

**Keywords:** cancer pain; epidural methadone; epidural dexamethasone

# Epidural methadone results in dose-dependent analgesia in cancer pain, further enhanced by epidural dexamethasone

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**Background:** This study was designed to evaluate the role of epidural methadone-lidocaine in cancer pain combined or not to epidural dexamethasone.

**Methods:** In all, 72 cancer patients, 32- to 67-year-old were randomized to six groups ( $n=12$ ) and prospectively studied to examine analgesia and adverse effects for 3 weeks. Patients received single-dose protocol epidural test drugs: Control group (CG) received epidural 40-mg lidocaine diluted to 10-ml volume with saline. Dexamethasone group (DG) 40-mg lidocaine plus 10-mg dexamethasone. The 2.5MetG 2.5-mg epidural methadone with 40-mg lidocaine; the 5MetG, 5-mg epidural methadone plus 40-mg lidocaine, the 7.5MetG, 7.5-mg epidural methadone plus 40-mg lidocaine and finally the 7.5Met-DexG, 7.5-mg methadone with 40-mg lidocaine and 10-mg dexamethasone.

**Results:** Groups CG, DG and 2.5MetG were similar regarding analgesia and side effects. Patients from 5MetG and 7.5MetG took  $3 \pm 1$  and  $5 \pm 1$  days, respectively, to restart oral morphine. Patients from 7.5MetDG took  $14 \pm 2$  to restart oral morphine ( $P < 0.001$ ). Daily somnolence and appetite improved in the 7.5MetDG during 2-week evaluation ( $P < 0.005$ ). Fatigue improved for both DG and 7.5MetDG during 2-week evaluation ( $P < 0.005$ ). By the third week of evaluation, all patients were similar.

**Conclusions:** Epidural methadone plus lidocaine resulted in dose-dependent analgesia, further improved by epidural dexamethasone, which also improved fatigue.

Spinal analgesics have been suggested as the fourth step in the World Health Organisation guidelines in the management of cancer pain for those patients who suffer from severe and refractory pain, or are incapable to bear the adverse effects from oral opioids (Christo and Mazloomdoost, 2008; Hattori *et al*, 2009). Although there are not sufficient clinical trials to evaluate spinal opioids in adult cancer patients (Kurita *et al*, 2011), morphine has been one of the cornerstones for the management of chronic intractable cancer pain. Due to the proximity to the receptor sites, the therapeutic efficacy of spinal opioid application lasts longer and also reduces systemic side effects. However, some patients unable to tolerate spinal morphine may suffer with side-

effects from high doses. The opioid methadone has a broad-spectrum of suggested spinal actions:  $\mu$  receptor agonist, *N*-methyl-D-aspartate receptor (NMDA) receptor antagonist (Sotgiu *et al*, 2009), glial activator (Hutchinson *et al*, 2010), and has been increasingly used as a second-line opioid in recent years in the management of cancer-related pain (Leppert, 2009; Anghelescu *et al*, 2011; Mercadante, 2012). In addition, corticosteroids were described to be commonly used in cancer pain, in spite of its limited scientific evidence (Leppert and Buss, 2012). The purpose of the present study was to examine the potential role of epidural methadone in cancer pain therapy. Its efficacy was further evaluated by the association of epidural dexamethasone.

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## MATERIALS AND METHODS

The Ethics Committee at the University of São Paulo's Teaching Hospital, Ribeirão Preto, approved the study protocol. After written informed consent, 72 from the total of 112 patients suffering from cancer pain were selected at the Pain Clinic (~64% inclusion). The 72 patients were randomized to one of six groups ( $n=12$ ) and prospectively studied using a placebo-controlled design to examine analgesia and adverse effects and assigned to treatments using a randomized number generator in a computer programme.

The study was designed to have a power of 80% to detect a treatment difference of 1-day analgesia on a two-sided level of significance of  $\alpha=0.05$  assuming a standard deviation of 2 days, and a minimum number of eight patients per group. Eligible patients were aged 32–67 year-old, with a diagnosis of cancer, documented history of moderate/severe, chronic cancer pain, classified as Tumour-Node-Metastasis stage III or IV, requiring round-the-clock opioid, and capacity to understand the study protocol. Patients were excluded from the study for the following reasons: evidence of clinically unstable disease, clinically significant gastro-intestinal disease, cyclic chemotherapy within 3 weeks before screening visit or planned during the core study (shown in the past to influence bowel function); radiotherapy that would influence bowel function or pain, refusal, allergy to any of the drugs used or inability to ingest the oral rescue analgesic morphine. The concept of a visual analogue scale (VAS), which consisted of a 10-cm line with 0 equalling 'no pain at all' and 10 equalling 'the worst possible pain' was introduced. The patient brought the VAS scores and daily morphine consumption recorded each day at the weekly appointments (21-day study). However, patients were free to contact one of the authors anytime by a personal phone number, through a collect call, whenever necessary.

All patients were regularly taking oral amitriptyline 25 mg at bedtime as part of our institutional protocol, and oral morphine regimen individually adjusted to a maximal oral dose of 80–90 mg per day, in order to keep the VAS score  $<4/10$ . When patients complained of pain (VAS  $\geq 4/10$ ), despite the 80–90 mg daily oral morphine, they were submitted to the epidural test drugs and all patients were blind to the treatments. The day before the epidural test block was considered day-zero, and the day of the epidural block was performed was considered day-1 of the study. The groups were computer divided into six as follow: The Control group (CG) received epidural 40 mg lidocaine (1%, 20 ml ampoule with no adrenaline, Cristalia) diluted to 10-ml volume with saline. The Dexamethasone group (DG) received 40 mg lidocaine plus 10 mg dexamethasone (8 mg dexamethasone acetate + 2 mg dexamethasone phosphate, Ache). The 2.5MetG received 2.5 mg epidural methadone (Methadone, 1 ml ampoule, dl-racemic mixture, 10 mg/ml, conservative-free, Cristalia) combined with 40 mg lidocaine; the 5MetG received 5 mg epidural methadone plus 40 mg lidocaine, the 7.5MetG received 7.5 mg epidural methadone plus 40 mg lidocaine and finally the 7.5Met-DG received 7.5 mg epidural methadone combined with 40 mg lidocaine and 10 mg dexamethasone. All patients received sacral block only, which was done under aseptic conditions always by the same anaesthetist that was unaware of the study drug prepared by a second anaesthetist. The drugs were diluted in a 10-ml covered syringe in order to keep the blindness of the study. The correct position of the needle as assessed by fluoroscopy and by injection of 1 ml contrast (Omnipaque, 300 mg/ml iohexol, Sanofi). All sacral blocks were performed in the morning. Patients were free to manipulate their daily oral morphine consumption, in order to keep daily pain VAS  $<4/10$  and were followed on a weekly basis during 3 consecutive weeks. The 10 mg morphine tablets were given by the government. All patients registered once a day before bed-time (at 23-h) the VAS resembling the pain average of the day, the final

daily consumption of oral morphine and the listed adverse effects. Patients assigned as 'yes' or 'no' the final impression of the side effects listed at the final of each week evaluation: (1) daily somnolence, (2) nocturnal insomnia, (3) nausea, (4) occurrence of vomiting, (5) constipation, (6) diminished appetite, (7) fatigue, (8) sadness. Complain of nausea  $>3$  cm in a 10 cm VAS and occurrence of vomiting was treated with 8 mg sublingual ondansetron two-three times daily, if necessary. Constipation was treated with improved ingest of fibres and/or oral laxative if necessary. Patients had free access to the personal cell phone of one of the authors that was unaware of the study groups.

**Statistical analysis.** The normality of the distributions was assessed using the Shapiro–Wilk's test. Groups were compared for demographic data (age, weight, and height) by one-way ANOVA. Incidence of adverse events, gender and site of primary disease were compared among groups by  $\chi^2$  analysis corrected for multiple comparisons.  $P$  was considered significant if  $<0.008$ . VAS scores; and the daily morphine consumption from day-zero to day-21 were compared among groups by two-way ANOVA for repeated measures (Dexter and Chestnut, 1995). The statistical analysis compared among the six different groups on each day of the study. Tukey Honest analysis was applied to correct  $P$  values for multiple group comparisons.  $P<0.05$  was considered significant. Data are expressed as mean  $\pm$  s.d., otherwise stated.

## RESULTS

Four patients from the CG, 3 from the DG, 2 from the 2.5MetG, 5Met and 7.5Met G; and finally one from the 7.5MetDG were excluded from the final analysis due to incomplete data collection. However, the minimum of eight patients per group was maintained for statistical purposes. The exclusion reasons are detailed: three patients from the CG took their own decision to take oral codeine or diclofenac during the study period combined with oral morphine, while the remaining patient did not come to the last appointment. Related to the DG group, two patients forgotten to make notes related to VAS pain scores or oral morphine consumption, and other patient included by its own oral diclofenac during the study period. Two patients from 2.5MetG and 7.5MetG and 1 from the 5MetG were also excluded due to incomplete data collection regarding oral morphine consumption and pain VAS. One patient from 5MetG did not come to the last week appointment. Finally, 1 patient from the 7.5MetDG was excluded due to ingestion of oral metamizol for pain control during the study period.

The groups showed no differences regarding gender, weight, age and height (Table 1), distribution of the primary site of the cancer pathology (Table 2) and incidence of metastasis, which varied from

Table 1. Demographic analysis

	Gender (male/female) <sup>a</sup>	Weight (kg) <sup>a</sup>	Age (age) <sup>a</sup>	Height (cm) <sup>a</sup>
CG	3/5	58 $\pm$ 11	53 $\pm$ 14	165 $\pm$ 9
DG	4/5	55 $\pm$ 8	56 $\pm$ 9	162 $\pm$ 7
2.5MetG	4/6	57 $\pm$ 7	53 $\pm$ 11	167 $\pm$ 9
5MetG	4/6	66 $\pm$ 16	50 $\pm$ 8	167 $\pm$ 8
7.5MetG	5/5	56 $\pm$ 13	52 $\pm$ 13	164 $\pm$ 6
7.5MetDG	5/6	54 $\pm$ 12	47 $\pm$ 13	162 $\pm$ 6

Abbreviations: CG = control group; DG = dexamethasone group; 2.5MetG = 2.5 mg methadone group; 5MetG = 5 mg methadone group; 7.5MetG = 7.5 mg methadone group; 7.5MetDG = 7.5 mg methadone-dexamethasone group.  $P>0.05$ .

<sup>a</sup>Data are expressed as mean  $\pm$  s.d.

Table 2. Distribution of the primary site of the cancer pathology and incidence of metastasis among the groups

	CG (n = 8)	DG (n = 9)	2.5MetG (n = 10)	5MetG (n = 10)	7.5MetG (n = 10)	7.5MetDG (n = 11)
Oropharynx	1	1	1	2	1	1
Breast	3	4	4	3	3	4
Lung	1	0	1	0	1	0
Uterus	2	1	2	1	1	2
Prostate	1	2	1	2	2	2
Digestive tract	0	0	0	1	1	1
Kidney	0	0	1	0	1	0
Liver	7	1	0	1	0	1
Incidence of metastasis (%)	63%	66%	60%	70%	60%	73%

Abbreviations: CG = control group; DG = dexamethasone group; 2.5MetG = 2.5 mg methadone group; 5MetG = 5 mg methadone group; 7.5MetG = 7.5 mg methadone group; 7.5MetDG = 7.5 mg methadone-dexamethasone group.  $P > 0.05$ . Incidence of metastasis at the time of inclusion at the study protocol.

60% to 73% ( $P > 0.05$ ; Table 2). In addition, all overall daily VAS scores were  $< 4$  cm to all groups during the study period ( $P > 0.05$ , data not shown). On day-zero (day before the epidural test drugs) all patients were taking 80–90 mg oral morphine, as part of the study protocol ( $P > 0.05$ ). On the following days, patients were free to take oral 10 mg morphine as much as necessary in order to keep pain VAS  $< 4$  cm. Final VAS scores.

On day-1 (the day patients were submitted to epidural test drugs), only the CG, DG and 2.5MetG kept the daily oral consumption of 80–90 mg morphine. These three groups gradually increased daily oral morphine consumption until day-21 (150–170 mg morphine) ( $P > 0.05$ ). CG = DG = 2.5MetG during all the 21-day evaluation regarding oral daily morphine consumption ( $P > 0.05$ ; Figure 1).

Related to the 5MetG, from day-1 to day-3, the daily intake of oral morphine was: 5MetG = 7.5MetG = 7.5MetDG ( $P > 0.05$ )  $<$  CG = DG = 2.5MetG ( $P < 0.001$ ). From day-4, patients started getting daily increasing oral morphine intake, which was similar to the CG, DG and to the 2.5MetG from day-7 forwards (daily evaluation- $P > 0.05$ ; Figure 1). The evaluation of the 7.5MetG revealed that from day-1 to day-5, the daily intake of oral morphine was: 7.5MetG = 7.5MetDG ( $P > 0.05$ )  $<$  CG = DG = 2.5MetG ( $P < 0.001$ ). From day-6, patients started getting daily increasing oral morphine intake, which was similar to the CG, DG and to the 2.5MetG from day-10 forwards (daily evaluation- $P > 0.05$ ; Figure 1). Related to the 7.5MetDG, from day-1 to day-15, the daily intake of oral morphine was lesser when compared with the CG = DG = 2.5MetG ( $P < 0.001$ ). On day-4, 7.5MetDG  $<$  5MetG ( $P < 0.05$ ). On day-6, 7.5MetDG  $<$  7.5MetG ( $P < 0.05$ ). From day-15, the oral intake of daily morphine was similar to all groups ( $P > 0.05$ ).

The incidence of adverse effects is described in Table 3. The complaints of gastric upset, constipation, sadness and nocturnal insomnia were similar among groups at day-7, -14 and -21 evaluations ( $P > 0.05$ ). Related to all adverse effects questioned, daily somnolence and appetite improved in the 7.5MetDG during at day-7 and -14 evaluations ( $P < 0.005$ ). Fatigue improved for both DG and 7.5MetDG during at day-7 and -14 ( $P < 0.005$ ). However, all side effects were similar at the third week evaluation ( $P > 0.05$ ). No other adverse effects rather than the questioned were spontaneously described by the patients.

DISCUSSION

In the present study, patients suffering from cancer pain treated chronically with oral morphine at round clock and amitriptyline

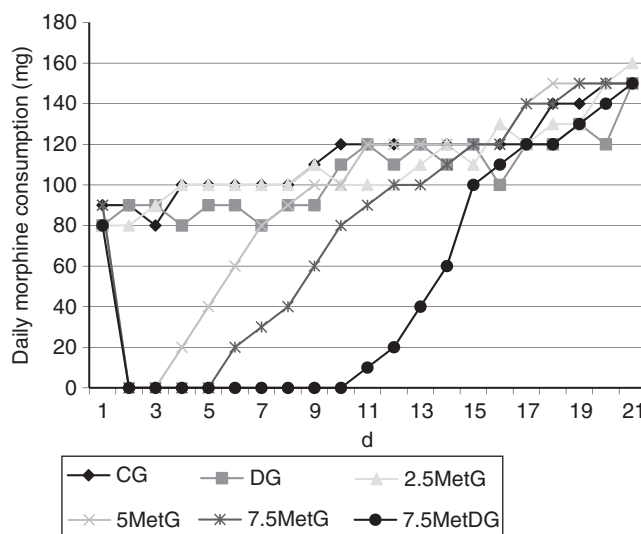


Figure 1. Daily consumption of oral morphine in the groups. CG = control group; 2.5MetG = 2.5 mg methadone group; 5MetG = 5 mg methadone group; 7.5MetG = 7.5 mg methadone group; 7.5MetDG = 7.5 mg methadone-dexamethasone group. Day-1 = the CG, DG and 2.5MetG kept the daily oral consumption of 80–90 mg morphine ( $P > 0.05$ ). CG = DG = 2.5MetG during all the 21-day evaluation regarding oral daily morphine consumption ( $P > 0.05$ ). Patients started the evaluation on day-1 taking 80–90 mg oral morphine, which was gradually increasing for CG, DG and 2.5MetG until day-21 (150–170 mg morphine) (daily evaluation- $P > 0.05$ ). 5MetG = from day-1 to day-3, the daily intake of oral morphine was: 5MetG = 7.5MetG = 7.5MetDG ( $P > 0.05$ )  $<$  CG = DG = 2.5MetG ( $P < 0.001$ ). From day-4, patients started getting daily increasing oral morphine intake, which was similar to the CG, DG and to the 2.5MetG from day-7 forwards (daily evaluation- $P > 0.05$ ). 7.5MetG = from day-1 to day-5, the daily intake of oral morphine was: 7.5MetG = 7.5MetDG ( $P > 0.05$ )  $<$  CG = DG = 2.5MetG ( $P < 0.001$ ). From day-6, patients started getting daily increasing oral morphine intake, which was similar to the CG, DG and to the 2.5MetG from day-10 forwards (daily evaluation- $P > 0.05$ ). 7.5MetDG = from day-1 to day-15, the daily intake of oral morphine was lesser when compared with the CG = DG = 2.5MetG ( $P < 0.001$ ). On day-4, 7.5MetDG  $<$  5MetG ( $P < 0.05$ ). On day-6, 7.5MetDG  $<$  7.5MetG ( $P < 0.05$ ). From day-15, the oral intake of daily morphine was similar to all groups ( $P > 0.05$ ).

before bedtime showed a dose-dependent analgesia after a single dose of 2.5, 5 and 7.5 mg epidural methadone, which was further increased by the addition of epidural dexamethasone. Previously,

Table 3. Number of patients who complained at day-7 and day-14 evaluation (total number of patients complaining per group)

	CG	DG	2.5MetG	5MetG	7.5MetG	7.5MetDG
Daily somnolence <sup>+</sup>	8	9	10	9	5	1
Nocturnal insomnia	6	7	7	7	6	5
Nausea	6	5	7	6	5	2
Vomiting	2	0	2	2	2	1
Constipation	8	8	8	7	8	7
Diminished appetite	8	6	9	10	9	1
Fatigue	8	3 <sup>+</sup>	10	10	10	2
Sadness	8	7	10	9	10	6

Abbreviations: CG = control group; 2.5MetG = 2.5 mg methadone group; 5MetG = 5 mg methadone group; 7.5MetG = 7.5 mg methadone group; 7.5MetDG = 7.5 mg methadone-dexamethasone group. Daily somnolence and appetite improved in the 7.5MetDG at day-7 and -14 evaluations ( $P < 0.005$ ). Fatigue improved for DG and 7.5MetDG at day-7 and -14 ( $P < 0.005$ ).

doses varying from daily epidural 12–32 mg methadone were formerly described to result in pain control in 80% of cancer patients suffering from visceral or somatic pain, with an average of 27-daily infusion and no serious side-effects (Shir *et al*, 1991). We used a single bolus of epidural racemic methadone for treating cancer pain, as the purpose of the study. Methadone was demonstrated to act primarily as agonist of  $\mu$ -opioid receptor, and its d isomer has also NMDA receptor antagonist activity (Inturrisi, 2005). It has high lipid solubility that could facilitate its entrance from the epidural space into the spine, although a peripheral action has also been described (He *et al*, 2010). Nevertheless, epidural methadone has an intrinsic spinal effect regardless of whether or not there is extra-spinal action arising from systemic absorption (Parramon *et al*, 2003).

Epidural methadone combined (Prieto-Alvarez *et al*, 2002; Pérez *et al*, 2010) or not (Parramon *et al*, 2003) to local anaesthetic has been described before as analgesic for acute pain in patients and horses (Olbrich and Mosing, 2003). Different combinations have been used in the actual multimodal cancer pain study. Clinically used  $\text{Na}^+$  channel blockers such as lidocaine, at doses which do not block conduction can relieve spinal sensitization and facilitator processes in dorsal horn neurons via blockade of  $\text{Na}^+$  and  $\text{K}^+$  channels (Olschewski *et al*, 2009), can directly modulate NMDA-receptor in the superficial dorsal horn, can inhibit persistent  $\text{Na}^+$  current in injured dorsal root ganglion neurons (Dong *et al*, 2008), and additionally may have a general glycine-like action of lidocaine or some of its metabolites on inhibitory strychnine-sensitive receptors and on strychnine-insensitive glycine receptors (Muth-Selbach *et al*, 2009; Furutani *et al*, 2010). Other inherent action of lidocaine would be the phosphorylation attenuation of p38 mitogen-activated protein kinase in the activated microglia of spinal cord, reversing established tactile allodynia in chronic constriction injury model of rats (Gu *et al*, 2008). In our study, the association of low-dose lidocaine and escalating doses of epidural methadone was evaluated. The results demonstrated that neither the epidural dose of 40 mg lidocaine alone nor combined with 2.5 mg methadone were effective for improving cancer pain. Lidocaine has been previously demonstrated to produce analgesia for somatic and visceral pain at the spinal level, which was synergistic with a non-NMDA glutamate receptor antagonist in rats (Imamashi *et al*, 1999). Isobolographic analysis also revealed that the epidural opioid morphine and lidocaine interacted synergistically in both somatic and visceral nociception tests, and naloxone antagonised the antinociceptive effects produced by the combination (Kaneko *et al*, 1994). Whether local anaesthetics would act as anti-inflammatory and in micro-molar concentrations would inhibit extracellular oxygen release in spinal microglia; as described elsewhere for neutrophil priming and activation (Ploppa *et al*, 2010), is unknown.

A different combination of drugs was the DG, which patients received both epidural dexamethasone and lidocaine. Dexamethasone profits may be secondary to glucocorticoid receptor activation, in turn rapidly suppressing basal and stress-induced hypothalamus–pituitary–adrenal activity partly through a central mechanism of action (Andrews *et al*, 2012). At the level of the paraventricular nucleus, dexamethasone rapidly reduced hypothalamus–pituitary–adrenal axis activation in a non-genomic, membrane-associated manner, involving cannabinoid receptor type 1 signalling (Evanson *et al*, 2010). Apart, corticosteroid was demonstrated to effectively reduce myelin changes accompanying brain oedema (Kozler *et al*, 2011) that would benefit patients suffering from oedema secondary to spinal metastasis or to hydroelectrolytic disturbances. In addition, high levels of glucocorticoid receptor and mineralocorticoid receptor are colocalized in the substantia gelatinosa where pain pathways appear to be under a strong regulation of these receptors, and nociception was attenuated by spinal dexamethasone (Gu *et al*, 2011). Other possible speculated mechanism of action for the epidural dexamethasone could be the attenuation of the cyclooxygenase-2-dependent production of prostanoids, mainly vasoactive prostaglandin-E(2) (Font-Nieves *et al*, 2012) from the astrocytes that surround the synapse between the first- and second-order neuron in the spinal cord. Apart from spinal mechanism of action, dexamethasone could also decrease astrocyte-to-neuron communication in the hypothalamus through inhibition of production of the gliotransmitter prostaglandin-E(2) (Clasadonte *et al*, 2011). Dexamethasone also prevented lidocaine-induced neurotoxicity in tumour cells through prevention of mitochondrial potential decline and also increased levels of threonine-serine protein kinase B phosphorylation (Ma *et al*, 2010). Finally, the final combination evaluated in this clinical setting was epidural lidocaine plus methadone plus the glucocorticoid dexamethasone. Co-administration of dexamethasone and glutamate receptor antagonists (such as spinal methadone and lidocaine) for treating nociception have been previously described in rats in the periphery (Lam and Ng, 2012) and centrally (Bertorelli *et al*, 1998). In accordance, our results revealed around 14 days of pain relief from a single bolus dose of the combination of the three drugs.

Additional benefits in patients who received epidural dexamethasone included decreased incidence of daily somnolence, decrease fatigue and appetite improvement after both dexamethasone and 7.5 mg methadone during the first 14 days evaluation, while only fatigue improved for DG at day-7 and -14. Probably somnolence and appetite improvement were not enriched in this group due to the higher oral daily dose of morphine consumption they displayed. The gradual increase in morphine consumption to all groups after day-15 was probably reflection of the particularity of the study population (high incidence of metastasis) and of the

study drug protocol, where only morphine was allowed as rescue analgesic. Another point to be considered is that cancer patients suffer from stress of the disease knowledge, anxiety and pain that may result in dysfunction of glutamatergic neurotransmission, including effects on glutamate release, glutamate receptors and glutamate clearance and metabolism (Popoli *et al*, 2011). A positive effect of the combination of lidocaine, methadone and dexamethasone in this population could be at least partly due to their neuroprotective effect on the dorsal root ganglion and Schwann cells (Zhu and Glaser, 2008; Ma *et al*, 2010), as antagonists of NMDA receptor combined with dexamethasone have been described to reduce the production of tumour necrosis factor level in the brain.

In summary, dexamethasone would enhance methadone analgesia partly through: (1) overwhelming the hypothalamus–pituitary–adrenal activity (Andrews *et al*, 2012), that would be further enhanced by cyclooxygenase-2 attenuation at astrocytes in the hypothalamus (Clasadonte *et al*, 2011); (2) inhibition of glutamate release at the dorsal raphe serotonergic 5-HT neurons (Evanson *et al*, 2010; Wang *et al*, 2012); and (3) cyclooxygenase-2 attenuation (Font-Nieves *et al*, 2012) from the astrocytes at the spine (Clasadonte *et al*, 2011). In addition, because mental fatigue is related to activation of NMDA receptors (Morimoto *et al*, 2012), it would be improved by NMDA antagonist such as methadone. Another detail that deserves attention is that cannabinoids have been described to improve fatigue in cancer patients (Johnson *et al*, 2012) and dexamethasone is known to bind at glucocorticoid receptors, activate G-protein coupled receptors and be signalled by endocannabinoid messengers (Morimoto *et al*, 2012) and could therefore diminish fatigue by acting indirectly as adjuvant cannabinoid.

Other adverse effects described in the literature, however, not mentioned by our population was pruritus and urinary retention. The incidence of pruritus after epidural methadone was significantly slighter compared with morphine. Epidural morphine was also associated with a significantly greater incidence of urinary retention than methadone (Gedney and Liu, 1998).

In conclusion, epidural 2.5–7.5 mg methadone combined to low-dose lidocaine (40 mg) resulted in dose-dependent analgesia in cancer pain patients. This analgesic effect was further enhanced by 10 mg epidural dexamethasone, associated with improvement of fatigue, daily somnolence and appetite.

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