HEPMP
Higher Education Pain Medicine Project

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Strengthening Capacities for Higher Education of Pain Medicine in Western Balkan countries – HEPMP

Placebo in Clinical Trials and Migraine

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Placebo in Clinical Trials

Placebo:

- The use of placebo in clinical trials is increasingly controversial, particularly once treatment of established efficacy becomes available

(Emanuel et al, J Am Med Assoc 2000)

- ‘a new method should be tested against…the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.’

(World Medical Association. (2008) Declaration of Helsinki)

Placebo can be considered:

- withholding the best current treatment will result in only temporary discomfort and no serious adverse consequences
- a comparative study of two active treatments would not yield reliable scientific results

(Miller FG, Shorr AF. Arch Intern Med 2002)

Principali Malattie Dolorose

- Cefalee primarie (Emicrania)
- Osteoartrosi - Artrite Reumatoide
- Dolore Post-operatorio
- Dolore Neuropatico
- Dolore oncologico
- Etc.

Placebo?

Principi Generali – EMEA – http://www.emea.eu.int

- Placebo-controlled designs with appropriate use of rescue medication are recommended.
- Confirmatory trials randomized parallel group design
- Exploratory trials in chronic recurrent pain (dysmenorrhea) cross-over design
- If :
  - (i) placebo is unacceptable;
  - (ii) non superiority trial;
  - non inferiority margin (δ) ← statistical/clinical reasoning (Giudance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96)

Principi Generali – EMEA – http://www.emea.eu.int

Exploratory Studies (Phase I) (Placebo YES)

- Beginning of the program (healthy subjects)
- Intensity of the stimulus is limited
- Chronic pain model is not feasible
- Obtain data on:
  - Best dose/interval regimen
  - Time of onset
  - Peak effect
  - Single vs. multiple dose

Principi Generali – EMEA – http://www.emea.eu.int

Type of Pain	Intensity	Duration	Model
Acute	Mild Moderate	Days w<1	Tooth extr, Sore throat, Low back pain, Dysmen.
Acute	Moderate Severe	<48h 1w	Renal Biliary Colic Abdominal surg Episiotomy
Chronic	Mild Moderate	>3 m	OA, RA, low back pain
Chronic	Moderate Severe	>1 m	Cancer, metastasis

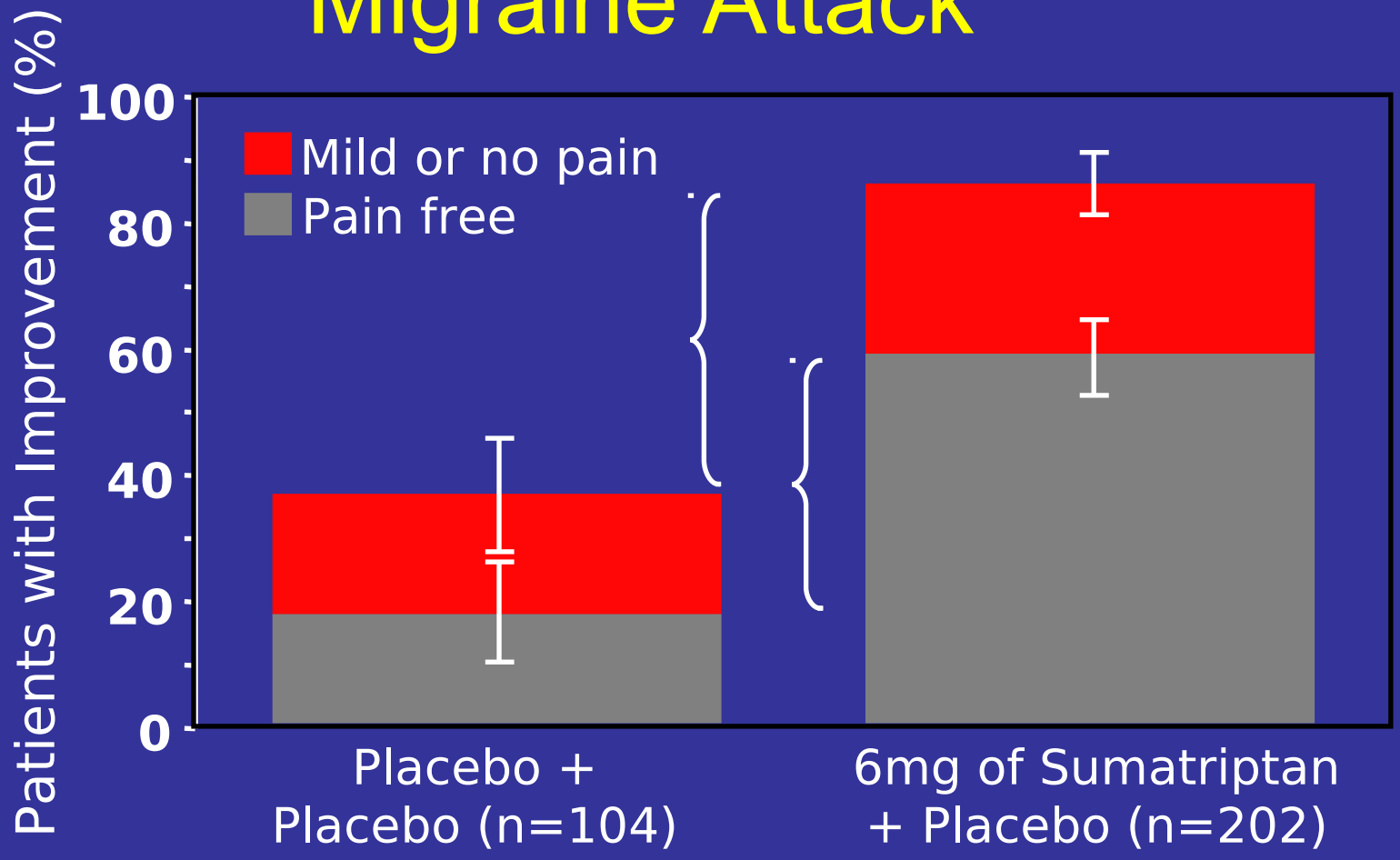
Principi Generali – EMEA – http://www.emea.eu.int

- Visual analogue scale (no – the worst)
- Numerical pain scale (0 – 10)
- Multidimensional assessment (MMPI, etc)
- Children ????

Placebo

- Che tipo e quantità di dolore misuriamo?
- In base al tipo di misura cosa cambia?

Sumatriptan, sc in Migraine Attack



N Engl J Med 1991; 325:316-321

Placebo Response and Pain Free in Migraine Metanalysis (31 studies with Triptans)

Response (0-3 scale):

- Responders (average) 28.9% (SD 8.55)
- Range 17-50% (Q-test variability P<0.001)

Pain Free (2 h) :

- Pain Free (average) 6.08% (SD 4.83)
- Range 5-17% (Q-test variability P<0.001)

Loder et al, Cephalalgia, 2004

Placebo in Migraine

Randomization ratio, year of publication, location does not explain variability

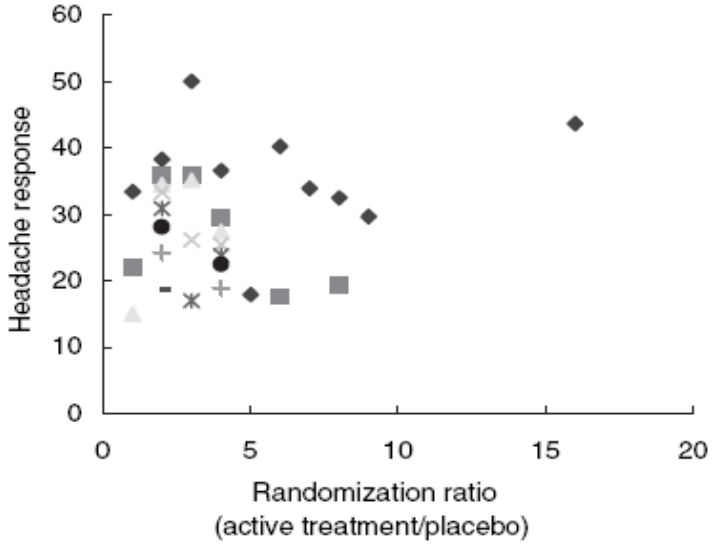


Figure 1 The percentage of patients reporting a headache response 2 h after receiving placebo does not appear to be influenced by patient expectations about the likelihood of receiving placebo. A prior study suggested that patients in studies where most subjects received active treatment (high randomization ratio) were more likely to report a headache response to placebo.

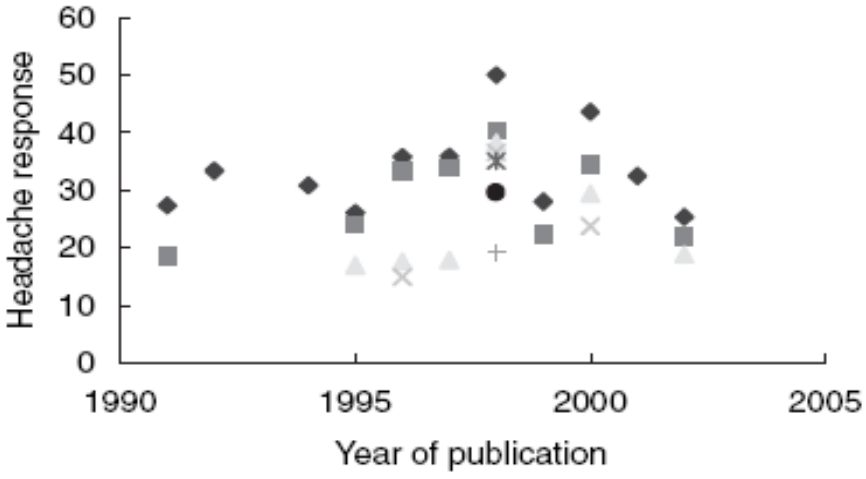


Figure 2 There has been no significant change in the average percentage of patients reporting a headache response to placebo over the period of this study.

Loder et al, Cephalalgia, 2004

Nocebo in Migraine

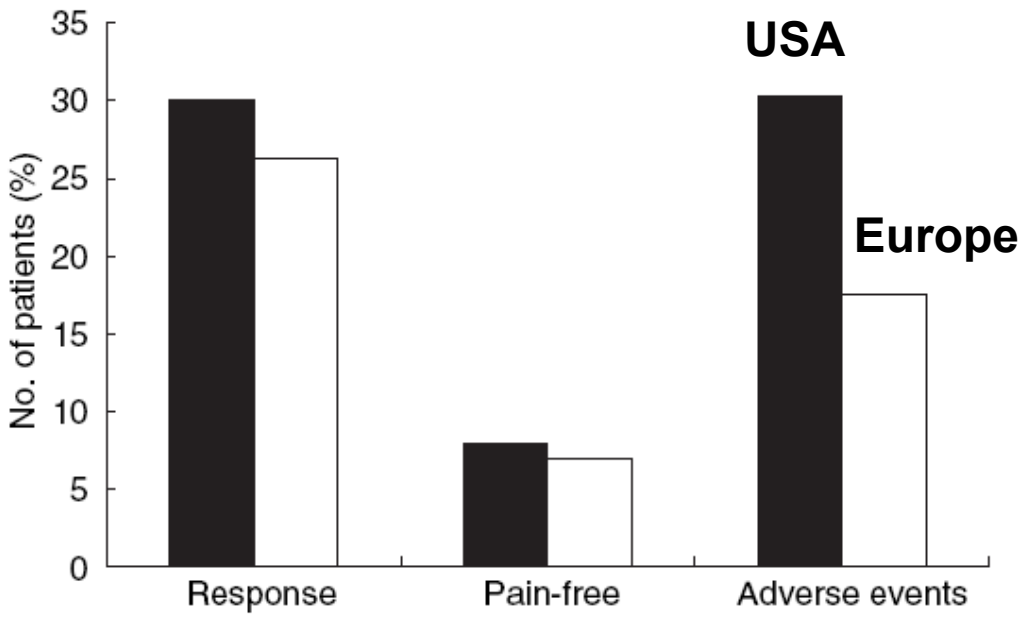


Figure 3 The percentage of patients reporting adverse events two hours after taking placebo is significantly higher in studies performed in North America (■) than in Europe (□). The percentage of patients who are pain-free or report a headache response two hours after taking placebo is not statistically different between the two locations.

The reason for this association is unclear. However, this observation is consistent across a variety of disease states, including hypertension, anxiety and ulcer disease

Loder et al, Cephalalgia, 2004

Migraine

- This analysis indicates that placebo effects in trials of oral triptans for the acute treatment of migraine are variable and substantial

- Placebo responders to acute headache treatment include subjects
  - whose headaches have spontaneously improved
  - those with a response based on expectation, conditioning, or other nonspecific factors.

- Based on the significant variability in placebo rates from study to study, it seems important for future trials of acute migraine therapy to include placebo.

Migraine

- Acute treatment :
  - Randomized, double blind, placebo controlled
  - Three arm trials active comparator (high placebo effect)
  - 1 attack out of 5 placebo/4 out of 5 with verum
  - Rescue medication from 2 h onwards
- Prophylaxis :
  - No open/single blind trials
  - Two arms, randomized, placebo-controlled, double blind, parallel
  - Cross-over, only in exploratory, proof-of-concept trials
  - Three arm (active comparator + placebo) or superiority two arm trial
  - Run in period (1 m)

Migraine

CGRP Receptor Antagonist – Inhibits Neurogenic Vasodilalatation

Olesen et al, N Eng J Med, 2004

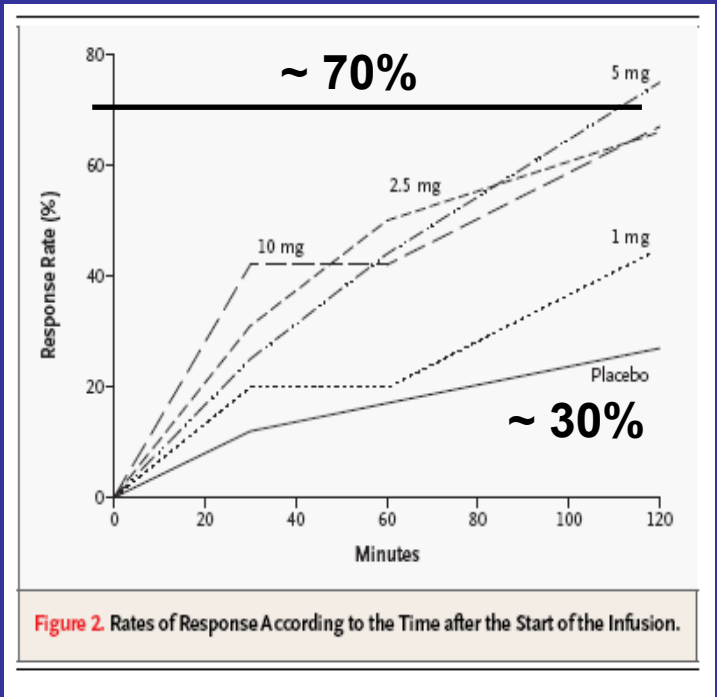


Figure 2. Rates of Response According to the Time after the Start of the Infusion.

Olgecepant

Mild or No Pain

Ho et al, Lancet, 2008

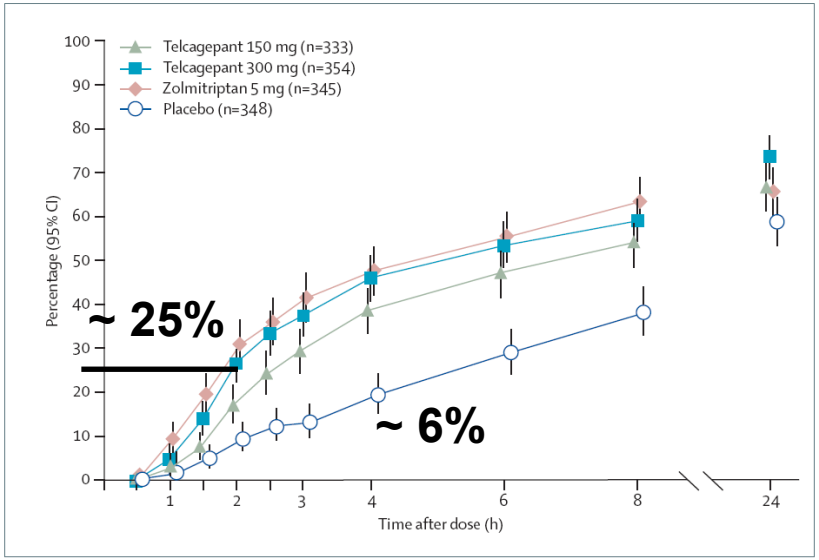


Figure 2: **Observed percentage of patients reporting pain freedom up to 24 h after dosing**
Data were calculated with a last-observation-carried-forward approach to impute missing values, with the proviso that missing baseline values were not imputed. Significant (p≤0·05) differences versus placebo were seen from 1 h for telcagepant 300 mg and zolmitriptan 5 mg, and from 1·5 h for telcagepant 150 mg. Data after 2 h include patients who took an optional second dose or rescue drugs.

Telgacepant

Pain Free

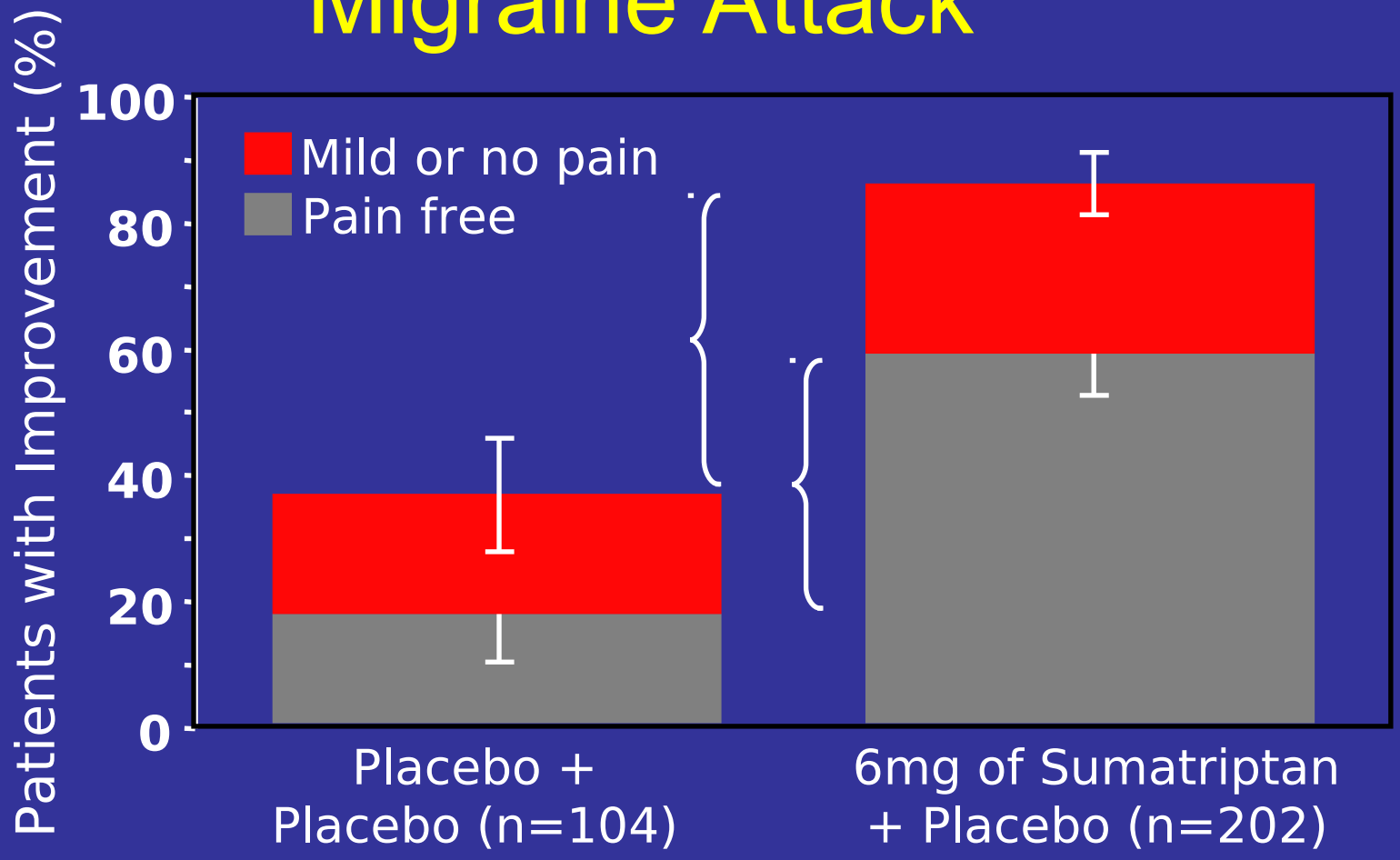
Neuropathic Pain

- Diabetic neuropathy
- Viral (HIV) neuropathy
- Post Herpetic Neuralgia
- Trigeminal Neuralgia, etc.

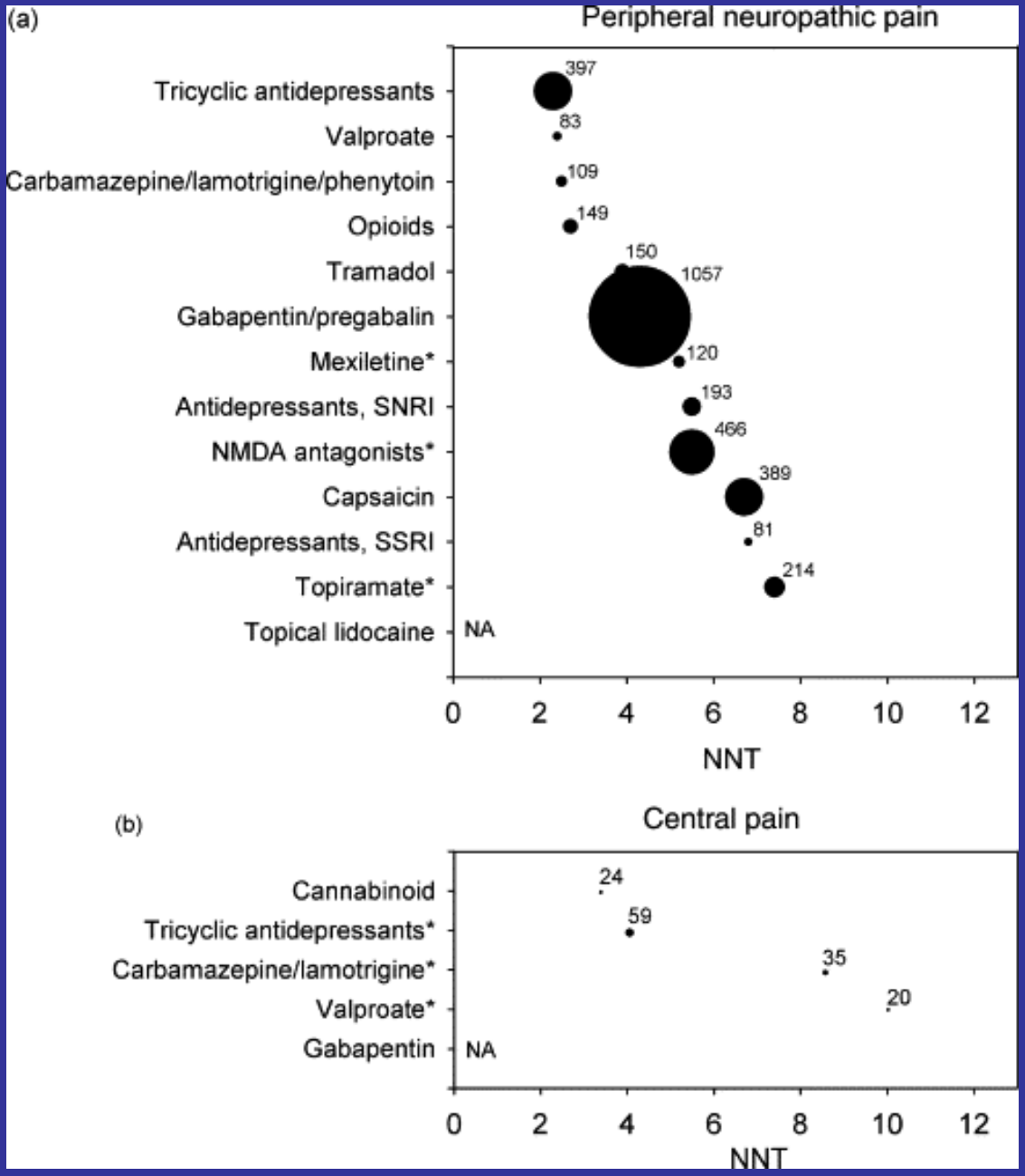
- CNS
- PNS

- Neuropathic Cancer Pain

Sumatriptan, sc NNT ~ 2.5
Migraine Attack



N Engl J Med 1991; 325:316-321



- painful polyneuropathy
- postherpetic neuralgia,
- peripheral nerve injury pain

NNT = to obtain one patient with more than 50% pain relief

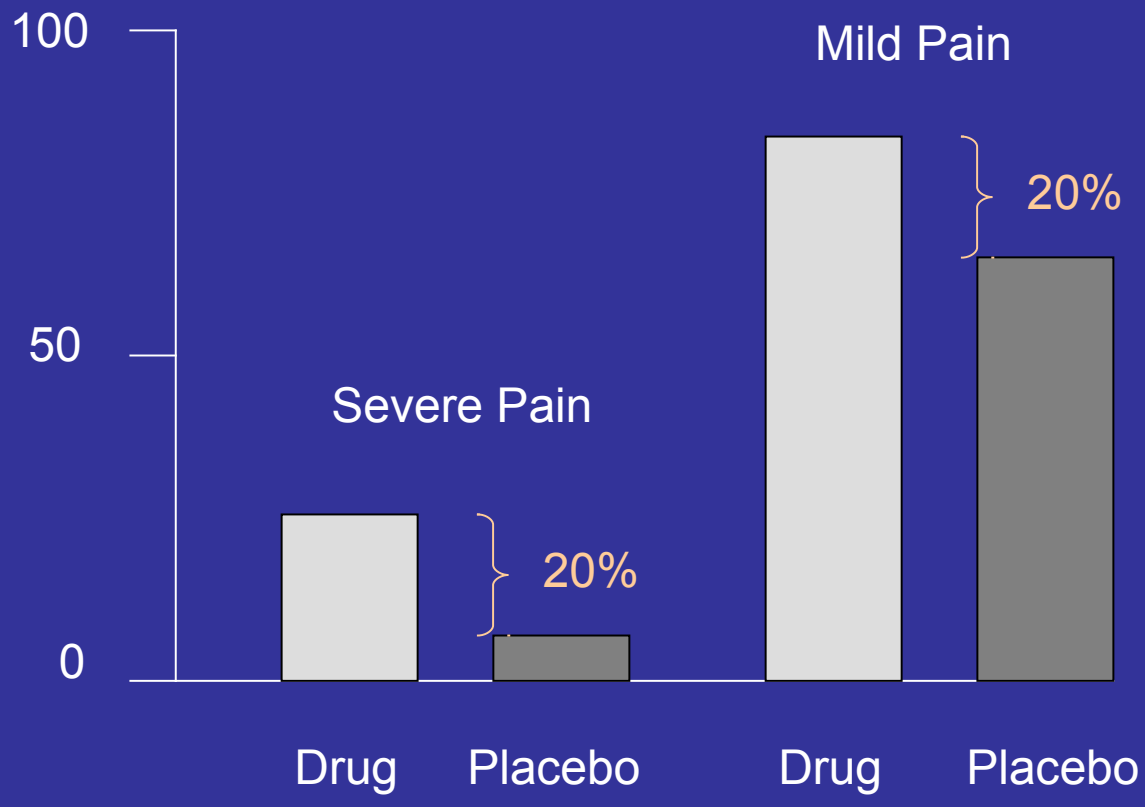
- post-stroke pain,
- pain following spinal cord injury
- multiple sclerosis

Finnerup NB, Pain, 2005

NNT in Neuropathic Pain

NNT = 5

(20% of Responders to Active Treatment)



Neuropathic Pain

- Moderate pain (VAS>40 mm, NRS >4) because high placebo effect
- Mild pain accepted in confirmatory trials
- Pain should be present >3 m
- Electrophysiology does not correlate
- In dose-response study a placebo arm is needed

- Randomized, double blind, placebo controlled trials
- If treatment is available – Three arm study (drug – comparator - placebo)
- Reduce the patients on placebo, but check the power
- Extended study (tolerance) in 6-12 m studies - no placebo

Densità nel Reclutamento in Trials con farmaci Biotecnologici nel Mondo

Tanezumab

anti-NGF monoclonal antibody RN624

Pfizer Phase II (PF-4383119) *New York, NY*, (860) 732-5156
Rinat Neuroscience *South San Francisco, CA*

back pain, cancer pain, musculoskeletal pain neuralgia, pain associated with interstitial cystitis

Phase II (860) 732-5156

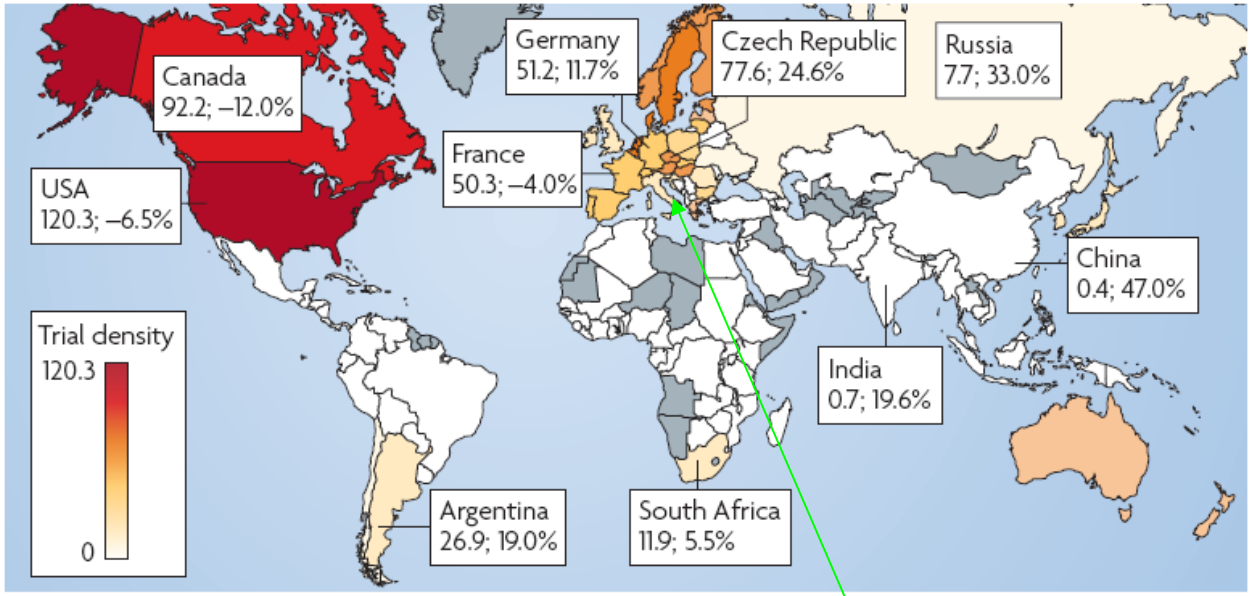


Figure 1 | **Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide.** Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007.

Italy – 34.6% (8.1%)

Thiers et al, Nature Rev Drug Dis, 2008