

## Quetiapine reverses paclitaxel-induced neuropathic pain in mice: Role of alpha2- adrenergic receptors

Alireza Abed<sup>1</sup>, Mohammad Javad Khoshnoud<sup>2</sup>, Mehdi Taghian<sup>3</sup>, Mahbubeh Aliasgharzadeh<sup>4</sup>, Azam Mesdaghinia<sup>5, 1\*</sup>

<sup>1</sup> Department of Pharmacology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran

<sup>2</sup> Department of Toxicology and Pharmacology, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>3</sup> Department of Oral and Maxillofacial Surgery, School of Dentistry, Mazandaran University of Medical Science, Sari, Iran

<sup>4</sup> School of Pharmacy, International Branch, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>5</sup> Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran

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### ABSTRACT

**Objective(s):** Paclitaxel-induced peripheral neuropathy is a common adverse effect of cancer chemotherapy. This neuropathy has a profound impact on quality of life and patient's survival. Preventing and treating paclitaxel-induced peripheral neuropathy is a major concern. First- and second-generation antipsychotics have shown analgesic effects both in humans and animals. Quetiapine is a novel atypical antipsychotic with low propensity to induce extrapyramidal or hyperprolactinemia side effects. The present study was designed to investigate the effects of quetiapine on the development and expression of neuropathic pain induced by paclitaxel in mice and the role of  $\alpha_2$ -adrenoceptors on its antinociception.

**Materials and Methods:** Paclitaxel (2 mg/kg IP) was injected for five consecutive days which resulted in thermal hyperalgesia and mechanical and cold allodynia.

**Results:** Early administration of quetiapine from the 1<sup>st</sup> day until the 5<sup>th</sup> day (5, 10, and 15 mg/kg PO) did not affect thermal, mechanical, and cold stimuli and could not prevent the development of neuropathic pain. In contrast, when quetiapine (10 and 15 mg/kg PO) administration was started on the 6<sup>th</sup> day after the first paclitaxel injections, once the model had been established, and given daily until the 10<sup>th</sup> day, heat hyperalgesia and mechanical and cold allodynia were significantly attenuated. Also, the effect of quetiapine on heat hyperalgesia was reversed by pretreatment with yohimbine, as an alpha-2 adrenergic receptor antagonist.

**Conclusion:** These results indicate that quetiapine, when administered after nerve injury can reverse the expression of neuropathic pain. Also, we conclude that  $\alpha_2$ -adrenoceptors participate in the antinociceptive effects of quetiapine.

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### Introduction

Peripheral neuropathy is a common disorder of cancer chemotherapeutic agents, specifically paclitaxel (1). Peripheral neuropathy, which is predominantly sensory neuropathy presents as paresthesia, numbness and/or pain, which can severely affect the quality of life and results in chemotherapy dose reduction and/or premature treatment discontinuation (2).

The mechanisms responsible for the development of neurotoxicity are often linked to the cytotoxicity mechanisms, implying the obvious difficulty in reducing neurotoxicity without diminishing anticancer efficacy (3).

Preventing and treating paclitaxel-induced peripheral neuropathy are major concerns in clinical cancer therapy. A wide variety of neuroprotective agents have been examined in both animals and humans to prevent paclitaxel neurotoxicity (4).

The most widely used drugs include the tricyclic antidepressants (TCAs), serotonin/norepinephrine reuptake inhibitors (SNRIs) and antiepileptic agents such as pregabalin and gabapentin, (5-8). However, there is still a need to find newer additional therapeutic agents for the management of this complicated and debilitating disorder.

Recently it has been demonstrated that first- and second-generation antipsychotics have analgesic effects, both in humans and animals (9). Some second-generation antipsychotics have antidepressant and anxiolytic effects. Several old and new antipsychotics improve sleep parameters in healthy subjects (10).

Quetiapine was approved for the treatment of refractory major depression and bipolar depression (11, 12). Quetiapine belongs to newer atypical antipsychotics with a dopamine, serotonin, adrenergic, and histamine antagonistic properties. Quetiapine occupies

\*Corresponding author: Azam Mesdaghinia. Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran. Tel: +98-31-55542999; email: mesdaghinia-a@KaUMS.ac.ir

serotonin receptors and acts as an antagonist at 5-HT<sub>2A</sub> receptors (13). It has been shown that 5-HT<sub>2A</sub> receptors in the peripheral sensory terminals are responsible for serotonin-induced hyperalgesia and pretreatment with 5-HT<sub>2A</sub> receptor antagonist attenuates the pain (14).

Also, growing evidence suggests that specific cytokines and chemokines play an important role in pain signaling and behavioral changes (15). It has been demonstrated that atypical antipsychotics modulate cytokines production (16). Quetiapine significantly reduced TNF- $\alpha$  release from microglia and its anti-inflammatory effects are well established (17). Current evidence suggests that quetiapine is able to control fibromyalgia (18).

Among the antipsychotic drugs, quetiapine very rapidly dissociates from the D<sub>2</sub> receptors. So physiological surges of dopamine in the nigrostriatal and tuberoinfundibular pathways will occur and risk of side-effects such as extrapyramidal and hyperprolactinemia will diminish (19).

Each of these properties indicates that quetiapine could be a novel alternative for the management of paclitaxel-induced neuropathic pain.

Also, quetiapine and *N*-Desalkylquetiapine are potent norepinephrine reuptake inhibitors and increase noradrenergic transmission. Norepinephrine reuptake inhibition caused the stimulation of the descending noradrenergic pain inhibitory pathway that produced antinociception through  $\alpha$ -2 adrenergic receptors (20). So, we assumed that this drug produced antinociceptive effects through the stimulation of the descending noradrenergic pain inhibitory pathway and  $\alpha$ <sub>2</sub>-adrenoceptor.

The aim of this study was to evaluate the antinociceptive effect of quetiapine in attenuating the behavioral scores of neuropathic pain and to determine the role of  $\alpha$ <sub>2</sub>-adrenoceptors in the antinociceptive effect of quetiapine.

## Materials and Methods

### Chemicals

Quetiapine (Seroquel®) was purchased from AstraZeneca Pharmaceuticals and dissolved in saline (0.9%) solution. Paclitaxel was purchased from Stragen Pharma SA (Chemin du Pré-Fleuri 3, 1228 Plan-les-Ouates, Switzerland).

### Animals

NMRI mice weighing 20–30 g were used. They were housed under a 12 hr light/dark cycle and had free access to food and water. Animals were randomly assigned to different treatment groups (n=8 in each group).

### General procedures for drug administration

To induce the neuropathic pain, paclitaxel (2 mg/kg) was injected IP on the 1<sup>st</sup> day and given daily

for 4 additional days with a cumulative dose of 10 mg/kg (paclitaxel group) (21, 22). Vehicle group received only the saline solution.

To investigate the effects of quetiapine on the development and expression of neuropathic pain we designed two different treatment protocols; early treatment which started in the development phase of neuropathic pain and late treatment which initiated after the nerve injury and when the pain had established.

Quetiapine was dissolved in saline 0.9% solution. Quetiapine's solution was prepared with different concentrations (0.5, 1, and 1.5 mg/ml). Quetiapine was administered orally (PO), in a volume of 10 ml/kg.

Quetiapine was administered directly into the stomach of mice. In this method, a bulb-tipped gastric gavage needle was attached to a syringe and used to administer the quetiapine into the stomach. The animal was gently restrained but not such that the animal vocalized or showed other signs of distress. The animals were maintained in an upright (vertical) position and the gavage needle passed along the side of the mouth.

To assess the effects of quetiapine on the development of neuropathic pain, this drug (5, 10, and 15 mg/kg P.O) was administered daily from the 1<sup>st</sup> day until the 5<sup>th</sup> day in the different mouse groups.

These doses were selected based on the Kim and his colleagues study. Considering their quetiapine (10 mg/kg) shows anti-inflammatory effects in an animal model of collagen-induced arthritis (23).

To determine the effects of quetiapine on the expression of neuropathic pain, quetiapine was administered (5, 10, and 15 mg/kg PO) once daily from the 6<sup>th</sup> day until the 10<sup>th</sup> day.

Considering our previous study, neuropathic pain following paclitaxel injections starts on the 6<sup>th</sup> day after first paclitaxel injections and lasts at least for two weeks. But the highest intensity of pain can be observed on the 11<sup>th</sup> day. So we choose this day to evaluate the pain scores (21).

Heat hyperalgesia, mechanical and cold allodynia were assessed on the 11<sup>th</sup> day after the first paclitaxel injections.

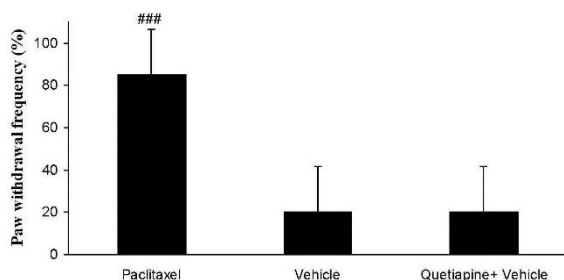
### Evaluation of the role of $\alpha$ <sub>2</sub>-adrenergic receptor

To identify the role of the  $\alpha$ <sub>2</sub>-adrenergic receptor in the anti-nociceptive effect of quetiapine, animals were treated with yohimbine (5 mg/kg IP) on the 10<sup>th</sup> day, 15 min before last administration of quetiapine (10 mg/kg PO).

### Behavioral tests of neuropathic pain

#### Cold allodynia (acetone test)

Animals were placed on top of an aluminum mesh table. They were allowed to adapt for 15 min. Cold allodynia was assessed by applying an acetone drop



**Figure 1.** Effects of quetiapine (15 mg/kg PO) administration on paw withdrawal frequency compared to the vehicle-treated group. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with saline 0.9% solution and did not receive paclitaxel. The quetiapine+vehicle group received quetiapine (15 mg/kg PO) dissolved in a saline solution. The results are expressed as Mean $\pm$ SEM, ### $P$ <0.001 versus the vehicle group,  $n$ =8 in all groups

via a needle to the plantar surface of the hind paw five times with a 60 sec interval. Paw withdrawal frequency was calculated and stated as a percentage with the following formula (number paw withdrawal /total number of trial)  $\times$  100 (24).

#### **Mechanical allodynia (von Frey filament stimulation)**

For mechanical allodynia assessment, von Frey filaments (Steeling, Wood Dale, IL, USA) ranging from 0.16 to 10  $g$  were used as previously described. The animals were placed on a wire mesh in a plexiglass box (18 $\times$ 18 $\times$ 25 cm). After the animals were adapted to the new environment, von Frey filaments, in an ascending order of forces, were used to measure mechanical allodynia. Each filament was applied to the plantar surface of the hind paw three consecutive times for 1 sec with 5 sec intervals. The smallest filament size which evoked 3 withdrawal responses was considered as withdrawal threshold (25, 26).

#### **Thermal hyperalgesia (plantar test)**

Using the plantar test and infrared radiation from the plexiglass surface to the animal's hind paw, heat hyperalgesia to the radiant heat stimulus was measured.

Paw withdrawal latency was expressed as the latency (sec) between the radiant stimulus start and paw withdrawal. Thermal stimulation was repeated three times with 5 to 10 min intervals. A cut-off time of 22 sec was used to avoid skin surface damage (27).

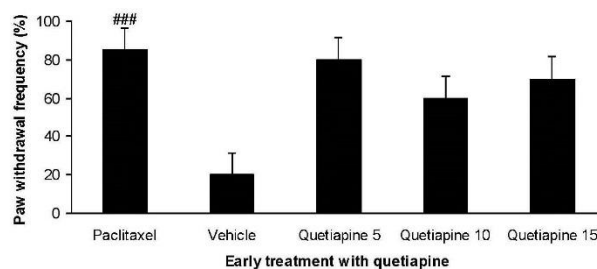
#### **Data analysis**

Statistical analysis was done by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. Results are expressed as Mean $\pm$ SEM.

## **Results**

### **Effect of quetiapine on the paw withdrawal frequency in vehicle-treated mice**

Quetiapine (15 mg/kg PO) administration did not



**Figure 2.** Effect of quetiapine (5, 10 and 15 mg/kg PO) administration from 1<sup>st</sup> day to the 5<sup>th</sup> day on the development of cold allodynia. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with a saline 0.9% solution and did not receive paclitaxel. The results are expressed as Mean $\pm$ SEM, ### $P$ <0.001 versus the vehicle group,  $n$ =8 in all groups

alter paw withdrawal frequency compared to the vehicle-treated group (Figure 1).

#### **Effect of quetiapine on the development of cold allodynia**

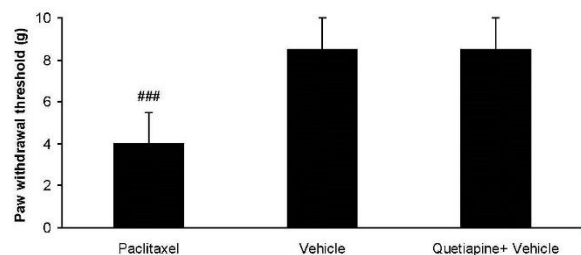
As shown in Figure 2 paclitaxel injections significantly induced cold allodynia in comparison with the vehicle group ( $P$ <0.001). Quetiapine (5, 10, and 15 mg/kg PO) administration during the development phase did not alter cold allodynia.

#### **Effect of quetiapine on the mechanical allodynia in vehicle-treated mice**

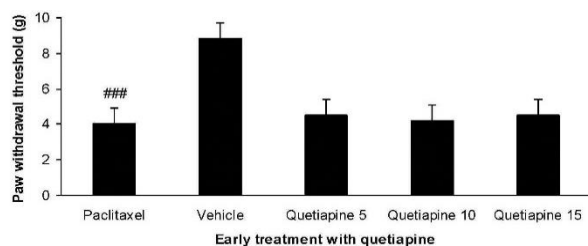
Quetiapine (15 mg/kg PO) administration did not alter paw withdrawal threshold compared to the vehicle-treated group (Figure 3).

#### **Effect of quetiapine on the development of mechanical allodynia**

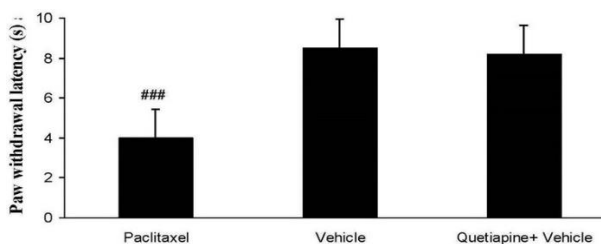
Paclitaxel injection significantly reduced paw withdrawal threshold compared to the vehicle group ( $P$ <0.01). However early treatment with quetiapine (5, 10, and 15 mg/kg PO) did not reduce the mechanical allodynia (Figure 4).



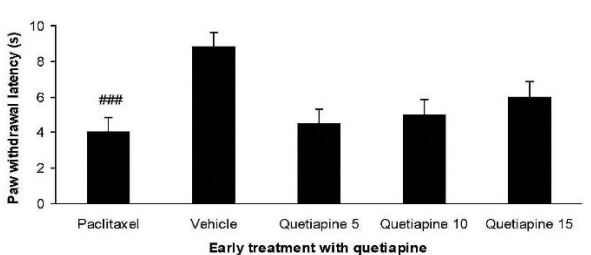
**Figure 3.** Effects of quetiapine (15 mg/kg PO) administration on paw withdrawal threshold compared to vehicle-treated group. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with a saline 0.9% solution and did not receive paclitaxel. The quetiapine+vehicle group received quetiapine (15 mg/kg PO), which was dissolved in a saline solution. The results are expressed as Mean  $\pm$  SEM, ### $P$ <0.001 versus the vehicle group,  $n$ =8 in all groups



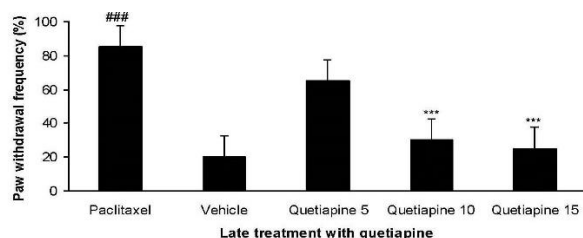
**Figure 4.** Effect of quetiapine (5, 10 and 15 mg/kg PO) administration from 1<sup>st</sup> day to the 5<sup>th</sup> day on the development of mechanical allodynia. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with a saline 0.9% solution and did not receive paclitaxel. The results are expressed as Mean ± SEM, <sup>###</sup>*P*<0.001 versus the vehicle group, n=8 in all groups



**Figure 5.** Effects of quetiapine (15 mg/kg PO) administration on paw withdrawal latency compared to the vehicle-treated group. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with a saline 0.9% solution and did not receive paclitaxel. The quetiapine+vehicle group received quetiapine (15 mg/kg PO,) which was dissolved in a saline solution. The results are expressed as Mean±SEM, <sup>###</sup>*P*<0.001 versus vehicle group, n=8 in all groups



**Figure 6.** Effect of quetiapine (5, 10, and 15 mg/kg PO) administration from 1<sup>st</sup> day to the 5<sup>th</sup> day on the development of heat hyperalgesia. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with a saline 0.9% solution and did not receive paclitaxel. The results are expressed as Mean±SEM, <sup>###</sup>*P*<0.001 versus the vehicle group, n=8 in all groups



**Figure 7.** Effect of quetiapine (5, 10 and 15 mg/kg PO) administration from 6<sup>th</sup> day to the 10<sup>th</sup> day on the expression of cold allodynia. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with a saline 0.9% solution and did not receive paclitaxel. The results are expressed as Mean±SEM, <sup>###</sup>*P*<0.001 versus the vehicle group, <sup>\*\*\*</sup>*P*<0.001 versus the paclitaxel group, n=8 in all groups

**Effect of quetiapine on the paw withdrawal latency in vehicle-treated mice**

Quetiapine (15 mg/kg PO) administration did not alter paw withdrawal latency compared to the vehicle-treated group (Figure 5).

**Effect of quetiapine on the development of heat hyperalgesia**

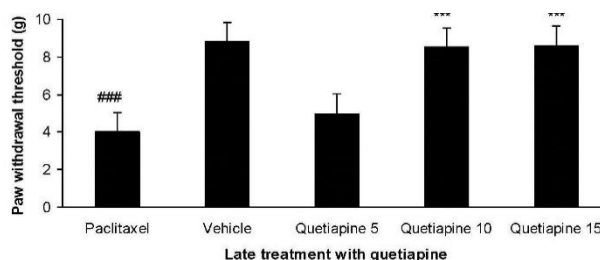
Paclitaxel injection decreased paw withdrawal latency (Figure 6). Early treatment with quetiapine did not significantly affect paw withdrawal latency.

**Effect of quetiapine on the expression of cold allodynia**

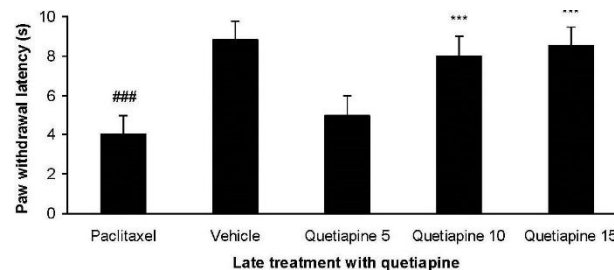
Quetiapine (10 and 15 mg/kg PO) administration from the 6<sup>th</sup> day until the 10<sup>th</sup> day, i.e. during the expression phase significantly reduced cold allodynia compared to the paclitaxel-treated group (*P*<0.001) (Figure 7).

**Effect of quetiapine on the expression of mechanical allodynia**

Administration of quetiapine (10 and 15 mg/kg PO) during the expression phase augmented paw withdrawal threshold and attenuated mechanical allodynia in von Frey monofilament test (*P*<0.001) (Figure 8).

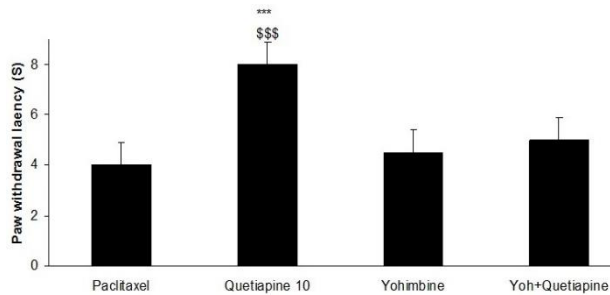


**Figure 8.** Effect of quetiapine (5, 10, and 15 mg/kg PO) administration from 6<sup>th</sup> day to the 10<sup>th</sup> day on the expression of mechanical allodynia. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with a saline 0.9% solution and did not receive paclitaxel. The results are expressed as Mean ± SEM, <sup>###</sup>*P*<0.001 versus the vehicle group, <sup>\*\*\*</sup>*P*<0.001 versus the paclitaxel group, n=8 in all groups



**Figure 9.** Effect of quetiapine (5, 10, and 15 mg/kg PO) administration from 6<sup>th</sup> day to the 10<sup>th</sup> day on the expression of heat hyperalgesia. The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The vehicle group was only treated with a saline 0.9% solution and did not receive paclitaxel. The results are expressed as Mean±SEM, <sup>###</sup>*P*<0.001 versus the vehicle group, <sup>\*\*\*</sup>*P*<0.001 versus the paclitaxel group, n=8 in all groups





**Figure 10.** The effects of yohimbine on the anti-hyperalgesic effect of quetiapine administration (10 mg/kg daily from day six until the 10<sup>th</sup> day). The paclitaxel group only received paclitaxel (2 mg/kg IP) for five consecutive days, which resulted in neuropathic pain. The quetiapine 10 group received paclitaxel (2 mg/kg IP) for five consecutive days and quetiapine (10 mg/kg PO daily from day six until the 10<sup>th</sup> day). The yoh+quetiapine group received paclitaxel (2 mg/kg IP) for five consecutive days, quetiapine (10 mg/kg PO daily from day six until the 10<sup>th</sup> day) and yohimbine (5 mg/kg IP) on the 10<sup>th</sup> day, 15 min before last administration of quetiapine (10 mg/kg PO). The results are expressed as Mean±SEM, \*\*\* $P < 0.001$  versus the paclitaxel group, \$\$\$ $P < 0.001$  versus the yoh+quetiapine group,  $n = 8$  in all groups

#### Effect of quetiapine on the expression of heat hyperalgesia

Quetiapine (10 and 15 mg/kg PO) administration from day 6 until the 10<sup>th</sup> day after paclitaxel injection produced significant anti-hyperalgesic effects compared to the paclitaxel group (Figure 9).

#### The effects of yohimbine on quetiapine-induced effects

Yohimbine reduced the antihyperalgesic effect of quetiapine (10 mg/kg daily from day six until the 10<sup>th</sup> day) (Figure 10). Nevertheless it could not significantly change the effect of quetiapine in the mechanical and cold allodynia. Moreover, yohimbine (5 mg/kg IP) solely did not alter the nociceptive thresholds.

## Discussion

In this experimental research, 5 day paclitaxel injection induced neuropathic pain and mice demonstrated a severe sensitivity to heat, cold, and mechanical stimulus. This is in accordance with results obtained by Nieto *et al* who have reported that paclitaxel (2 mg/kg) injections (IP), in a volume of 10 ml/kg, once per day for 5 consecutive days produces a painful neuropathy in rodents (22).

Considering our results, early treatment with quetiapine did not affect heat hyperalgesia and mechanical and cold allodynia and quetiapine could not inhibit the development of neuropathic pain.

Neuropathy is one of the most common and serious disorders of paclitaxel treatment and usually is the main reason for cancer chemotherapy discontinuation (28).

Axonal damage induced by paclitaxel is the supposed pathogenesis of this neuropathy (29).

However, the exact pathogenesis of this disorder is not clear and various mechanisms are involved in this complication. The cytotoxicity of these drugs is

often responsible for the development of neurotoxicity (30). Due to the lack of an effective protective layer, Dorsal Root Ganglions (DRG) are more sensitive to this neurotoxic effects (31). It has been suggested that disrupting energy mechanisms in the axon through damage of mitochondria are involved in the nerve degeneration induced by paclitaxel (32, 2). Considering our results early treatment with quetiapine did not affect the development of this neuropathy. Therefore, it is proposed that quetiapine did not interfere with cytotoxic effects of paclitaxel or did not show any neuroprotective effects.

However when quetiapine (10 and 15 mg/kg PO) administration was started on the 6<sup>th</sup> day after first paclitaxel injections, once the neuropathy had been induced and administered daily until the 10<sup>th</sup> day, thermal hyperalgesia and mechanical and cold allodynia were significantly attenuated and quetiapine relieved the expression of neuropathic pain.

It has been shown that atypical anti-psychotics inhibit TNF- $\alpha$  and IL-6 production (33). Quetiapine considerably reduces NO generation and inhibits TNF- $\alpha$  release from activated microglia (34). In the central nervous system (CNS) these cytokines mediate the inflammatory process and contribute to the progress of the neuropathic pain (35, 36). Releasing of these pro-inflammatory cytokines by sensitization of nociceptors caused mechanical hypersensitivity (37).

Moreover, quetiapine can block 5-HT<sub>2A</sub> receptors with great affinity (13, 14). Following nerve damage, serotonin release occurs from mast cells which stimulate 5-HT<sub>2A</sub> receptors in the DRG (38, 39). It has been shown that 5-HT<sub>2A</sub> receptors are involved in the development of hyperalgesia (40). Additionally, quetiapine modulates glutamate receptor activity. This would decrease the neurotoxicity following cancer chemotherapy (41)

*N*-desalkylquetiapine is a 5-HT<sub>1A</sub> receptor agonist with high affinity for this receptor (42, 43).

At the spinal level, presynaptic activation of this receptor modulates pain sensation (44).

According to our results and mechanisms involved in pain modulation, it could be suggested that quetiapine is able to control the pain expression.

Also, norquetiapine acts as a norepinephrine reuptake inhibitor and stimulates the descending noradrenergic pain inhibitory pathway (45, 46). Stimulation of  $\alpha_2$ -adrenoceptors in the dorsal root ganglia (DRG) modulates pain sensitivity (47, 48). Role of  $\alpha_2$ -adrenoceptor in the anti-nociceptive effect of quetiapine especially in neuropathic pain remains elusive.

Considering our results yohimbine (5 mg/kg IP), an  $\alpha_2$ -adrenoceptor antagonist, reversed the antihyperalgesic effect of quetiapine in the plantar test but couldn't influence the effect of quetiapine on the cold and mechanical allodynia. These data

suggest that alpha 2- adrenoceptor participates in the antinociceptive effect of quetiapine.

### Conclusion

Our results have demonstrated that quetiapine prevents the expression of paclitaxel-induced neuropathic pain. In contrast considering our results, quetiapine cannot prevent the development of this neuropathy. Quetiapine is a novel antipsychotic agent with low propensity to induce extrapyramidal or hyperprolactinemia side effects and this study identifies quetiapine as a new potential treatment for paclitaxel-induced neuropathic pain.

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### Conflict of interest

The authors declare no conflicts of interest.

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