CMRO

Current Medical Research & Opinion 2014, 1–6

0300-7995
doi:10.1185/03007995.2014.934793

Article ST-0040.R2/934793


Brief report

# Tapentadol at medium to high doses in patients previously receiving strong opioids for the management of cancer pain



Sebastiano Mercadante
Anesthesia & Intensive Care and Pain Relief & Supportive Care, La Maddalena Cancer Center, Palermo, Italy
University of Palermo, Palermo, Italy

Giampiero Porzio
Home Care Program, L'Aquila per la vita, Department of Oncology, University of L'Aquila, Italy

Claudio Adile
Anesthesia & Intensive Care and Pain Relief & Supportive Care, La Maddalena Cancer Center, Palermo, Italy

Federica Aielli
Home Care Program, L'Aquila per la vita, Department of Oncology, University of L'Aquila, Italy

Andrea Cortegiani
Department of Biopathology, Medical and Forensic Biotechnologies (DIBIMEF), Section of Anesthesia, Analgesia, Intensive Care and Emergency, University of Palermo, Palermo, Italy

Anthony Dickenson
Department of Pharmacology, University College, London

Alessandra Casuccio
Department of Sciences for Health Promotion and Mother–Child Care 'G. D'Alessandro', University of Palermo, Italy

**Address for correspondence:**
Prof. Sebastiano Mercadante, Anesthesia and Intensive Care Unit & Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Via san Lorenzo 312, 90145, Palermo, Italy.
Tel.: +39 091 6806521; Fax: +39 0916806110;
terapiadeldolore@lamaddalenanet.it;
03sebelle@gmail.com

**Keywords:**
Adverse effects – Cancer pain – Palliative care – Tapentadol

Accepted: 10 June 2014; published online: 27 June 2014
*Citation:* Curr Med Res Opin 2014; 1–6

## Abstract

**Objective:**
The aim of this study was to assess the efficacy and tolerability of tapentadol (TP) for a period of 4 weeks in patients who were already treated by opioids.

**Methods:**
A convenience sample of 30 patients was selected for a prospective observational cohort study. Cancer patients who were receiving at least 60 mg of oral morphine equivalents were selected. Patients discontinued their previous opioid analgesics before starting TP, in doses calculated according the previous opioid consumption (1:3.3 ratio with oral morphine equivalents). The subsequent doses were changed according to the patients' needs for a period of 4 weeks. Oral morphine was offered as a breakthrough pain medication. Pain and symptom intensity were recorded at weekly intervals. Distress score (DS) was calculated from the sum of symptom intensities. TP opioid escalation indexes (TPEI) for the study period were calculated.

**Results:**
Nineteen patients were male, and the mean age was 63.5 years (±11.5). The mean Karnofsky status was 62.9 (±10). The mean dose of oral morphine equivalents before switching to TP was 112 mg (±57) and the initial mean dose of TP was 343 mg (±150). Pain intensity significantly decreased. Tapentadol escalation index in percentage was 1.26 (TPEI% ± 2.6) and Tapentadol escalation index in mg was 2.76 (TPEImg ± 4.96). No significant relationships were found with primary tumor (TPEI%, $p = 0.204$; TPEImg, $p = 0.180$), pain mechanism (TPEI%, $p = 0.863$; TPEImg, $p = 0.846$), age (TPEI%, $p = 0.882$; TPEImg, $p = 0.884$), or gender (TPEI%, $p = 0.287$; TPEImg, $p = 0.325$). DS decreased, but non-significantly ($p = 0.1$). Ten patients did not complete the study period: five patients discontinued TP for uncontrolled pain, despite increasing doses of TP over 600 mg/day. Two patients discontinued TP for adverse effects and three patients dropped out, one patient for poor compliance and two patients for unrecorded reasons.

**Conclusion:**
In our sample, TP used in doses of 350–450 mg/day was well tolerated and effective in opioid tolerant patients with cancer pain and could be considered as a flexible drug to be used for the management of moderate to severe cancer pain. Like most studies in patients with cancer pain, it was limited by its open-label, uncontrolled design, the number of patients lost in follow-up, and discontinuation of the treatment for several reasons. Further studies in a large number of patients should confirm these preliminary results.

## Introduction

Cancer pain management is based on a sequential approach of drugs, suggested by WHO, through steps corresponding to drugs with different potencies.

 

The application of the WHO three-step analgesic ladder has been reported to provide satisfactory pain relief in up to 90% of patients with cancer pain[1]. Opioids are the cornerstone of analgesic therapy in cancer patients with chronic pain. Opioids produce analgesia by binding to opioid receptors in the central nervous system. These receptors are inhibitory, as their activation hyperpolarizes neurone transmitter release in the dorsal horn of the spinal cord, interrupting the transmission of pain signals from incoming fibers by their presynaptic inhibitory action, and also reduces spinal neuronal activity through postsynaptic receptors. However, opioids also produce various adverse effects. New analgesics have been developed with the purpose of improving the pharmacological profile of opioids, by reducing adverse effects.

Tapentadol (TP) is a centrally analgesic agent acting with two mechanisms of action: mu-opioid receptor agonism and norepinephrine reuptake inhibition. The moderate affinity to mu receptors and the opioid-sparing effect of inhibition of norepinephrine reuptake suggest that TP should produce fewer opioid-related adverse effects than typical mu-agonists[2]. TP has been shown to be effective in different pain models[3–5]. TP has been developed for the management of moderate to severe chronic pain. In humans, efficacy and safety of TP have been shown in comparative studies with placebo and oxycodone in several non-malignant conditions. A recent systematic review of TP trials clearly shows that for certain domains fewer adverse effects are reported. The benefit ratio of tapentadol appears to be better compared to other strong opioids[6]. Recent recommendations did not include this new drug, because it was made available after their development[7]. Based on literature research, there is a paucity of information regarding the efficacy and tolerability in cancer pain management.

In preliminary studies, TP has been found to be effective and well tolerated in the management of opioid-naïve patients with cancer pain[8,9]. However, cancer patients with pain often require changes in opioid therapy during the course of disease, due to disease factors and pain characteristics as well as prolonged use of opioids, in an attempt to improve the analgesic response or reduce adverse effect intensity[10]. The anti-hyperalgesic effects of TP could be potentially helpful in states of hyperexcitation such as those observed in patients who have received multiple trials of opioids unsuccessfully[11]. In the literature no data are available on the use of TP in patients who are tolerant to opioids and may require higher doses of TP than those reported in existing studies. The highest suggested dose is 500 mg/day. However, this information is not supported by specific studies. TP could be of benefit in patients requiring relatively high doses of opioids, because of its dual analgesic effect due to its pharmacological characteristics. The aim of this study was to assess the efficacy and tolerability of TP for a period of 4 weeks in cancer patients who were already receiving strong opioids.

## Methods

A prospective study was carried out in a convenience sample of consecutive cancer patients admitted to an acute palliative care unit in Palermo and a home care program in L'Aquila for a period of 1 year, from January to December 2013. For recruitment medical staff asked patients to participate. Informed consent and institutional approval were obtained.

The study included patients who were at least 18 years of age, had a diagnosis of cancer pain, were receiving at least 60 mg/day of oral morphine equivalents. A WHO step III analgesic must have been required for the management of cancer pain with an intensity of more than 4 on an 11 point numerical rating scale (0 = 'no pain' to 10 = 'pain as bad as you can imagine'), or because of the occurrence of adverse effects, or for convenience (see below). Exclusion criteria included the following: a history of or laboratory values reflecting severe renal or hepatic impairment, patients who were receiving monoamine oxidase inhibitors within 14 days prior to screening or non-stable doses of selective serotonin reuptake inhibitors. The same protocols and modality of drug administration were provided in inpatient unit and home care patients. Patients were visited or contacted telephonically at least every 2 days to monitor and eventually changing the treatment.

Patients stopped taking their previous opioid analgesics before receiving their first dose of TP. An oral morphine equivalent dose of the previous opioid was determined for each patient using current tables for opioid conversion used in the unit[10]. The calculated dose was converted to TP, using a conversion rate of 3.3, according to previous findings[12]. Doses were then rounded according to existing dose tablets. The subsequent doses were flexible and were changed according to the clinical situation to find the best balance between pain and opioid-related symptoms, according to the amount of drugs consumed as rescue doses in the previous day and clinical judgment. Oral morphine was offered as a breakthrough pain medication. Adjuvant drugs, previously administered to control symptoms due to illness or treatment, were continued at the same doses during switching, or were administered to assist opioid switching in case of need. Non-opioid analgesics were also continued if previously administered, at the same doses. No patient received anticancer therapy during the course of the study.

For each patient the following data were measured at weekly intervals for 4 weeks:

(a) Pain intensity measured using patients' self report on a numerical scale from 0 to 10.

 

(b) Symptoms associated with opioid therapy or commonly present in advanced cancer patients – such as nausea and vomiting, drowsiness, confusion, constipation, dry mouth, myoclonus, sweating – using a scale from 0 to 3, corresponding to a verbal scale (not at all, slight, a lot, awful), were recorded. A distress score (DS) was also calculated as a sum of symptom intensity. Although never validated, this score has been used previously in different studies for determining the 'weight' of adverse effects. Symptoms were assessed by the patient, whenever possible, at time of switching and at week intervals for four weeks.

(c) Previous daily opioid doses (oral morphine equivalents), doses of TP, and DS before switching (T0), and at weekly intervals for 4 weeks (T1–4).

(d) TP escalation index percent (TPEI%) was calculated at T4. This score expresses the mean increase of opioid dosage percent from opioid starting dose (TPSD), according the following formula: ([TPMD - TPSD]/TPSD)/days × 100, where TPMD is the maximal dose of TP. TP escalation index in mg (TPEImg) was calculated as the mean increase of TP dosage in mg using the following formula: (TPMD - TPSD)/days[8,13].

Patients who were switched to TP were divided into four categories, according to previous research experience[10]:

(a) Patients presenting relevant adverse effects despite good pain control.

(b) Patients with a poor analgesic response despite having their dose doubled in 1 week.

(c) Patients with both poor pain control and prevalent adverse effects.

(d) Patients who were switched for patient's preference and/or convenience, because they had adequate pain control and acceptable adverse effects.

Age, gender, primary cancer, and performance status were recorded.

### Statistical analysis

Data were analyzed with IBM SPSS Software 21.0 version (SPSS Inc., Chicago, IL, USA) and Epi Info software, version 3.2.2 (Centers for Disease Control and Prevention). Statistical analysis of quantitative and qualitative data, included descriptive statistics, was performed for all the items. The paired samples Student's *t*-test was used to compare opioid mean dose in the four weekly periods. The paired Wilcoxon signed-rank test was used to compare pain intensity scores and symptom intensity scores in the four weekly periods. The one-way analysis of variance (ANOVA) and Kruskal Wallis statistic test were used to evaluate the differences in TPEI% and TPEImg for parametric and nonparametric variables, respectively. All *p* values were two-sided and *p* values less than 0.05 were considered to indicate statistical significance.

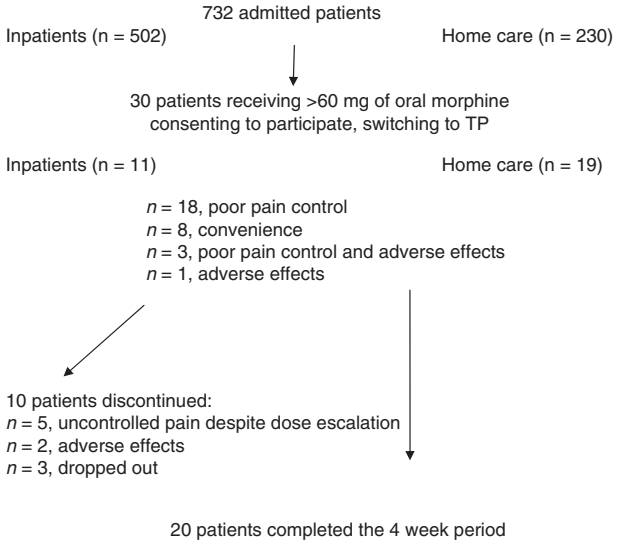


Figure 1. Patient flow chart.

## Results

From a sample of 732 consecutive patients, admitted as inpatients ($n = 502$) and home care ($n = 230$), assessed in 1 year, 30 patients who were receiving at least 60 mg/day of oral morphine equivalents gave consent to take part in the study in a period of 1 year. Eleven and nineteen patients were recruited in inpatient units and home care, respectively (Figure 1). Nineteen patients were male (63%), and the mean age was 63.5 years (SD 11.5). The mean Karnofsky status was 62.9 (SD 10). Primary tumors were in a rank order: lung ($n = 12$), urogenital ($n = 6$), gastrointestinal ($n = 3$), head–neck ($n = 3$), liver ($n = 2$), myeloma ($n = 2$), and breast ($n = 2$). Mixed pain mechanisms (nociceptive and neuropathic pain) were found in the majority of patients ($n = 19$), pure neuropathic pain mechanism was observed in one patient, while the remaining ten patients had nociceptive pain.

The majority of patients were switched to TP from oral morphine ($n = 23$), five patients were switched from hydromorphone and two patients from transdermal fentanyl. Eighteen patients were started with TP for poor pain control (60%), eight patients for convenience, one patient for adverse effects (26.6%), and three patients for poor pain control and adverse effects (10%).

The mean dose of oral morphine equivalents before switching to TP was 112.2 mg (SD 57.4). The initial mean dose of TP was 343.3 mg (SD 150.1). Seven patients

Table 1. Previous opioid doses (OME, oral morphine equivalents), tapentadol (TAP) doses, pain intensity, and DS (see text) at time intervals: T0 = baseline, T1 = 1st week, T2 = 2nd week, T3 = 3rd week, T4 = 4th week.

| *N* patients | T0<br>30 | T1<br>30 | T2<br>28 | T3<br>22 | T4<br>20 | *p* |
|---|---|---|---|---|---|---|
| Opioid dose (OME) mg<br>TAP dose mg | 112 (57)<br>343 (150) | 431 (163)* | 435 (201) | 409 (208 | 427 (178) | 0.001 T1 vs T0<br>0.013 T2 vs T0<br>0.077 T3 vs T0<br>0.028 T4 vs T0 |
| Pain | 5 (1.8) | 2.7 (2.1)* | 2.7 (1.9)* | 2.5 (1.7)* | 2.6 (1.6)* | <0.0005 T1 vs T0<br><0.0005 T2 vs T0<br>0.001 T3 vs T0<br>0.002 T4 vs T0 |
| DS | 3.3 (2.4) | 3.3 (2.6) | 3 (2) | 2.6 (1.9) | 2.3 (1.8) | 0.675 T1 vs T0<br>0.961 T2 vs T0<br>0.438 T3 vs T0<br>0.566 T4 vs T0 |

*indicates those values which are statistically significant.

received 600 mg/day of TP. None of them dropped out because of adverse effects. One of them changed treatment due to inefficacy in controlling pain. TPEI% was 1.26 (SD 2.6) and TPEImg was 2.76 (SD 4.96). No significant relationships were found with primary tumor (TPEI%, $p = 0.204$; TPEImg, $p = 0.180$), pain mechanism (TPEI%, $p = 0.863$; TPEImg, $p = 0.846$), age (TPEI%, $p = 0.882$; TPEImg, $p = 0.884$), or gender (TPEI%, $p = 0.287$; TPEImg, $p = 0.325$). Doses of TP, pain intensity, and DS at week intervals are described in Table 1. TP doses significantly increased ($p = 0.05$), while pain intensity significantly decreased ($p = 0.001$). A non-significant decrease in DS was reported ($p = 0.1$). The numbers of patients presenting opioid-related symptoms with an intensity of 2–3 and receiving adjuvants at the different time intervals are reported in Table 2. A significant decrease in constipation was observed ($p = 0.031$).

Ten patients (33%) did not complete the study period. Globally, five patients discontinued TP for uncontrolled pain, despite increasing doses of TP. Two patients discontinued TP for adverse effects and three patients dropped out: one patient for poor compliance and two patients for unrecorded reasons.

Table 2. Number of patients with the most important opioid-related symptoms with intensity 2–3 and frequency of use of adjuvants at time intervals: T0 = baseline, T1 = 1st week, T2 = 2nd week, T3 = 3rd week, T4 = 4th week.

| *N* patients | T0<br>30 | T1<br>30 | T2<br>28 | T3<br>22 | T4<br>20 | *p** |
|---|---|---|---|---|---|---|
| Nausea | 1 | 2 | 0 | 0 | 1 | 0.558 |
| Drowsiness | 2 | 2 | 2 | 0 | 0 | 0.406 |
| Dry Mouth | 13 | 10 | 10 | 7 | 7 | 0.820 |
| Constipation | 10 | 5 | 4 | 1 | 1 | 0.031* |
| Confusion | 0 | 0 | 0 | 0 | 0 | |
| Myoclonus | 0 | 0 | 0 | 0 | 0 | |
| Sweating | 0 | 0 | 0 | 0 | 0 | |
| Antiemetics | 8 | 7 | 5 | 3 | 3 | 0.737 |
| Laxatives | 11 | 9 | 9 | 4 | 3 | 0.384 |
| Corticosteroids | 7 | 8 | 7 | 5 | 4 | 0.987 |
| Antidepressants | 5 | 5 | 6 | 5 | 6 | 0.789 |
| Anticonvulsants | 13 | 12 | 10 | 10 | 10 | 0.886 |
| Neuroleptics | 0 | 2 | 1 | 1 | 2 | 0.537 |
| Benzodiazepines | 0 | 0 | 1 | 0 | 0 | 0.452 |
| NSAIDs/paracetamol | 9 | 7 | 5 | 4 | 2 | 0.506 |

*Paired Wilcoxon signed-rank test.
*indicates those values which are statistically significant

## Discussion

The present study evaluated TP in opioid-tolerant patients with higher starting doses than those commonly used in opioid-naïve patients. The doses were calculated from the previous opioid consumption, with a conversion ratio with morphine of 3.3. Pain intensity significantly decreased to acceptable levels during the study period. The dose of TP, given according to patients' clinical response, slowly increased over 4 weeks, with low escalation indexes. TPEI% and TPEImg calculated in this study were similar to those observed in opioid-naïve patients in a similar study period of 4 weeks[8], despite TP being started in patients who were already tolerant to opioids, with doses of more than 300 mg/day. The final doses of TP recorded at the end of the study were significantly higher and were still effective in most patients. The initial ratio, suggested by previous experience, was as safe as effective. Indeed, it was already necessary after a week in most cases to increase TP doses. This is justified by the majority of patients who entered the study for poor pain control, despite receiving other strong opioids in mean doses of more than 110 mg of oral morphine equivalents, unsuccessfully.

Data regarding TP in cancer patients are limited. After an open-label preliminary report in opioid-naïve patients[8],



 

only two other trials were published. In a well powered, randomized, double-blind study performed in opioid-naïve cancer patients for 4 weeks, TP in doses of 25–200 mg/day provided similar analgesic efficacy and a better gastrointestinal tolerability compared to oxycodone in doses of 5–40 mg/day[9]. In a double-blind controlled study, patients were initiated with TP 100–250 mg/day, or morphine 40–100 mg/day. After a titration period, TP patients were treated with placebo or TP, while patients on morphine continued the same treatment, for a maintenance period of 4 weeks. Small differences with placebo were found, possibly because of the use of as needed medications which flattened the pain intensity levels. TP and morphine provided similar analgesic efficacy in modal daily doses of 300 mg and 120 mg, respectively (ratio 2.5:1)[13]. In both studies information regarding higher TP doses is lacking.

TP could be particularly attractive for patients with neuropathic pain[5,11,14]. TP was equally effective regardless of the mechanisms assessed by clinical judgment. However, the relatively low number of patients participating in this preliminary trial does not allow definite information to be obtained, and trials with a larger number of patients could identify subclasses of patients who could benefit from TP. In a previous study with a large number of patients, for the subgroup of patients with a neuropathic pain component, responder rates during the maintenance period were 73.5% in the TP group, and 67.6% in the morphine group[15]. This point needs to be better determined with a more selected population.

TP was relatively well tolerated. One-third of patients discontinued TP for alternative treatments, particularly when further dose increments were ineffective, or because of poor compliance with TP therapy. Only two patients dropped out because of adverse effects. This rate was considered acceptable, given the reported need to switch to other opioids from morphine due to unfavorable responses in the cancer population, and the different levels of TP dosage, never reported before, used in a context of increased requirements of opioid dosing[16,17]. Seven patients received an off-label high dose, which was well tolerated until the end of the study, except for one patient who changed treatment due to inefficacy in controlling pain. No symptoms possibly linked to inhibition of norepinephrine reuptake at such high doses were recorded. In a controlled study with placebo and morphine, TP was generally well tolerated, with a low incidence of adverse effects leading to discontinuation during both the titration and maintenance periods. During titration, the incidence of gastrointestinal adverse effects was lower in the TP group than in the morphine group[15].

The use of adjuvant drugs administered prior to entering the study or symptomatic drugs did not change or decreased during the study period, confirming the efficacy and tolerability of the drug, particularly regarding gastrointestinal adverse effects, which are frequently associated with opioid therapy[18]. In this study a decrease in the frequency of constipation was observed.

This study confirms previous data obtained in observational and comparison studies with TP in cancer patients[6,8,15]. These findings require confirmation in controlled studies with a larger number of patients with different levels of opioid consumption. The present data should be interpreted with caution, because preliminary and obtained in a low number of patients. Like most studies in patients with cancer pain, it was limited by its open-label, uncontrolled design, the number of patients lost to follow-up, and discontinuation of the treatment for several reasons.

Adjuvant analgesics could have influenced the effects of TP, although doses were unchanged per protocol. More data on different kinds of cancer population are needed, for example patients with a lower performance status or specific cancer pain syndromes. Finally, the possible role of TP as add-on therapy should be investigated.

## Conclusion

TP used in doses of 350–450 mg/day was well tolerated and effective in opioid tolerant patients with cancer pain and could be considered as a flexible drug to be used for the management of moderate to severe cancer pain. In patients tolerant to mean doses of oral morphine equivalents of more than 110 mg/day, TP dose increases were effective in improving analgesia while maintaining adverse effect intensity at acceptable levels without increasing the use of adjuvants. Further studies in a large number of patients should confirm these preliminary results.

## Transparency

**Declaration of funding**

This study was not funded.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Declaration of financial/other relationships**

S.M. has disclosed that he acts as advisor for TEVA, Molteni, Grunenthal, and Janssen. G.P., C.A., F.A., A.Co., A.D., and A.Ca. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

*CMRO* peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

**Acknowledgments**

The authors thank the nursing staff of L'Aquila per la vita, L'Aquila, and the pain relief and supportive care unit of La Maddalena Cancer center, Palermo.

## References

1. Mercadante S, Fulfaro F. World Health Organization guideline: a reappraisal. Ann Oncol 2005;16(Suppl 4):iv132-5
2. Shafer M. Novel concepts for analgesia in severe pain: current strategies and future innovations. Eur J Pain 2009;(Suppl 3):6-10
3. Cristoph T, De Vry J, Tzeschentke TM. Tapentadol, but not morphine, selectively inhibits disease-related thermal hyperalgesia in a mouse model of diabetic neuropathic pain. Neurosci Lett 2010;470:91-4
4. Buynak R, Shapiro DY, Okamoto A, et al. 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. Exp Opin Pharmacother 2010;11:1787-814
5. Schroder W, De Vry J, Tzeschentke TM, et al. Differential contribution of opioid and noradrenergic mechanisms of tapentadol in rat models of nociceptive and neuropathic pain. Eur J Pain 2010;14:814-21
6. Riemsma R, Forbes C, Harker J, et al. Systematic review of tapentadol in chronic severe pain. Curr Med Res Opin 2011;27:1907-30
7. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012;13:e58-68
8. Mercadante S, Porzio G, Ferrera P, et al. Tapentadol in cancer pain management: a prospective open-label study. Curr Med Res Opin 2012;28:1775-9
9. 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;29:1399-409
10. Mercadante S, Ferrera P, Villari P, et al. Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. J Pain Symptom Manage 2009;37:632-41
11. Christoph T, De Vry J, Schiene K, et al. Synergistic antihypersensitive effects of pregabalin and tapentadol in a rat model of neuropathic pain. Eur J Pharmacol 2011;666:72-9
12. Mercadante S, Porzio G, Aielli F, et al. Opioid switching from and to tapentadol extended release in cancer patients: conversion ratio with other opioids. Curr Med Res Opin 2013;29:661-6
13. Mercadante S, Dardanoni G, Salvaggio L, et al. Monitoring of opioid therapy in advanced cancer pain patients. J Pain Symptom Manage 1997;13:204-12
14. Bee LA, Bannister K, Rahman W, Dickenson AH. Mu-opioid and noradrenergic $\alpha$2-adrenoreceptor contributions to the effects of tapentadol on spinal electrophysiological measures of nociception in nerve-injured rats. Pain 2011;152:131-9
15. Kress HG, Koch ED, Kosturski H, et al. Efficacy and safety of oral tapentadol extended release for the management of moderate to severe, chronic malignant tumor-related pain. Presented at ASRA 11th annual meeting, 12–15 November 2012, Miami, FL, USA
16. Dale O, Moksnes K, Kaasa S. European Palliative Care Research Collaborative pain guidelines: opioid switching to improve analgesia or reduce side effects. A systematic review. Palliat Med 2011;25:494-503
17. Mercadante S, Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. Palliat Med 2011;25:504-15
18. Pergolizzi J, Alegre C, Blake D, et al. Current considerations for the treatment of severe chronic pain: the potential for tapentadol. Pain Pract 2012;12:290-306