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REVIEW

Tapentadol: an overview of the safety profile

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Abstract: Long-term opioid therapy may be associated with analgesic efficacy and also predictable adverse events, including cardiovascular and pulmonary events, gastrointestinal disorders, endocrinological harms, psychological problems, impairment of driving ability, and risk of abuse. These effects of opioids are mostly due to the wide expression of the mu receptor. Tapentadol, a centrally acting analgesic, is the first agent of a new class of drugs (MOR-NRI), since it combines two mechanisms of action, namely μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition. Noteworthy, MOR activation with tapentadol is markedly lower compared with that exerted by classical opioids, thus likely resulting in fewer opioid-related adverse effects. In this review, we discuss current safety data on tapentadol, with a focus on some specific events, risk of abuse, and driving ability, a well-accepted proxy of the ability of taking critical decisions.

Keywords: tapentadol, safety, pain

Introduction

Opioids are a recognized analgesic treatment, used in clinical practice to manage both acute and chronic pain conditions.[1,2] However, long-term opioid therapy may be associated with a number of adverse events (AEs), including cardiovascular and pulmonary events, gastrointestinal disorders, endocrinological harms, psychological problems, and risk of abuse; those events are frequently observed from the very beginning of therapy.[1,3] Moreover, well-grounded evidence shows that opioid use may be associated with an increased risk of vehicle crashes, a surrogate for safety-sensitive work and decision tasks.[3] The abovementioned effects of opioids are due to the wide expression of the mu receptor.[4]

Tapentadol, a centrally acting analgesic, has been suggested to be the first agent of a new class of drugs (MOR-NRI).[5,6] It combines two mechanisms of action, namely μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI), thus providing a strong analgesic effect by a synergic action.[7] Indeed, traditional opioids (eg, morphine, oxycodone) exert their analgesic effects primarily through a single mechanism—MOR activation.[8] Therefore, the contribution of the opioid component to adverse effects is 100%. In contrast, tapentadol produces its analgesic effect via two separate and complementary analgesic mechanisms, only one of which is targeting MOR, and the other NRI. Remarkably, this last component of tapentadol action can be inhibited by NRI blockers.[9] Moreover, the administration of opioid antagonist like naloxone does not inhibit tapentadol efficacy, thus further supporting the double mechanism of action of this molecule.[10,11] Experimental evidence supporting that NRI is a key mechanism (descending modulating spinal pathway) that can be predominant in chronic/neuropathic pain, reinforces the concept that tapentadol is different to classical opioids and may

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therefore be an a priori choice for the treatment of chronic, neuropathic and mixed pain.[12]

This concept has been strengthened and expanded to other drugs by Raffa and Pergolizzi; they state that the categorization of all analgesics that have any component of opioid mechanism of action into the same class is anachronistic and misleading.[8,13] Noteworthy, MOR activation with tapentadol is markedly lower compared with that exerted by classical opioids, thus likely resulting in fewer opioid-related AEs.[14] In this line, a very recent study suggested that the "μ-load" (the percentage contribution of the opioid component to the adverse effect magnitude relative to a pure/classical μ-opioid at equianalgesia) of tapentadol is ≤40% with respect to pure MOR agonists; this reduced μ-load may translate into a more favorable tolerability profile compared with strong opioids.[13] Indeed, it has been shown that the different pharmacological effects of tapentadol are not synergic in terms of AEs.[15,16]

In this narrative review, we discuss current safety data on tapentadol, with a focus on some specific events, risk of abuse and effects on driving ability.

Overview of safety profile

A very recent comprehensive review by Stollenwerk et al has extensively discussed the tolerability profile of tapentadol on the bases of published studies (n=12,506) and "field-practice" post-marketing data from several databases, including some of Grunenthal (the manufacturer of tapentadol) property (n=10,689).[14] Overall, 7,185 subjects in clinical trials (57.5%) and 777 patients included in "field-practice" databases (7.3%) experienced tapentadol-related AEs, for a total of 18,028 events. μ-receptor-dependent events, such as gastrointestinal, and CNS-related drug reactions were the most frequent. On the other hand, noradrenergic-dependent reactions were negligible. The tolerability profile was similar in the elderly and younger populations.[14] This latter finding is in line with the results of a study by Biondi et al, who conducted a pooled *post hoc* analysis from three trials specifically comparing tapentadol prolonged release (PR) and oxycodone controlled release (CR) in patients aged ≥75 years with moderate-to-severe, chronic osteoarthritis knee or low back pain.[17] Overall, the incidence of gastrointestinal treatment-emergent AEs and vomiting and the composite of nausea and/or vomiting were significantly lower in the tapentadol PR group (all $p \leq 0.0206$).

It is also worth noticing that the long-term safety of tapentadol has been confirmed in several studies,[18,19] with specific data collected in a study over a 4-year period.[20]

Toxicities of special interest

Gastrointestinal effects

Constipation is a well-known side effect of opioid therapy. In recent years, some studies have evaluated the impact of tapentadol on constipation when compared with traditional opioids.

In 2011, Kwong et al examined patient-reported bowel function during two trials on the immediate release (IR) formulation of tapentadol versus placebo and oxycodone IR.[21] Bowel function was comparable between patients on tapentadol IR and those on placebo, and better versus oxycodone IR, both over a short- and long-term period; similar findings were reported for PAC-SYM summary scores collected over a longer term; the use of laxatives was also lower with tapentadol IR.

The low incidence of gastrointestinal AEs with tapentadol was confirmed in *post hoc* meta-analysis of three randomized, multicenter, double-blind trials on tapentadol extended release (ER).[22] Patients affected from moderate-to-severe chronic osteoarthritis knee pain or low back pain treated by either tapentadol ER (n=978) or oxycodone CR (n=999) were investigated. The primary endpoint was a ≥30% pain relief without nausea/vomiting/constipation and without discontinuations (≥30% pain relief/tolerability). After 12 weeks of treatment, patients on tapentadol PR were more likely to have ≥30% than oxycodone CR recipients (OR, 3.15; 95% CI: 2.47–4.00; $p<0.001$), and the achievement of this endpoint was associated with improved quality of life (QoL). These findings suggest that tapentadol ER was associated with significantly better composite outcomes than oxycodone CR.

Similar results were achieved in a pooled analysis of data from four Phase III studies.[23] Patients affected from moderate-to-severe chronic osteoarthritis hip and knee pain or low back pain assigned to placebo (n=993), tapentadol PR (n=1874) or oxycodone CR (n=1224) were investigated. In the placebo, tapentadol PR and oxycodone CR groups, the incidence of gastrointestinal AEs was 26.6% (264/993), 47.3% (887/1,874), and 65.4% (800/1,224), respectively. In the placebo, tapentadol PR, and oxycodone CR groups, moderate or severe constipation was reported in 2.4% (24/993), 8.6% (161/1,874), and 18.5% (226/1,224) of patients, respectively. The superiority of tapentadol PR over oxycodone CR was also reported about other gastrointestinal AEs such as moderate-to-severe nausea and vomiting. These findings were also confirmed in a more recent meta-analysis of two double-blind, randomized, placebo-, and oxycodone CR-controlled Phase III trials enrolling a total of 1,357 patients.[24] Overall, compared with oxycodone CR, the

gastrointestinal tolerability was better with, regardless of patients' age.

Despite these favorable results in a meta-analysis of nine studies with ≥4 weeks' duration on 4,159 patients with non-cancer pain lasting at least 3 months, the pooled analysis on the subgroup of patients with osteoarthritis pain showed no difference between tapentadol PR and oxycodone CR in terms of tolerability.[25] Unfortunately, tolerability was analyzed only in terms of generic withdrawal because of AEs and not considering specific outcomes of gastrointestinal tolerability, such as constipation, nausea, and vomiting. Afterward, superiority of tapentadol PR over oxycodone CR about gastrointestinal tolerability, especially in terms of constipation, nausea, and vomiting, was demonstrated in other studies.[26,27]

While superiority of tapentadol PR over oxycodone CR in terms of gastrointestinal tolerability can be considered as well established, somehow conflicting results seems to emerge from the literature with regards to the comparison with the oxycodone/naloxone PR combination. However, data supporting the gastrointestinal safety of tapentadol PR were collected in studies with a more rigorous design.

Indeed, a systematic review by Thakur et al analyzed the impact of oxycodone/naloxone PR on daily functioning in comparison with tapentadol PR in adult patients with moderate-to-severe chronic cancer and non-cancer.[28] Gastrointestinal AEs (including constipation) in this systematic review demonstrated no statistically significant different incidences between tapentadol PR and oxycodone/naloxone PR. However, this study was affected by severe limitations, including a higher level of baseline pain severity in the tapentadol group and some methodological issues.[29]

Baron et al compared tapentadol PR versus oxycodone/naloxone PR in patients with severe chronic low back pain with a neuropathic component.[30] Tapentadol PR was noninferior to oxycodone/naloxone PR from baseline to final evaluation. In addition, tapentadol PR was associated with significantly lower incidences of constipation and vomiting than oxycodone/naloxone PR during both the titration and overall treatment periods, as well as a significantly lower incidence of mild, moderate or severe nausea, vomiting, or constipation during the titration period.

Ueberall et al evaluated efficacy and tolerability of oxycodone/naloxone PR in comparison with tapentadol PR by data randomly extracted from German Pain Registry on adult patients with chronic low back pain with neuropathic component.[31] Constipation was assessed using bowel function index (BFI) at the end of each treatment week. BFI scores increased from baseline to the end of the observation from 14.9±15.5 to 18.0±15.5 ($p<0.001$) with tapentadol PR and from 16.7±17.1 to 23.2±17.6 ($p<0.001$) with oxycodone/naloxone PR. Percentages of patients with BFI scores within the normal range (ie, ≤28.8) at the end of observation were 72.2% (96/133) for tapentadol PR and 68.0% (87/128) for oxycodone/naloxone PR ($p=0.457$). Regarding the incidence of gastrointestinal AEs, no statistically difference was registered on nausea, vomiting, abdominal pain and constipation; this finding can be attributed, at least in part, to the inherent limitations of the study design.[31–33] However, constipation affected six patients taking oxycodone/naloxone PR and only one patient taking tapentadol PR, nearly achieving statistical significance.

Tapentadol PR and oxycodone/naloxone PR were recently compared also in the field of postoperative pain treatment in orthopedic trauma surgery by Haeseler et al.[34] In this randomized, observer-blinded, active-controlled prospective clinical trial, gastrointestinal AEs showed no statistically difference between the two drugs. In particularly, constipation occurred during observation in 35% of the tapentadol PR patients and in 30% of the oxycodone/naloxone PR patients while vomiting occurred in 3% of the tapentadol PR patients and in 8% of the oxycodone/naloxone PR patients.

Finally, a recent Australian report by Abeyaratne et al focuses on AEs related to tapentadol PR and oxycodone/naloxone PR treatment.[35] The public case reports were extracted from the Australian Therapeutic Goods Administration for tapentadol PR (104 reports) and April 2011–March 2017 for oxycodone/naloxone PR (249 reports). Regarding gastrointestinal AEs, this observation revealed 18 reports for tapentadol PR (17.3%) and 73 for oxycodone/naloxone PR (29.3%). Interestingly, constipation is not reported in detail as AEs for both drugs, while most of the reported gastrointestinal AEs were nausea, abdominal pain and diarrhea.

Hypertension

Hypertension is one of the most frequent co-existing conditions in patients with chronic pain; therefore, the potential effects of analgesic therapy on heart rate and blood pressure are a major concern in patients with this condition. Biondi et al specifically investigated changes in blood pressure and heart rate with tapentadol PR in a large population (n=1464) of patients with hypertension enrolled in three Phase III trials comparing tapentadol with placebo and oxycodone CR.[36] Overall, least-

squares mean changes from baseline to 15 weeks for heart rate with placebo, tapentadol PR, and oxycodone were −0.7 (0.44), 0.2 (0.43), and −0.9 (0.45) bpm. Corresponding figures for systolic blood pressure were −2.4 (0.64), −2.7 (0.64), and −3.7 (0.67) mmHg; and −1.0 (0.39), −1.3 (0.39), and −2.3 (0.41) mmHg for diastolic blood pressure. No clinically meaningful mean changes in heart rate or blood pressure were observed for the evaluated cohorts of patients with hypertension who were treated with tapentadol ER (100–250 mg twice daily). These findings were also consistent when only patients on anti-hypertensive treatment were analyzed. Available data demonstrate that tapentadol has a good cardiovascular safety profile.

Pulmonary function

In a recent randomized, cross-over, placebo-controlled study on 15 healthy volunteers, Van der Schrier et al compared the respiratory effects of tapentadol 100–150 mg with those of oxycodone 20 mg.[37] The main endpoint was the effect of treatment on the ventilatory response to hypercapnia and ventilation at an extrapolated end-tidal CO_2 of 55 mmHg (VE55). Overall, oxycodone 20 mg determined a significantly greater respiratory depressant effect than tapentadol 100 mg (mean difference −5.0 L min^{-1}, 95% CI: −7.1 to −2.9 L min^{-1}, $p<0.01$). Therefore, tapentadol has a lower impact than a μ-pure agonist opioid on respiratory function, probably due to its low μ-load.[8]

Serotonin syndrome

Serotonin syndrome is a collective term for a spectrum of serotonergic adverse reactions that result from overactivation of both central and peripheral serotonin receptors due to increased serotonin levels. This syndrome is characterized by neuromuscular and autonomic hyperactivity, and altered mental status. In the comprehensive analysis of tapentadol-associated AEs by Stollenwerk,[12] there were no reports of correctly diagnosed – namely by the Hunter criteria[38] – serotonin syndrome with tapentadol in clinical trials and only one case in "field-practice" databases. ICT database of Phase II, III, and IV prospective trials report only one case in the NIT database, occurred in a patient on concomitant serotonergic medication. Remarkably, the SmPC of tapentadol has been changed to better define serotonin syndrome according to the Hunter criteria, and avoid false reporting.

The recent Australian report by Abeyaratne et al on adverse drug events related to tapentadol PR treatment showed 52 patients on 104 (50%) reporting nervous system disorders, 16 of which suffering from serotonin syndrome (23.2%).[35] In 14 of 16 patients, the concomitant use of one or more serotonergic agents (tramadol, duloxetine, venlafaxine, amitriptyline, sertraline, desvenlafaxine, escitalopram) was reported. Gressler et al in a systematic review of the literature concluded that the currently available data do not allow to find or to exclude a correlation between tapentadol and serotonin syndrome.[39,40]

Endocrine-related toxicity

Opioid-induced androgen deficiency (OPIAD) is commonly reported in association with opioid therapy.[41,42] Noteworthy, it has been suggested that drugs characterized by dual activity, such as tapentadol, may be associated with a more favorable pattern of endocrine-related toxicity.[42] Eichenbaum et al evaluated the effects of tapentadol in healthy male volunteers versus placebo and morphine and in patients with osteoarthritis, compared with placebo and oxycodone.[41] In addition, they conducted three randomized, double-blind, placebo-controlled clinical studies: a single-dose comparison study of tapentadol IR versus morphine in healthy volunteers, a single dose-escalation study in healthy volunteers without an active comparator, and a multiple-dose study versus oxycodone CR in patients with osteoarthritis. In the first study, serum total testosterone concentrations were similar at baseline for all treatment periods; 6 hrs after dosing, mean concentrations were comparable between placebo (8.6 nmol/L) and tapentadol IR (9.3 nmol/L) but were lower after the administration of morphine IR 30 mg (5.4 nmol/L). Similar results were reported in the second study (tapentadol IR vs placebo). In the third trial, decrease in testosterone concentration from baseline for patients on tapentadol PR (100 mg, −1.9 nmol/L; 200 mg, −2.1 nmol/L) was numerically smaller than with oxycodone CR (−2.7 nmol/L), but higher compared with placebo (−0.3 nmol/L).

In a landmark study, Baron et al compared the effectiveness of tapentadol PR versus oxycodone/naloxone PR in opioid-naive patients with severe chronic low back pain with a neuropathic pain component.[30] The effects of these analgesic therapies on the concentration of testosterone were specifically investigated in male patients aged ≤64 years enrolled in that study who had normal baseline testosterone levels and had completed the opioid treatment. In the tapentadol group, the average testosterone concentration did not change from baseline to final evaluation, while a significant decrease in the

average testosterone concentration was observed with oxycodone/naloxone. Furthermore, a higher percentage of these patients had a low testosterone concentration (<8.4 nmol/L) in the oxycodone/naloxone PR group than in the tapentadol PR.[30] Therefore, available data suggest that tapentadol has a minimal or no impact on testosterone levels and on OPIAD.

Convulsion

Chronic use of opioids in neuropathic pain has been the subject of numerous critical analysis and the relationship between the therapeutic effect and the side effects (particularly on the abuse potential) has been widely debated. Convulsions are a known effect of opioid therapy, likely due to the inhibition of hippocampal gamma-aminobutyric acid release by interneurons, which leads to excitatory effects.[14] However, most opioid convulsions are observed only at dosages higher than those commonly used in clinical practice. In the comprehensive analysis of tapentadol safety by Stollenwerk et al,[14] there were no reports of convulsion in clinical trials or of seizures in "field-practice" studies.

Risk of abuse

An unintended, but frequent, consequence of prescribing opioid analgesics is represented by abuse and diversion of these medications.[43] In 2012, Dart et al estimated abuse and diversion rates for tapentadol IR compared with oxycodone, hydrocodone, and tramadol, by analyzing the RADARS® database.[43] Overall, during the 24 months immediately following its introduction, tapentadol was associated with very limited rates of abuse and diversion. These findings are in line with those of a more recent study but require further analyses before definite conclusions can be reached.[44]

Driving

Some studies evaluating the efficacy and safety of therapeutic opioids report that patients on stable doses of opioid analgesics may be able to drive safely based on individual evaluation.[45–47] However, several medications, including opioid analgesics, are associated with an increased risk of motor vehicle collision and decreased driving ability.[48,49] Medications with MOR activity may adversely affect Tapentadol, in a randomized, controlled Phase III study,[50] was associated with a lower incidence of dizziness and fewer discontinuations due to nervous system adverse effects than oxycodone CR. Based on these considerations, Sabatowski et al conducted a multicenter, open-label, Phase IIIb trial with the aim of evaluating the effects of tapentadol PR on driving ability.[49] In total, 36 patients who had completed previous tapentadol PR trials for severe low back or osteoarthritis pain were evaluated; after ≥6 weeks on a stable dose of tapentadol PR, patients continued treatment (50–250 mg twice daily) and could take tapentadol 50 mg IR, except on the day before or day of the driving test (before the test). The Vienna Test System-Traffic Plus was used to assess cognitive and psychomotor function, and other battery tests were employed to evaluate driving ability. Overall, approximately two-thirds (65.7%) of the patients were deemed to be fit to drive based on the global judgment of driving-specific ability. Total daily tapentadol PR dose (>200 vs ≤200 mg/day) did not affect the evaluation of driving ability.

Although not specifically related to driving, a very recent study on a small number of subjects (n=24, of whom 12 were healthy volunteers) suggested a potential impairment in movement variability during treadmill walking with tapentadol.[51] These findings are to be considered not conclusive so far, and should be investigated in larger studies.

Conclusion

The safety of a drug is a particularly important aspect in chronic therapies, in comorbid patients and in the more sensitive age groups, such as elderly and children (the European Medicines Agency has recently approved a pediatric formulation of tapentadol, on the basis of its safety in this population).[52] Long-term treatment with opioids can be associated with several AEs, also of major severity, risk of abuse and impaired ability to take critical decisions. These effects are largely due to the wide expression of the μ receptor in the different organs and apparatuses.

Therefore, a drug characterized by a dual mechanism of action, such as tapentadol, may exert an effective analgesia while sparing from opioid-related AEs. Indeed, the large experience collected in clinical trials and in "field-practice" studies does support the good tolerability profile of tapentadol. Importantly, safety data for this drug extend up to 4 years, a follow-up period longer than other opioids: in a recent Cochrane meta-analysis on opioids for non-cancer pain, the longest study was 13 months in duration.[1] Over this observation period, no serious or unexpected AEs occurred during treatment with tapentadol.

Tapentadol appeared also to be better tolerated compared with opioids in studies evaluating specific AEs, such as gastrointestinal events, hypertension, pulmonary dysfunction, serotonin syndrome, endocrine toxicity – important for young and

adult patients – convulsions. Although some of these studies were limited in sample size, they were designed with the aim to investigate the abovementioned events and therefore may provide well-grounded evidence on the safety of tapentadol.

Remarkably, a favorable tolerability profile over a long-term period is a key determinant of treatment selection in clinical practice, as it can be associated with maintenance of QoL and improved compliance. We believe that the available safety data on tapentadol PR, together with its marked analgesic efficacy, support the use of this drug for the treatment of chronic painful conditions.

Key points

- The safety of a drug is a particularly important aspect in chronic therapies.
- Long-term treatment with opioid can be associated with several AEs, also of major severity, risk of abuse and impaired ability to take critical decisions. These effects are largely due to the wide expression of the μ receptor in various body system and apparatus.
- Therefore, a molecule characterized by a dual mechanism of action, like tapentadol, with a moderate affinity for different receptors may exert effective analgesia while sparing from opioid-related AEs.
- Safety data for tapentadol extend up to 4 years, a follow-up longer than for opioids. Over this observation period, no serious or unexpected AEs occurred during treatment with tapentadol
- Tapentadol also appeared better tolerated than opioids in studies evaluating specific AEs, such as gastrointestinal events, hypertension, pulmonary dysfunction, serotonin syndrome, endocrine toxicity, and convulsions.

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