions in gastrointestinal side effects when compared with equi-analgesic doses of oxycodone controlled release, associated with patients remaining on therapy for longer (Lange et al, 2010).

Cautions

Tapentadol immediate or prolonged release should be administered with caution to patients with respiratory depression.

Patients receiving other mu-opioid receptor agonist analgesics, phenothiazines, sedative agents or other CNS depressants concomitantly with tapentadol may exhibit additive CNS depression. Tapentadol immediate or prolonged release should not be used in patients who may be susceptible to the effects of raised CSF pressure, including patients with evidence of head injury and increased intracranial pressure.

Tapentadol immediate or prolonged release is a mu-opioid agonist and is a schedule II controlled substance. It can be abused in a manner similar to other opioid agonists.

Conclusions

Tapentadol (immediate or prolonged release) is a novel orally-available centrally-acting opioid analgesic combining mu-opioid receptor agonism and noradrenaline reuptake inhibition in a single molecule. It has been shown to be effective in managing moderate to severe acute nociceptive pain, and severe chronic nociceptive and neuropathic pain. At equi-analgesic doses, tapentadol appears to have an improved gastrointestinal tolerability profile as well as lower rates of discontinuation as a result of side effects compared to oxycodone. **BJHM**

Conflict of interest: Dr V Mendis was a principal investigator for the open label phase III drug trial on tapentadol conducted by Grunenthal Ltd and has received funding for sitting on advisory boards, chairing the drug launch in Essex and giving talks for GPs.

Afilalo M, Etropolski MS, Kuperwasser B et al (2010) Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig* **30**(8): 489–505

Buynak R, Shapiro DY, Okamoto A et al (2010) 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* **11**(11): 1787–804

Carter GT, Sullivan MD (2002) Antidepressants in pain management. *Curr Opin Investig Drugs* **3**: 454–8

Daniels SE, Upmalis D, Okamoto A, Lange C, Haeussler J (2009a) A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. *Curr Med Res Opin* **25**(3): 765–76

Daniels S, Casson E, Stegmann JU et al (2009b) A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin* **23**(6): 1551–61

Grunenthal Ltd (2011a) Summary of Product Characteristics Palexia 50 mg film-coated tablets. www.medicines.org.uk/EMC/medicine/24387/SPC/Palexia+50+mg+film-coated+tablets/ (accessed 21 February 2012)

Grunenthal Ltd (2011b) Summary of Product Characteristics Palexia SR 50 mg prolonged-release tablets. www.medicines.org.uk/EMC/medicine/24389/SPC/Palexia+SR+50+mg+prolonged-release+tablets/ (accessed 21 February 2012)

Hale M, Upmalis D, Okamoto A, Lange C, Rauschkolb C (2009) Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Curr Med Res Opin* **25**(5): 1095–104

Hartrick C, Van Hove I, Stegmann JU, Oh C, Upmalis D (2009) Efficacy and tolerability of tapentadol immediate release and oxycodone HCI immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10 day, phase III, randomised, double-blind, active- and placebo-controlled study. *Clin Ther* **31**(2): 260–71

Kress HG (2010) Tapentadol and its two mechanisms of action: Is there a new pharmacological class of centrally-acting analgesics on the horizon? *Eur J Pain* **14**: 781–3

Lange B, Kuperwasser B, Okamoto A et al (2010) Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv Ther* **27**: 381–99

Lintz W, Erlacin S, Frankus E, Uragg H (1981) Biotransformation of tramadol in man and animal [German]. *Arzneimittelforschung* **31**: 1932–43

Mao J, Price DD, Lu J, Keniston L, Mayer DJ (2000) Two distinctive antinociceptive systems in rats with pathological pain. *Neurosci Lett* **280**: 13–16

Martin TJ, Eisenach JC (2001) Pharmacology of opioid and nonopioid analgesics in chronic pain states. *J Pharmacol Exp Ther* **299**: 811–17

Monory K, Greiner E, Sartania N et al (1999) Opioid binding profiles of new hydrazone, oxime, carbazone and semicarbazone derivatives of 14-alkoxymorphinans. *Life Sci* **64**(22): 2011–20

Ossipov MH, Malseed RT, Goldstein FJ (1982) Augmentation of central and peripheral morphine analgesia by desipramine. *Arch Int Pharmacodyn* **259**: 222–9

Poulsen L, Arendt-Nielsen L, Brosen K, Sindrup SH (1996) The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* **60**: 636–44

Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL (1992) Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther* **260**: 275–85

Schwartz S, Etropolski M, Shapiro DY et al (2011) Safety and efficacy of tapentadol ER in patients with painful diabetic neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin* **27**(1): 151–62

Scottish Medicines Consortium (2011) Resubmission. Tapentadol, 50, 100, 150, 200 and 250mg prolonged-release tablets (Palexia® SR). SMC No. (654/10). www.scottishmedicines.org.uk/files/advice/tapentadol_Palexia_SR_RESUBMISISON_FINAL_MAY_2011_for_website.pdf (accessed 21 February 2012)

Terlinden R, Kogel B, Englberger W, Tzschentke T (2010) In vitro and in vivo characterization of tapentadol metabolites. *Methods Find Exp Clin Pharmacol* **32**(1): 31–8

Tzschentke TM (2002) NA and 5-HT reuptake inhibitors and α2 agonists. In: Buschmann H, Christoph T, Friderichs E, Maul C, Sundermann B, eds. *Analgesics. From Chemistry and Pharmacology to Clinical Application.* Wiley-VHC, Weinheim, Germany: 264–84

Tzschentke TM, Christoph T, Kogel B et al (2007) (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol Hydrochloride (Tapentadol HCl): a novel opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther* **323**: 265–76

Wild JE, Grond S, Kuperwasser B et al (2010) Long term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Pract* **10**(5): 416–27

KEY POINTS

- Tapentadol is a novel centrally-acting analgesic with a dual mode of action – mu opioid receptor agonism and noradrenaline reuptake inhibition.
- It appears to have fewer gastrointestinal side effects compared to other opioids of similar efficacy, and thus patients remain on therapy for longer.
- Its analgesic effects are independent of metabolic activation.
- Tapentadol has no active metabolites.
- It is an effective analgesic for a wide range of acute and chronic pain conditions.
- Owing to its dual mechanism of action, tapentadol is effective for the treatment of both nociceptive and neuropathic pain conditions.