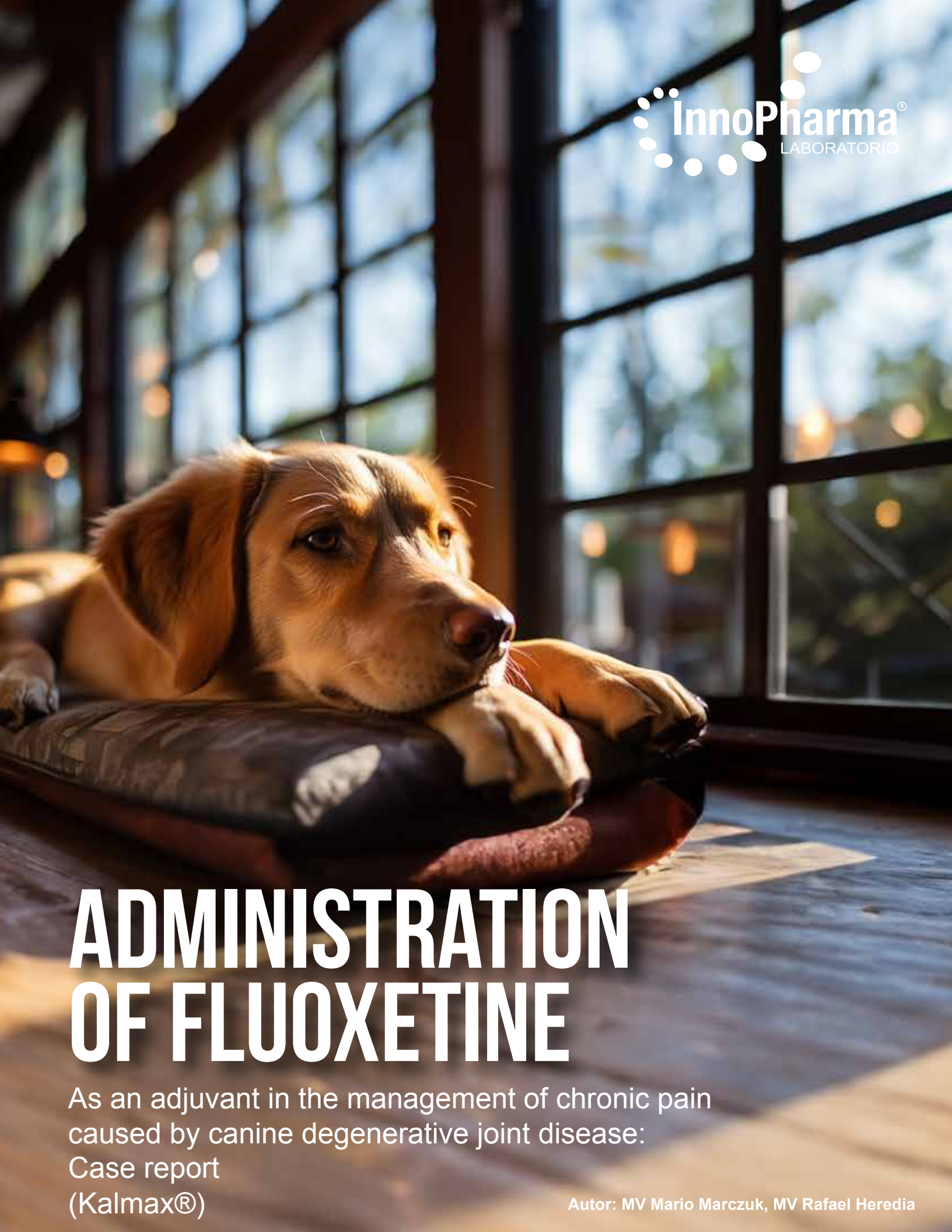

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ADMINISTRATION OF FLUOXETINE

As an adjuvant in the management of chronic pain caused by canine degenerative joint disease: Case report (Kalmax®)

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ADMINISTRATION OF FLUOXETINE

As an adjuvant in the management of chronic pain caused by canine degenerative joint disease

ABSTRACT

In recent decades, pain management has evolved, from its diagnosis, measurement (knowing how much it hurts), as well as its management, through the combination of different drugs, as well as the use of complementary therapies and supplements, with the aim of improving quality of life, reducing pain, and improving patient mobility.

Fluoxetine has been associated with correcting the chemical imbalance in neurotransmitter levels. It has been postulated that the therapeutic effects of fluoxetine may be mediated more by its influence on neuroplasticity by affecting gene expression, inducing epigenetic changes, and modifying synaptic transmission through synaptic remodeling or long-term potentiation.

RESULTS

In the initial evaluations, the patient had a score on the Helsinki scale of 24/44 and parasympathetic activity values of 48/100. In the second evaluation, the patient had a Helsinki scale of 22/44 and PTA 60/100, and the caregiver reported that separation anxiety-associated behavior was not present. In the third evaluation, they obtained 22/44 on the Helsinki scale with an increase to 26/44, and the PTA decreased to 45/100. The patient showed a lot of discomfort upon palpation of the right coxofemoral joint. At this point, amantadine was discontinued, and gabapentin and fluoxetine (Kalmax®) were prescribed.

CONCLUSIONS

Supplementing with fluoxetine in the plan for managing chronic pain due to osteoarticular disease improved the response in pain parameters as well as the patient's behavior, as well as the visual evaluation of gait, so its use should be considered in this type of patient as part of comprehensive management.

Keywords: osteoarthritis, pain, chronic pain, fluoxetine, canines.

INTRODUCTION

Osteoarthritis (OA) is a degenerative disease affecting all animals, including dogs (Schunck et al., 2017). Its prevalence has been estimated at 20%, particularly in working dogs with high physical demands, with chronic pain being the most common and relevant characteristic sign (Alves et al., 2022).

OA is one of the most commonly diagnosed canine diseases in most large breeds. Dogs often develop arthritis due to injuries, obesity, aging, or immune disorders. Some dog breeds are even genetically predisposed to develop OA (Deparle et al., 2005; Barbeau et al., 2022). The loss of joint cartilage is the most critical point in OA; subsequently, bone deformation, synovitis, reduction of the joint capsule, and muscle atrophy occur.

The cardinal signs of osteoarthritis are pain and lameness (Dobenecker et al., 2017). Hip dysplasia (Coxofemoral Dysplasia) is the most common orthopedic disease in dogs and consists of poor congruence of the acetabular cavity with the femoral heads that may appear dislocated or subluxated. It mainly affects large and medium breeds, rapidly growing and maturing, presenting decreased pelvic muscle masses and pectineus muscle abnormalities. It represents a degree of hip laxity that allows subluxation during the initial stage of life, resulting in a variable degree of loss of acetabular depth and flattening of the femoral head, ultimately leading to inevitable arthrosis (Canales, 2015). OA is a significant cause of chronic pain in many dogs and can compromise animal comfort. Non-steroidal anti-inflammatory drugs (NSAIDs) have been the first-line analgesics for canine OA pain treatment for many years, although other alternatives for OA treatment have been studied recently.

Some of these include piprants, opioids, monoclonal antibodies, corticosteroids, among others (Pye et al., 2022; Verrico et al., 2020). Fluoxetine is one of the most prescribed antidepressants in humans for treating depression and anxiety disorders. However, its use for treating pain in dogs with OA has been recently studied. Fluoxetine is part of a group of medications known as selective serotonin reuptake inhibitors (SSRIs), which has been shown to have effects on serotonin, in addition to having anti-inflammatory, antitumor, and neuroprotective effects (Zhang et al., 2022).

Fluoxetine has long been used to treat behavioral disorders in dogs, including aggression, compulsive disorder, and separation anxiety, due to its ability to restore thought and action disorders, reduce impulsivity, and provoke reflection before acting. However, its use in the treatment of osteoarticular pain in dogs has recently been analyzed, as it seems to have positive effects in relieving inflammatory osteoarticular pain (Sacchettino et al., 2023). OA poses both physical and well-being problems for many dogs, and having options for comprehensive pain management is important. This report presents how the administration of fluoxetine, in addition to the therapeutic plan for chronic pain caused by canine osteoarthritis, improves the patient's quality of life.

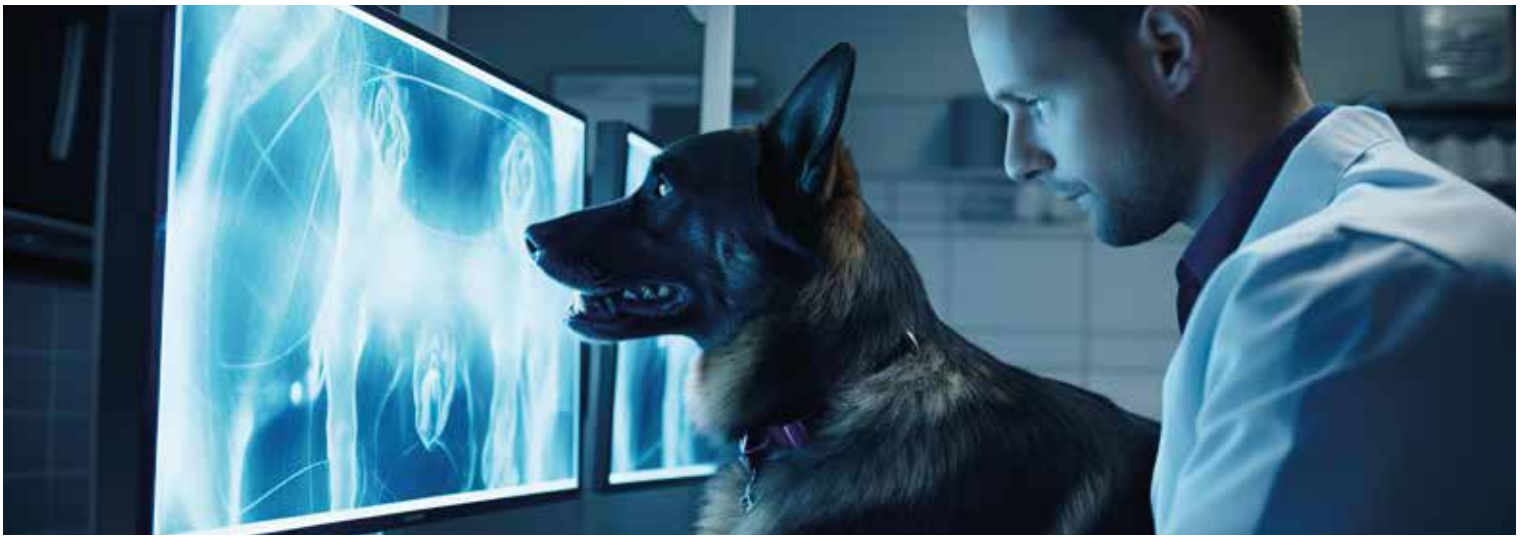
CASE PRESENTATION

A canine patient, mixed breed, neutered male, 7 years old, weighing 30 kilograms, with a body condition score of 5/9, was brought to the pain medicine service due to behavior consistent with osteo-myochondral pain (OMCP). The patient exhibited a grade 2/6 lameness in the right hind limb assessed through visual gait evaluation (VGE) (Oosterlinck et al., 2011) and discomfort upon palpation in the coxofemoral joint of the right hind limb. The caregiver reported during the consultation that they observed changes in behavior when the patient was left alone at home, noting damages to objects such as furniture, carpets, and toys, which was a new and different behavior from the patient's usual demeanor.

In February 2023, the patient was diagnosed with degenerative joint disease in the right hind limb and was started on the following treatment: carprofen 2.2 mg/kg every 12 hours for 14 days, gabapentin 10 mg/kg every 8 hours for 30 days, with favorable progression following this treatment.

In May of the same year, the patient was assessed and presented with right hind limb lameness, VGE 2/6, and discomfort upon palpation of the right coxofemoral region. Using the Helsinki index (Hielm-Björkman et al., 2008), a score of 24/44 was obtained, and a score of 48/100 was obtained using the parasympathetic activity monitor, indicating an autonomic imbalance consistent with osteo-myochondral pain. Additionally, the reported change in behavior by the caregiver might affect the autonomic imbalance and the patient's perception of pain. Therefore, the treatment was modified as follows: robenacoxib 1 mg/kg PO every 24 hours for 14 days, amantadine 10 mg/kg PO every 8 hours for 7 days, fluoxetine (Kalmax®) 1 mg/kg PO every 24 hours for 30 days.

In June 2023, the patient exhibited VGE lameness of 1/6, and upon deep palpation of the right coxofemoral region, there was a reduced degree of discomfort. The Helsinki index score was 22/44, PTA 60/100, and the caregiver reported that separation anxiety-associated behavior had disappeared, with no further reports of object destruction when the patient was alone at home.



CASE PRESENTATION

It was decided to initiate photobiomodulation and rehabilitation sessions twice-weekly for 6 weeks. By July 2023, the patient returned with VGE lameness of 3/6, having engaged in extreme physical activity, suggesting a pain exacerbation. The owner reported a return of behavioral changes, the Helsinki index score increased to 26/44, PTA decreased to 45/100, and the patient exhibited significant discomfort upon palpation of the right coxofemoral joint. Consequently, the treatment was adjusted to robenacoxib 1 mg/kg PO every 24 hours for 14 days, discontinuation of amantadine, and prescription of gabapentin 10 mg/kg PO every 8 hours for 21 days and fluoxetine (Kalmax®) 1 mg/kg PO every 24 hours for 30 days.

The patient returned for a follow-up in August 2023, showing recovery from discomfort upon palpation of the right coxofemoral joint, no evident lameness, and the disappearance of behavioral changes post-administration of fluoxetine. The following month (September 2023), the patient returned for a check-up without behavioral changes and with normal parameters (Helsinki Chronic Pain Index 22/44, PTA 65/100, lameness 1/6), no changes upon palpation, and the caregiver reported that 'his dog is happy,' which could be considered a parameter of well-being in the patient.

Table 1. Monthly Evaluation Results according to the Established Treatment in a Canine Patient with Myo-Osteo-Articular Disease.

Date	VGE	PTA	Helsinsky	Tratamiento
February	2/6	n/a	n/a	Carprofen 2.2 mg/kg, Gabapentin 10 mg/kg
May	2/6	48/100	24/44	Robenacoxib 1 mg/kg orally, Amantadine 10 mg/kg orally, Fluoxetine (Kalmax®) 1 mg/kg orally.
June	1/6	60/100	22/44	Photobiomodulation and rehabilitation,
July	3/6	45/100	26/44	Robenacoxib 1 mg/kg orally. Gabapentin 10 mg/kg orally. Fluoxetine (Kalmax®) 1 mg/kg orally.
August	n/a	n/a	n/a	Fluoxetine (Kalmax®) 1 mg/kg orally.
September	1/6	65/100	22/44	Fluoxetine (Kalmax®) 1 mg/kg orally.

VGE= (Visual Gait Evaluation). **PSA** Parasympathetic Activity Monitor. **n/a** not available.

DISCUSSION

Currently, there is scientific evidence supporting various medications for the control and treatment of osteoarticular pain. First-line medications include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, gabapentinoids, and corticosteroids. There is evidence of the efficacy of fluoxetine as a multimodal treatment for nociceptive pain in humans. While fluoxetine is primarily used for depressive disorder treatment, its effectiveness in pain management has been recently confirmed. There is uncertainty about whether fluoxetine alone is a reliable analgesic agent, as it has shown greater recognition in multimodal analgesia. The most probable beneficial use of fluoxetine in nociceptive pain treatment is relief of inflammatory pain. Fluoxetine does not carry the risk of respiratory depression, tolerance, dependence, peptic ulceration, or drug-induced pain (Katzung, 2014; Barakat et al., 2018).

The comorbidity of pain and depression has long been recognized, but the underlying basis of this comorbidity is complex. Most studies regarding how fluoxetine helps control pain have focused on the hypothalamic-pituitary-adrenal (HPA) axis, neurogenesis, and various neurotransmitters/neuromodulators, including serotonin. Central serotonin deficiency is considered a pain mechanism, as it participates in nociceptive pain signaling through ascending and descending modulatory pathways (Cai et al., 2019). A study in 2013 demonstrated the efficacy of fluoxetine in multimodal analgesia (Shen et al., 2013). They showed that morphine in combination with fluoxetine potentiated the analgesic effect due to their nociceptive synergy.

In our case, the patient showed significant improvement in VGE, PTA, and the Helsinsky index following the combination of robenacoxib, gabapentin, and fluoxetine. It is believed that fluoxetine's effect on pain regulation occurs through the inhibition of presynaptic serotonin transporters, causing a decrease in serotonin transport from the synapse to presynaptic neurons, thereby increasing serotonin levels in the synapse.

Robenacoxib is a widely studied drug in OA pain treatment, belonging to selective NSAIDs. Its mechanism of action involves reducing inflammation and pain by inhibiting cyclooxygenase II (COX-2), responsible for the production of proinflammatory prostaglandins. On the other hand, gabapentin is an anticonvulsant drug that, when used in combination with other drugs, can be considered an interesting therapeutic option for neuropathic diseases and analgesia in neuropathic pain (Kongara and Chambers, 2018; Di Cesare et al., 2023).

Fluoxetine may be considered an interesting therapeutic option for treating pain in canine osteoarthritis and chronic pain when other analgesics, such as gabapentin or NSAIDs, are not sufficient. However, further studies on the analgesic effect of fluoxetine as a single drug in pain or neuropathic diseases treatment are needed."

CONCLUSIONS

The administration of fluoxetine (Kalmax®) in this patient proved to be a good option as part of the comprehensive management of chronic pain, as it improved Helsinki Score values, parasympathetic activity, visual gait evaluation, and behavior.

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