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Neuropathic Pain and Fibromyalgia

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Definition of Neuropathic Pain

Neuropathic or neurogenic pain (NP) is defined by the International Association for the Study of Pain (IASP) as pain initiated or caused by a lesion or dysfunction of the nervous system. *Guevara-López U, Covarrubias-Gómez A, García-Ramos G, et al. Practice guidelines for neuropathic pain management. Rev Invest Clin 2006. 58(2):126-38.* This definition, although controversial, has been accepted by the members of the medical and scientific community interested in the subject.

Among the different causes of NP, this work will be limited to diabetic neuropathy, herpes zoster pain and trigeminal neuropathy.

What differentiates NP from other types of pain is its poor response to cyclooxygenase-2 inhibitors and opioids.

Epidemiology

Dieleman y col., Dielerman JP, Kerklaan J, Huygen F, et al. Incidence rates and treatment of neuropathic pain conditions in the general population.2008 Apr 23. [Epub ahead of print] A study of more than 362,000 persons in Netherlands found an incidence of NP of 818,2 cases per 100,000 persons/year. Within this group, diabetic neuropathy, postherpetic pain and trigeminal neuralgia were in the second, third and fifth place, respectively (Figure 1)

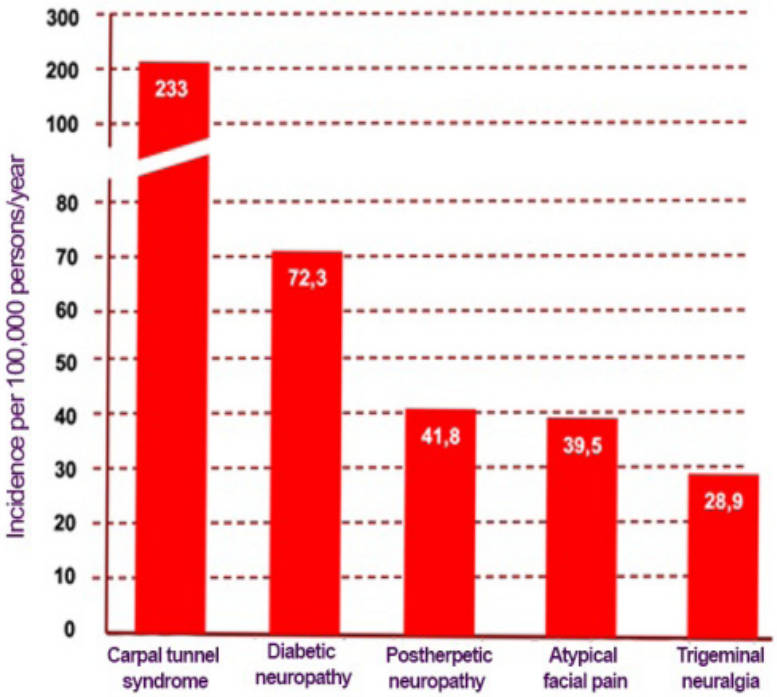

Figure 1. *Main types of NP and its incidence in a population. Source: Dielerman JP et al.*

The incidence of NP increases in a curve of continuous rise from late infancy to 60 years old when a plateau is established for the next two decades. At any stage of life, NP is more common in women than in men. Dielerman again.

Pathophysiological Mechanisms of NP

A focal peripheral nerve injury unleashes a range of peripheral and central nervous system processes that contribute to the persistence of pain. The inflammation, the reparatory mechanisms of neural tissues in response to injury, and the reaction of adjacent tissues to injury lead to a state of hyperexcitability in primary afferent nociceptors, a phenomenon termed peripheral sensitization. In turn, central neurons innervated by such nociceptors undergo dramatic functional changes including a state of hyperexcitability termed central sensitization. Normally, these sensitization phenomena extinguish themselves as the tissue heals and inflammation subsides. However, when primary afferent function is altered, the process persists and becomes resistant to treatment. *Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in Neuropathic Pain. Diagnosis, Mechanisms, and Treatment Recommendations. Arch Neurol. 2003;60:1524-1534.*

Positive sensory phenomena (spontaneous pain, allodynia and hyperalgesia) characteristic of NPhave many underlying mechanisms, including ectopic generation of impulses as well as the expression of new neurotransmitters and their receptors and ion channels. In conclusion, the processes involved in the pathophysiology of NPare the following: *Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain. 2003;102:1-8.*

- Increased firing of stimuli by the primary afferent nociceptor as a result of an abnormal amount of sodium channels in damaged peripheral nerves causing ectopic discharges.
- Decreased inhibition of neuronal activity in central structures due to loss of inhibitory neurons.
- Altered central processing (central sensitization) so that the input of sensory impulses is amplified and sustained.

NP Assessment and Diagnosis

The diagnosis of NPis not always straightforward because symptoms are very varied. A thorough medical history that includes the patient´s symptoms, work environment, social habits, exposure to toxins, alcoholism history, risk of human immunodeficiency virus and other infections and family history of neurological diseases is essential. Diabetes, vitamin deficiencies, liver or kidney dysfunction, and abnormal immune system activity should be ruled out. *National Institute of Neurological Disorders and Stroke. Peripheral Neuropathy. www.ninds.nih.gov/disorders/peripheralneuropath.*

In the patient´s anamnesis and clinical examination, pain is assessed according to: duration, site, distribution, intensity, associated sensory abnormalities (paresthesia, allodynia) and qualities (burning, tingling, shooting, stabbing, cramping, electric shock-like pains, etc.) *Dworkin, Guevara-López, Jensen TS, Gottrup H, Sindrup SH, et al.The clinical picture of neruopathic pain.Eur J Pharmacol 2001;429:1-11.*

Pain Estimation

There are different unidimensional and multi dimensional scales designed to assess pain intensity or severity. The visual analogue scale of 11 points and the verbal analogue scale of 5 points (no pain, mild pain, moderate pain, severe pain and pain as bad as it could be) have been used for the assessment of pain in general. *Guevara-López U, Coavarrubias-Gomez A, DeLille-Fuentes R, et al. Parámetros de práctica para el manejo del dolor agudo peripoeratorio. Cir Cir 2005;73:223-232.* Due to the complexity of this type pain, it is highly recommended to include special instruments such as brushes, swabs, sharp elements, test tubes with water at different temperatures and tuning forks.

Table 1 shows the type of pain, the mechanism that produces it and the method to explore it. *Jensen* again.

Table 1. *Type of pain, neurological mechanism and method of stimulation (examination technique)*

Type of pain	**Neurological mechanism**	**Examination technique**
Static hyperalgesia	Sensitization of C nociceptors.	Gentle mechanical pressure
Punctate hyperalgesia	Central sensitization and Sensitized A-delta nociceptors	Pinprick stimulus
Dynamichyperalgesia	Central sensitization due to loss of input	Light brush stimulus

Coldhyperalgesia	Central disinhibition because of loss of input	Cool stimulus (acetone, alcohol)
Heathyperalgesia	Sensitized c nociceptors	Radiating heat
Wind up likepain	Central sensitization due to increased input	Light brush or pinprick stimulus
Chemicalhyperalgesia	Sensitized mechanoinsensitive VR1/histamine receptors	Capsaicinorhistamine

Ancillary Studies

It is sometimes necessary to undergo ancillary studies for diagnosing neuropathic pain. Such studies are:

- Cerebrospinal fluid analysis: search of antibodies associated with neuropathy.
- Computed tomography: bone and vascular irregularities, tumors, cysts, herniated disks, encephalitis, spinal stenosis, etc.
- Magnetic resonance imaging: detect any fatty replacement of muscle tissue, nerve fibers that sustained compression, etc.
- Electromyography:this test can help differentiate between muscle and nerve disorders.
- Nerve conduction velocity: measures the degree of neurological damage in larger nerve fibers and distinguishes degeneration of the myelin sheath or the axon
- Nerve biopsy: It is usually obtained from nervous tissue from the calf. It is an invasive procedure which doctors prefer to avoid. This test has been replaced by skin biopsy which is less invasive and has fewer side effects.

Diabetic Peripheral Neuropathy

Introduction

Diabetic peripheral neuropathy (DPN) is fairly common, especially in type 1 diabetes where it can occur in up to 66% of patients, while in type 2 diabetes DPN can be present in up to 50% of the cases. Suffering from DPN does not mean that the patient always suffers pain, in fact, the presence of paraesthesia is more common; while between 15% and 30% of these patients have pain. *Jensen TS, Backonja MM, Hernandez Jimenez S, et al.: New perspectives on the management of diabetic peripheral neuropathic pain. DiabVascDis Res 2006, 3:108–119.*

Pathophysiology of DPN

Blood supply of nerves is provided by the microcirculation that surrounds them or *vasa nervorum*. Hyperglycemia together with proinflammatory cytokines affect the endothelium of these microvessels increasing their permeability, producing vasoconstriction and reducing blood flow. A degenerative damage is caused to nerve fibers that, as it advances, exhibits itself with different sensory symptoms. Initially, these symptoms are characterized by paresthesias and later the pain appears (Figure 2). *Kles KA, Vinik Ai. Pathophysiology and Treatment of Diabetic Peripheral Neuropathy: The Case for Diabetic Neurovascular Function as an Essential Component. Current Diabetes Reviews2006;2: 131-145.*

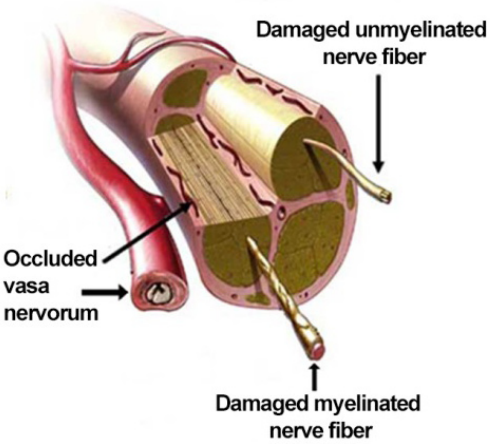

Figure 2. *Microvessels or vasa nervorum that surround nerves are damaged in diabetic patients and reduce the blood supply producing a progressive degeneration of the nervous fillets. Source: Kles KA y col.*

In addition to the aforementioned vascular factors, there are currently several theories that overlap each other to describe the mechanisms that cause DPN, and they are the following:

Hyperglycemia

Hyperglycemia affects the structure and function of nerve fibers directly on axons and indirectly altering the homeostasis of the endothelium of the vasa nervorum that supply nerve fibers. Kles again.

Hyperglycemia alters nervous tissue by reducing the activity of neuronal Na+/K+ adenosine triphosphatase, affecting nerve conduction and blood flow.

Hyperglycemia also contributes to the formation of free radicals.*Vague P, Coste TC, Jannot MF, Raccah D, Tsimaratos M. Cpeptide, Na+,K(+)-ATPase, and diabetes. Exp Diabesity Res 2004;5:37-50.*

Protein Kinase B (PKB)

PKB is an intracellular signal molecule that when activated by the metabolic disorders of diabetes produces vasoconstriction and increases the permeability of the vascular endothelium. Activation of PKB stimulates other molecules involved in angiogenesis and increase stress genes that damage nerves. *Kles* again.

Advanced Glycosylation Products (AGP)

Hyperglycemia followed by glucose autoxidation produce the formation of AGP that are characterized by initiating an inflammatory cascade. AGPs alter blood flow by causing the adhesion of erythrocytes to the vascular endothelium and also damage nerve neurofilaments. In addition, they also activate various proinflammatory cytokines that increase the production of reactive oxygen species (free radicals), and decrease the bioavailability of nitric oxide. *Kles* again.

Assessment of Patients with DPN

A Metabolic study is essential in DPN and it includes fasting blood glucose, glycosylated hemoglobin, lipid profile and kidney and thyroid function.

The clinical examination of the patient to investigate the DPN includes a series of procedures that are described in Table 2.

Table 2. *Examination of lower extremities in patients with DPN*

Type of examination	Results
Proprioception (awareness of the position of parts of the body)	Decreased proprioception in the foot
Stength	Reduced in extensors and dorsiflexion
Vibratory sense	With the use of tuning forks the vibratory sense decreases (120 Hz) from the foot towards the tibia plateau
Reflexes	There is no Achilles reflex, the sole may be normal.
Touch sensitivity	Hypoesthesia of the foot and part of the calf is detected by a cotton swab.
Temperature sensation	Cold or warm hypoesthesia in the foot and calf is detected with a test tube filled with cold or hot water.
Painful sensation	Hypoesthesia is confirmed with the use of a pin on the foot and calf

Postherpetic Pain

Introduction

The pain of herpetic neuralgia is characterized by a burning sensation, pain with a sensation of electric shock and intense itching. The diagnosis is confirmed with the appearance of skin rash since it is very unusual that herpetic neuralgia occurs without the presence of skin rash.Pain is associated with paresthesias, hyperalgesia, hyperesthesia and allodynia. *Dubinsky RM, Kabbani H, El-Chami Z, el tal. Practice Parameter: Treatment of postherpetic neuralgia: An evidence-based report of the Quality Standards Subcommittee of the American Academy of neurology. Neurology 2004;63:959–965.*

Post-herpetic neuralgia, i.e. the persistence of pain beyond the third month after the skin rash has disappeared, is observed in 10-15% of cases and increases with the age of the patient. In almost half of the cases, the postherpetic pain may last one year or more. *Helgason S, Petursson G, Gudmundsson S, et al. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow-up. BMJ 2000;321:794–796.*

Pathogeny

The virus can persist for years in the dorsal root ganglia of cranial or spinal nerves. In cases with decreased immunity, the virus travels down the sensory nerve and can cause skin lesions and dermatomal pain. Patients with postherpetic pain have showed damage to dorsal root ganglia and dorsal hornsof the spinal

cord. *Vasic-Kes V, Demarin V. Postherpetic neuralgia. Acta Clin Croat 2007;46:279-282.*

Trigeminal Neuralgia

General Characteristics

Trigeminal neuralgia affects one or more branches of the nerve, with the maxillary branch and the right side being the most affected. The condition has its peak during the sixth decade of life and is rare in adolescents and young adults. The incidence of trigeminal neuralgia in patients with multiple sclerosis is approximately 2 percent. Spontaneous remission is unusual and most patients have episodic attacks over many years. *Krafft RM. Trigeminal neuralgia. Am Fam Physician 2008;77:1291-1296.*

Pathophysiology

There is one theory that suggests that trigeminal neuralgia is caused by demyelination of the nerve that makes nonsynaptic contact with other fibers, producing ephaptic transmission of impulses (transmissions from one fiber to another without synapse intervention). Current theories regarding the cause of this demyelination center on vascular compression of the nerve root by aberrant tortuous vessels. Relief of symptoms by surgical techniques that separate these vessels further strengthens this theory. *Love S, Coakham HB. Trigeminal neuralgia: pathology and pathogenesis. Brain 2001;124(:2347-2360*

Clinical chart

The following are characteristics of trigeminal neuralgia:

- Paroxysmal attacks of pain of variable duration (from seconds to minutes)
- Pain is Intense, sharp and superficial
- Pain is caused by pressure on trigger zones or trigger factors.
- There is no neurologic deficit
- It is not caused by underlying processes.
- Painful episodes are stereotyped (the places, trigger zones, triggering factors and pain characteristics are always the same).

Pregabalin: Characteristics and Mechanisms of Action

Mechanisms of action

Pregabalin, a gamma-aminobutyric acid (GABA) analogue, was the first drug to receive approval in 1999 from the Food and Drug Administration (FDA) for the treatment of DPN and postherpetic neuralgia. *Zareba G. Pregabalin: a new agent for the treatment of neuropathic pain Drugs Today. 2005; 41:509-16.*

Pregabalin binds with a high degree of affinity to the alpha-2-delta protein in the brain. The alpha-2-delta site is an auxiliary protein associated with voltage-gated ionic calcium channels. Potent binding of pregabalin and its structural analogs at the alpha-2-delta site reduces depolarization-induced calcium influx at nerve terminals, with a consequential reduction in the release of several excitatory neurotransmitters, including glutamate, noradrenaline, substance P, and calcitonin gen-related peptide (CGRP). (Figure 3) It is probable that this modulation of neurotransmitter release by pregabalin contributes to the drug's anticonvulsant, analgesic, and anxiolytic effects. *Ben-Menachem E. Pregabalin Pharmacology and Its Relevance to Clinical Practice.Epilepsia 2004;45: 13-18.*

Pregabalin does not completely block calcium channel function or transmitter release, even at high concentrations. This property of pregabalin could have important implications as a safety mechanism in cases of overdose.

Pregabalin is structurally, but not functionally related to GABA and, therefore, in the administered doses does not act through the GABA via. Pregabalin itself is inactive at $GABA_A$, $GABA_B$, and benzodiazepine receptors, and is not converted metabolically into GABA or a GABA agonist. In addition, clinical concentrations of pregabalin have no effect on GABA uptake or degradation. This makes pregabalin more effective than classical antiepileptics and by not raising GABA levels in the optic nerve does not produce retinal lesions. *Errante LD, Petroff OA. Acute effects of gabapentin and pregabalin on rat forebrain cellular GABA, glutamate, and glutamine concentrations. Seizure 2002;12: 300–6*.

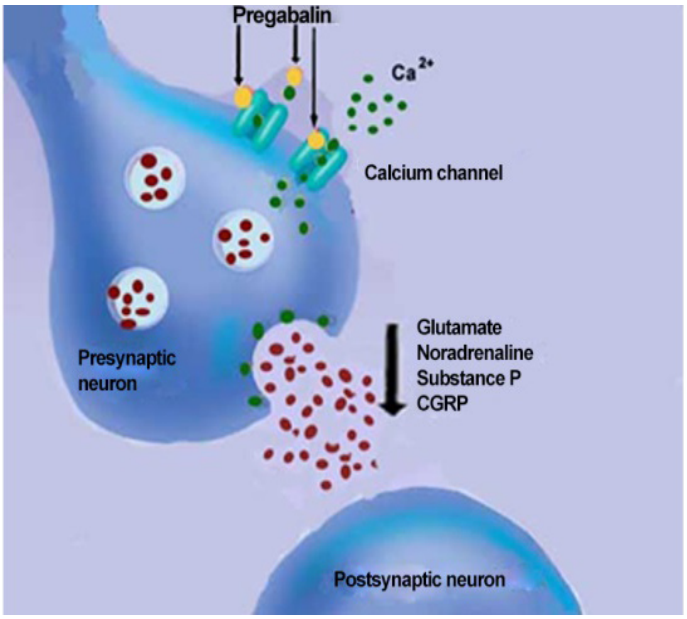

Figure 3. *Mechanism of action of pregabalin.Pregabalin (yellow molecules) binds to the α-2δ units of the ionic calcium channels (Ca2 +) of the presynaptic neuron, reducing the release of several neuroexcitatory transmitters (glutamate, noradrenaline, substance P and CGRP) on the postsynaptic neuron. CGRP: calcitonin gen-related peptide. Source: Blommel ML. Am J Health-Syst Pharm 2007;64:1475-1482.*

Pharmacokinetics

Pregabalin is rapidly absorbed within one hour of oral administration. The oral bioavailability of pregabalin is high at ≥90% and is independent of dose. Peak plasma levels occur one hour after administration. The administration of pregabalin together with food does not affect the degree of absorption of the drug. *Ben-Menachem* again.

The half-life of pregabalin is about 6 hours on average, it is not metabolized by the liver and 90% of the dose is eliminated in urine in unchanged form. The elimination of pregabalin in the urine is directly related to the blood creatinine values, therefore, the dose of the drug should be reducedin patients with renal insufficiency. Since it is neither transported by plasma proteins nor metabolized by the liver, pregabalin presents no drug interactions, what gives it the advantage of being co-administered with other antiepileptic agents. *Bockbrader HN, Burger PJ, Kugler AR, et al. Population pharmacokinetic (PK) analyses of commonly prescribed antiepileptic drugs (AEDs) co-administered with pregabalin (PGB) in adult patients with refractory partial seizures. Epilepsia 2001; 42(suppl 7): 84.*

Table 3 summarizes the clinical findings of the properties of pregabalin.

Table 3. *Properties of pregabalin and their clinical relevance*

Property	Clinical relevance
High affinity for alpha-2-delta binding site on calcium channels	Inhibits the release of several excitatory neurotransmitters
No effect on GABAergic mechanisms	No retinal or optic nerve damage
Potent anticonvulsant activity in the experimental phase.	Correlates with clinical experiences
Higher binding potency on calcium channels than gabapentin	Higher power than gabapentin
Lack of protein binding and it is not subject tohepatic metabolism	No druginteractions
Rapidly crosses blood–brain barrier	Fast and specificaction
T_{max}≤ 1 h and steady state in 24–48 h	Onset of action as early as week 1

Clinical Experiences with Pregabalin in DPN

Meta-analysis of 7 trials

Recently, *Freeman y col., Freeman R, Durso-De Cruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetrc peripheral neuropathy: Findings from seven randomized, controlled trials across a range of doses. Diabetes Care 31: 1448-1454* performed a meta-analysis of 7 randomized, controlled trials in order to determine efficacy, safety, and tolerability of pregabalin administered in different doses to painful DPNpatients.

Methods

The meta-analysis involved 1,510 patients, 557 of them received placebo, and 953 received pregabalin three times a day in a range of doses from 150 to 600 mg/day, divided in one, two or three doses, but when the doses were established, they were fixed. There was a slight predominance of men over women and the average age of the patients was 59 years. Treatment durations ranged from 5 to 13 weeks.

Participants had to update a daily questionnaire on the intensity and duration of pain based on a visual analog scale (VAS) and a numerical rating scale (NRS).

The main assessment criteria were based on the pain score in these scales and the Patient Global Impression of Change (PGIC) scale was used to determine the patient's perception of improvement.

Results

The following results were observed:

- Significant reductions in pain scores were observed for all three daily dosages investigated ($P = 0.007$ for 150 mg/day and $P < 0.0001$ for 300 and 600 mg/day vs. placebo) *versus* placebo (Figure).
- The 600 mg/day dosage, administered either three times a day or twice a day,was significantly superiorto placebo (P <0.001).
- The 300 mg/day dosage was significantly superior to placebo only when administered three times a day.
- The median time between the onset of treatment and an improvement of ≥ 50% of pain was significantly lower for doses of 600 and 300 mg/day compared to placebo.
- Sleep interference was significantly reduced with the 3 doses of pregabalin compared to placebo.
- The side effects of pregabalin were: 2.12% and 3.88% weight increase for the 300 mg and 600 mg doses, respectively. Higher frequency of peripheral edema was observed in the pregabalin groups.

Conclusion

Pregabalinadministered at the different doses was associated with a significant reduction in pain and sleep interference. The time interval between onset of treatment and pain reduction decreased as the dose of pregabalin increased.

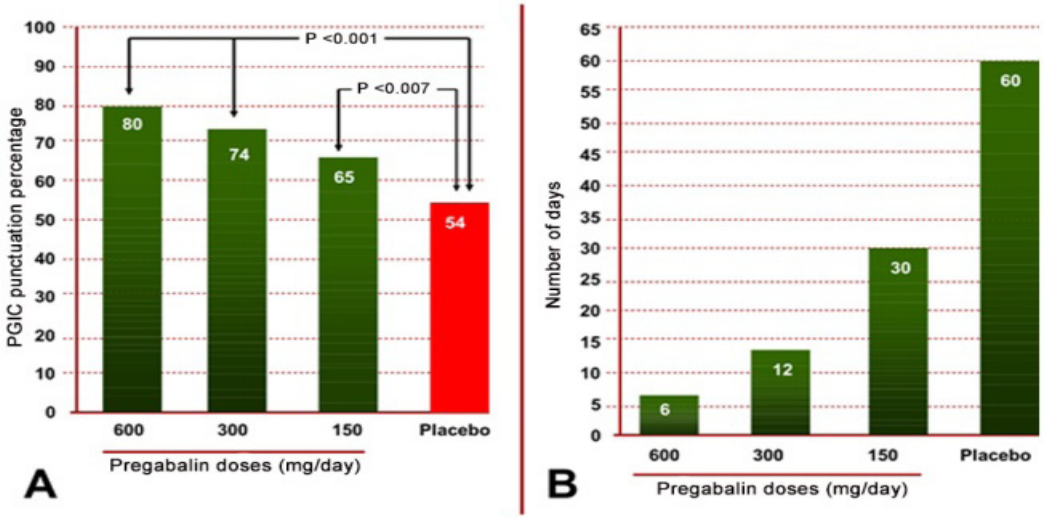

Figure 4. ***A:*** *Improvement of pain expressed as a percentage of Patient Global Impression of Change (PGIC) among the different doses of pregabalin and placebo.* ***B:*** *Time interval (days) between onset of treatment and pain reduction of ≥50% for the different pregabalin doses and placebo.*

Multicenter Trial to Evaluate Painful DPN Patients Treated with Pregabalin

The latest report on the efficacy of pregabalin in DPN pain was the result of a European multicenter study involving 58 centers in Germany, Hungary, Poland and the United Kingdom and to which institutions from Australia and South Africa were added.*Tolle T, Freynhagen R, Versavel M, et al. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. European Journal of Pain 2008;12:203–213.*

Methods

The study included 512 adults with DPN pain of ≥1 year duration. After a 7-day pharmacological clearance period, patients were randomly and double-blindly divided to receivefor 12 weeks placebo,pregabalin 150, 300 or 300/600 mg/day in two daily doses. Assessment criteria were: changes in pain-related sleep interference, Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC) and EuroQoL Health Utilities Index (EQ-5D). This last study determines through a score the impact on health through 5 combined dimensions that are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The drug safety was also evaluated.

Results

- The 600 mg/day dosage of pregabalin produced a significant pain reduction compared to the onset and placebo (p = 0.036).
- Pregabalin at a dose of 600 mg/day significantly improved the pain-related sleep interference (p = 0.003) compared to placebo, as well as the PGIC (p = 0.021) and CGIC (p = 0.009) scores.
- All doses of pregabalin were superior to placebo in improving the EQ-5D score (for all doses P = 0.026 versus placebo).
- Pregabalin was generally well tolerated and the adverse effects were mild to moderate.

Cost-Effectiveness of Pregabalin Compared with Gabapentin

A Canadian study, *Tarride JE, Gordon A, Vera-Llonch M, et al. Cost-Effectiveness of Pregabalin for the Management of Neuropathic Pain Associated with Diabetic Peripheral Neuropathy and Postherpetic Neuralgia: A Canadian Perspectiva. Clinical Therapeutics 2006; 28: 1922-1934*, compared pregabalin (150-600 mg/day) with gabapentin (900-3600 mg/day) during 12 weeks in patients with painful DPN. The report was contributed by 80 physicians who were given a questionnaire specially designed to evaluate the cost-effectiveness of these two drugs.

The study showed that, compared with gabapentin, pregabalinadded 6 additional days with no or mild pain, 5 days less with moderate pain and one day less with severe pain.

Clinical Experiences with Pregabalin in the Treatment of Postherpetic Pain

Table 4 describes several multicenter studies that administered pregabalin for the treatment of postherpetic pain.

Table 4. *Pregabalin studies for the treatment of postherpetic pain.*

Method	Results
Dworkin RH Multicenter, double-blind, placebo-controlled, 8-week study. 173 patients were divided in groups that received pregabalin 300 mg/day, 600 mg/day, or placebo.	Compared with placebo, pregabalin in both doses produced a significant reduction in pain and in sleep interference intervals (p = 0.0001 for both parameters)
Sabatowski R Multicenter, double-blind, placebo-controlled, 8-week study. 238 patients were divided in groups that received pregabaline150 mg/day, 300 mg/day, or placebo.	Efficacy of pregabalin was observed in the first week. A response ≥50% of pain reduction from the onset of the treatment was observed in 26%, 28% and 10% of pregabalin 150 mg/day, 300 mg/day and placebo groups, respectively. Compared with placebo, both pregabalin dosages significantly reduced pain-related sleep interferences.
Van Seventer R Multicenter, double-blind, placebo-controlled, 13-week study. 370 patients were divided in groups that received pregabalin150 mg/day, 300 mg/day, 600 mg/day or placebo dosed twice daily.	Pregabalin improved the different pain scale scores and the difference was significant as compared with placebo for the three doses: 150 mg/day, p = 0.0077; 300 mg/day, p = 0.0016; 600 mg/day, p = 0.0003.

Pregabalin in the Treatment of Trigeminal Neuralgia

Open-Dose Trial of Pregabalin

In *Obermann y col., Ombermann M, Yoon SM, Sensen K, et al. Efficacy of pregabalin in the treatment of trigeminal neuralgia. Cephalalgia 2007;28:174–181*, 52 patients with trigeminal neuralgia and a mean age of 62.7 years were evaluated. In 89% of cases, trigeminal neuralgia was idiopathic and in the remaining cases other causative pathologies were found, mainly sclerosis in plaques.The administered dose of pregabalin was adjusted as needed from 75 mg/day to 600 mg/day. During the year of treatment, patients were monitored periodically and were asked to complete a daily pain severity form on a verbal rating scale (VRS)from 0 to 10 score.

The primary outcome parameters were:

- Number ofasymptomatic patients or with pain reduction of ≥50%.
- Attack frequency reduction ≥50% after 8 weeks.

Secondary outcome was sustained pain relief after 1 year.

Results

After 8 weeks´ treatment, 74% of the patients improved with a mean dose of 270 mg/day, of which 25% became asymptomatic and 49% reported pain improvement> 50%. 26% of the patients did not respond to the treatment.

The multivariate analysis showed a significant reduction in pain after 4 weeks. The majority of patients who became asymptomatic stayed in this condition after one year. Patients without concomitant facial pain showed a much better response rate compared withpatients with concomitant chronic facial pain. Side-effects were reported by 22 patients (mainly somnolence and dizziness), which eased after 2 weeks of treatment. The majority of patients with pain reductionreceived additional anticonvulsant drugsand became asymptomatic. In conclusion, results are in line with previous trials where other anticonvulsant drugs (gabapentin, lamotrigineand carbamazepine) were administered. However, pregabalin has some advantages over other agents: fewer side-effects, more rapid titration potential, shorter onsetof action and can be administered twice daily.

Fibromyalgia

Definition and Characteristics

Fibromyalgia is a chronic syndrome characterized by widespread pain all over the body accompanied by hyperalgesia and allodynia, fatigue, sleep disturbance and altered bowel function. It is estimated that fibromyalgia affects 2-4% of the population. *Wolfe, F; Smythe HA, Yunus MB et al.The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis and Rheumatism 1990; 33: 160–172.*

Due to its characteristics, fibromyalgia would be part of the so-called functional somatic syndromes, a group of syndromes whose common element is the presence of a number of symptoms, disability and suffering that is not related to the few demonstrable alterations in function or organic structure.

Therefore, fibromyalgia shares several characteristics with functional somatic syndromes that are: clinical heterogeneity, high degree of symptoms overlaps, higher prevalence of psychiatric disorders than in the general population and refractory symptoms to medical treatment and palliative measures. *Martínez E, González O, Crespo JM. Fibromialgia: definición, aspectos clínicos, psicológicos, psiquiátricos y terapéuticos. Salud Global 2003; año 3, número 4:2-8.*

Pathophysiologic

Neuroendocrine Disorders

Fibromyalgia is considered a stress-related disorder due to an alteration of the hypothalamic-pituitary-adrenal axis, mainly characterized by an inability to suppress cortisol, a phenomenon that it shares with some psychiatric pathologies.*Bradley LA. Pathophysiologic mechanisms of fibromyalgia and its related disorders.J Clinic Psychiatry 2008;69(suppl 2):6-13.*

Sympathetic Nervous System Disorders

These alterations are characterized by a decrease in the vasoconstrictive response of the microcirculation, tendency to hypotension, variations in heart rate and sleep disorders. The latter is characterized by sleep interference and poor quality sleep.*Roizenblatt S, Moldofsky H, Benedito-Silva AA, et al. Alpha Sleep Characteristics in Fibromialgia. Arthritis & Rheumatism 2001;44:222–230.*

Increased Sensory Sensitivities

Patients with fibromyalgia presented a central and peripheral hypersensitivity similar to that described in the pathophysiology of DN. *Wood PB, Schweinhardt P, Jaeger e, et al. Fibromyalgia patients show an abnormal dopamine response to pain European J Neurosciences 2007;25:3576-3582*.

Predisposing Factors

Physical trauma and psychosocial variablesare considered as usual triggers of fibromyalgia.*Harkness EF, Macfarlane GJ, Nahit E, et al. Mechanical injury and psychosocial factors in the work place predict the onset of widespread body pain: a two-year prospective study among cohorts of newly employed workers. Arthritis Rheum 2004;50:1655-64*.

Diagnosis

- The American College of Rheumatology established the following diagnostic criteria for fibromyalgia: *Martinez Gonzales* again
- Widespread pain present for at least 3 months that is evident or exacerbated by the pressure of at least 11 out of 18 considered trigger points (Figure). These points are characterized by their frequency, reproducibility and inter and intraobserver concordance and allow physicians to differentiate fibromyalgia from rheumatoid arthritis and other chronic pathologies. Pain has an irreducible affective component and there are important relationships between psychosocial factors and pain in patients with FM. This is aggravated by stress, negative affectivity -depression and anxiety-, sleep disorders and maladaptive coping strategies.
- Skin hyperemia
- Livedoreticularis in extremities
- Joint hypermobility
- Fatigue
- Sleep disturbance
- Tendency to depression

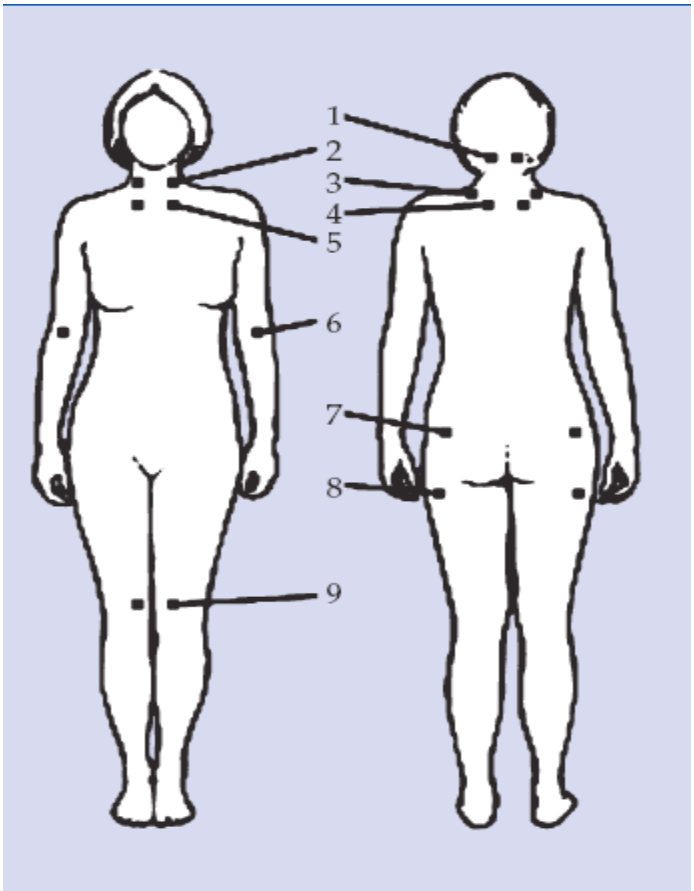

Figure 5. *Most prominent tender or trigger points in fibromyalgia. Source: Martínez E y col.*

Treatment

Integral treatment of fibromyalgia represents a real challenge for the primary care physician, due to the limited efficacy of drugs and the complexity of these patients. Currently, the treatment includes pharmacological and nonpharmacological measures, such as relaxation techniques, aerobic exercises, cognitive-behavioral therapy, among others. This work will refer to the experiencewith pregabalin in the treatment of fibromyalgia.

Clinical Experiences with Pregabalin in the Treatment of Fibromyalgia

Several anticonvulsant agents have been used to ease symptoms of fibromyalgia, but only in June 2007 the Food and Drug Administration (FDA) of the United States approved pregabalin as the first drug for the treatment of this syndrome. The evidence was based on experimental research, the preclinical phase and several controlled clinical studies that are described in Table 5. To evaluate the therapeutic effect, a special scale for fibromyalgia called FIQ (Fibromyalgia Impact Questionnaire) was included in these studies, which consists of 10 questions with several items each covering various aspects of daily and social activity, and the presence of symptoms such as pain,somnolence and fatigue. *Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. ClinExpRheumatol 2005; 23 (Suppl. 39): S154-S162.*

Table 5. *Pregabalin studies for the treatment of fibromyalgia*

Methods	Results
Arnold LM. Randomized, double-blinded, placebo-controlled study with the participation of 750 patients who were divided in the following groups: pregabalin300 mg/d, pregabalin450 mg/d, pregabalin 600 mg/d and placebo, administered in two doses during 14 weeks.	Compared with placebo, all 3 doses of pregabalin significantly improved PGIC scores (P <0.01 for all 3 pregabalin doses) as well as FIQ score for the 450 mg/d (P = .004) and the 600 mg/d (P = .003) doses. All 3 doses of pregabalin were associated with significant improvement in sleep quality.
Crofford LJ. Multicenter study in 1051 patients who receivedfree doses of pregabalin for 6 weeks. Then, patients who have improved ≥50%on the VAS pain scale and improved PGIC scale, were randomly and double-blindly divided in: a placebo group and groups that received during 26 weeks pregabalin at the optimal dose achieved during the first period.	At the end of the study, the therapeutic response achieved during the first period was lost in 61% of placebo patients and 32% of the pregabalin patients. The difference was statistically significant. 17% of the pregabalin patients had temporary side-effects. In conclusion, pregabalin was effective and safe in the optimal doses administered in the first period (300, 450 and 600 mg/day).
Mease PJ Multicenter, randomized, double-blind, placebo-controlled study in 748 patients divided in the following groups: placebo or pregabalin 300, 450, or 600 mg/day (dosed twice daily) during 13 weeks	Compared with placebo, all 3 groups that received pregabalin significantly improvedthe PGIC painscore. Improvements in FIQ score for the pregabalin groups were numerically but not statistically significant when compared with those for the placebo group; although, there was a significant improvement in sleep quality for the pregabalin groups.

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