

# Placebos, neuropathic pain and gender

## Los placebos, el dolor neuropático y de género

Carlos B. Moreno, Angela M. Gutiérrez

### RESUMEN

**INTRODUCTION:** the placebos' analgesic effect seems to depend on different factors such as socio-cultural, psychological and genetic aspects. The effects of gender on placebos' analgesic response have rarely been documented in clinical studies, even though there have been some reports in experimental studies.

**OBJECTIVE:** study the analgesic effect of anticonvulsant and antidepressive drugs in adults suffering from painful diabetic neuropathy and its relationship with gender

**MATERIAL AND METHODS:** a search and systematic selection was made of all clinical trials for analgesic treatment of diabetic neuropathy with anticonvulsant and antidepressive drugs published between January 2000 and February 2011. Randomized, placebo-compared clinical trials were included which had studied the analgesic effect of anticonvulsant and antidepressive drugs in adults suffering from painful diabetic neuropathy, evaluated in such a way that improvement in pain could be objectively classified. The following information was obtained from each article: criteria for diagnosing diabetic neuropathy, medicaments received and improvement of pain in the group being treated and in the placebo group according to patient gender.

**RESULTS:** 12 studies fulfilling the inclusion criteria were found which analyzed latest generation anticonvulsant and antidepressive agents used in managing pain in diabetic neuropathy. Only one study included gender-discriminated results regarding controlling pain in the placebo group.

**CONCLUSION:** the foregoing easily justifies the need for and importance of studying the relationship between gender and placebo response. This association has not been suitably reported to date, except by very few studies.

**KEY WORDS:** Pain, Pain Perception, Anticonvulsants, Antidepressive Agents, Gender and Health (MeSH).

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### SUMMARY

**INTRODUCCIÓN:** el efecto analgésico del placebo parece depender de diversos factores tales como los aspectos socio-culturales, psicológicos y genéticos. Los efectos del género en la respuesta analgésica del placebo rara vez se documenta en los estudios clínicos, a pesar de que ha habido algunos informes en los estudios experimentales.

**OBJETIVO:** estudiar el efecto de los antiepilépticos y fármacos antidepressivos en la neuropatía diabética en relación con el género

**MATERIAL Y MÉTODOS:** se realizó una búsqueda y selección sistemática de todos los ensayos clínicos para el tratamiento analgésico de la neuropatía diabética con antiepilépticos y fármacos antidepressivos publicados entre enero de 2000 y febrero de 2011. Se incluyeron todos los estudios clínicos aleatorizados, comparados con placebo que estudiaran el efecto analgésico de los antiepilépticos y fármacos antidepressivos en adultos con neuropatía diabética dolorosa, que evaluaran la mejoría en el dolor de manera objetiva. En cada artículo se obtuvo la siguiente información: criterios para el diagnóstico de la neuropatía diabética, medicamentos recibidos y mejoría del dolor en el grupo en tratamiento y en el grupo placebo, según el sexo del paciente.

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**RESULTADOS.** 12 estudios cumplían los criterios de inclusión. Sólo un estudio incluyó discriminación de género, los resultados en relación con el control del dolor en el grupo placebo.

**CONCLUSIONES:** los hallazgos de esta investigación justifica la necesidad y la importancia de estudiar la relación entre el género y la respuesta al placebo. Esta asociación no ha sido debidamente reportada hasta la fecha, excepto por muy pocos estudios.

**PALABRAS CLAVES:** Dolor, Percepción del Dolor, Anticonvulsivantes, Antidepresivos, Género y Salud (DeCS).

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## INTRODUCTION

The placebo effect has been broadly defined as being, “any therapeutic procedure (or that component of any therapeutic procedure) which is given deliberately to have an effect, or unknowingly has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated” (1). The intervention or procedure that elicits the placebo effect is known as the placebo (2).

The placebos’ potential analgesic effect for managing pain is well known and has been well documented (3). However, its action mechanism is not very clear as it seems that there is no single neurobiological or psychobiological process which explains the whole placebo effect. At least three mechanisms have been proposed which rely on some empirical evidence; the first concerns conditioning where the setting or context surrounding the procedure is the conditioned stimulus which could produce analgesia without an active drug being administered (4). The second emphasizes the expectations of the subject who will benefit from the analgesic drug (5,6) and the third suggests that the analgesic effect is due to endogenous opioid activity (7,8). The three mechanisms may play a role in placebo-generated analgesia.

The placebos’ analgesic effect also seems to depend on other factors such as socio-cultural, psychological and genetic aspects (2). The effects of gender on placebos’ analgesic response have rarely been documented in clinical studies, even though there have been some reports in experimental studies (9,10). The foregoing highlights the need for investigating the effects of gender on analgesic response to a placebo in different pathologies.

The present work has reviewed the available evidence in scientific literature concerning the effect of

gender on analgesic response to placebo in patients suffering from painful diabetic neuropathy.

## METHODOLOGY

A search and systematic selection was made of all clinical trials for analgesic treatment of diabetic neuropathy with anticonvulsant and antidepressive drugs published between January 2000 and February 2011. The search covered COCHRANE, MEDLINE, EMBASE and LILACS databases, using combinations of the following MeSH terms: “diabetic neuropathies”, “pain”, “anticonvulsant”, “antidepressive agents” [just serotonin reuptake inhibitors (SSRI) and serotonin and noradrenalin reuptake inhibitors (SNRI)]. Clinical trials on humans, published in English or Spanish, were the only search limits. Following the electronic search, the title and content of the corresponding articles’ summaries were analyzed; the complete text was obtained of those articles considered to be pertinent and all references presented in each article were reviewed. Randomized, placebo-compared clinical trials were included which had studied the analgesic effect of anticonvulsant and antidepressive drugs in adults suffering from painful diabetic neuropathy, evaluated in such a way that improvement in pain could be objectively classified. Studies lacking relevant categorical measurements, case reports, summarized publications and studies of treatments in investigation phase were all excluded. All the studies were independently read and analyzed by each author; discrepancies were resolved by them reaching agreement. The following information was obtained from each article: criteria for diagnosing diabetic neuropathy, medicaments received and improvement of pain in the group being treated and in the placebo group according to patient gender.

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## RESULTS

8 studies fulfilling the inclusion criteria were found which analyzed latest generation anticonvulsant (11-18) and 4 analyzing antidepressive drugs (19-22) used in managing pain in diabetic neuropathy. Studies regarding nefazodone, sertraline, venlafaxine, sibutramine, fluvoxamine, citalopram and paroxetine were found for the other antidepressants, but none of them fulfilled study inclusion criteria.

Only Ziegler et al.'s study (22) (from those mentioned above) included gender-discriminated results regarding controlling pain in the placebo group. This investigation used data from 3 multicentre, double-blind, randomized studies (19-21) which were controlled with placebo and followed-up for 12 weeks. The study included 685 patients treated with duloxetine and 330 with placebo; 178 males and 152 females received the placebo and finished the study. The males reported an average 1.56 improvement on the visual analogue scale (VAS) whilst females had an average 1.61 improvement; the data presented in the article by Ziegler et al. (22), did not allow this difference's statistical significance to be analyzed. The data presented in the other studies did not discriminate placebo group results by gender.

## DISCUSSION

This investigation has confirmed different authors' observations that gender is not taken into account for evaluating placebo effects or the medicaments used for analgesic management of patients suffering from different painful pathologies (9,10,23). Plentiful scientific literature has shown gender differences in analgesic response to opioids (in animals and humans) which could reflect gender differences regarding these substances' pharmacodynamics and pharmacokinetics (24,25). Differences have been found between the sexes in opioid receptor expression in rat mesencephalic periaqueductal grey matter (26) which seem to be essential in explaining sexual dimorphism in morphine analgesia. Gender differences in morphine's analgesic effect have been reported in rodents since the end of the 1980s, showing that administering systemic morphine produced a greater degree of analgesia in male animals than female ones (27-29). It has been reported that human females feel more pain than

males (30) and need more morphine than they do for obtaining similar analgesia during immediate after surgical procedures (31). As previously mentioned, sufficient evidence has shown endogenous opioids' essential role in placebo analgesic response. Several studies have revealed gender differences in response to medicaments, not only regarding physiological aspects but differences are also known in several pharmacokinetic (body composition, enzymatic activity, gastric emptying time) and pharmacodynamic factors, with both opioids and non-steroid anti-inflammatory drugs (23). On the other hand, there are gender differences regarding adverse effects to analgesic medicaments; females have reported having more adverse effects to perioperative analgesic drugs (32) and medicament complications are twice more prevalent in females than in males (33).

## CONCLUSION

The foregoing easily justifies the need for and importance of studying the relationship between gender and placebo response. This association has not been suitably reported to date, except by very few studies.

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