

COURSES ABOUT PAIN THERAPY OF SCHOOL OF MEDICINE IN FLORENCE

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Main chronic pain conditions explored at Italian Universities

- Primary headaches (Migraine)
- Osteoarthritis
- Rheumatoid Arthritis
- Post-operative pain
- Neuropathic pain
- Cancer pain
- Etc.

General principles– EMEA – <http://www.emea.eu.int>

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

General principles– 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 |

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)

General principles– EMEA –

<http://www.emea.eu.int>

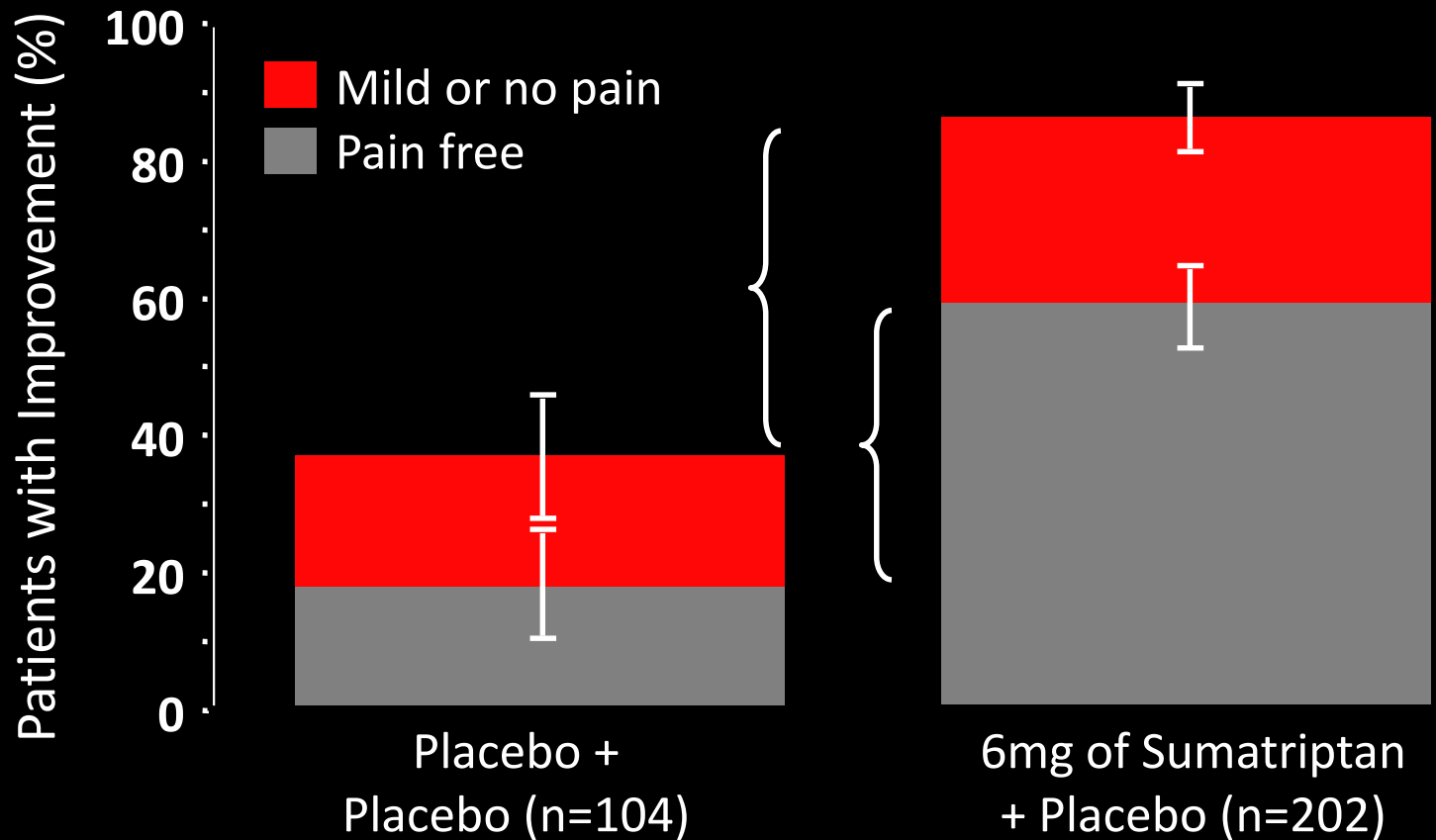
- Placebo-controlled designs with appropriate use of rescue medication are recommended.
- Confirmatory trials randomized parallel group design
- Exploratory trials in chronic recurrent pain (dysmenorrhea) cross-over design
- If :
 - (i) placebo is unacceptable;
 - (ii) non superiority trial;
 - non inferiority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

General principles– 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

Sumatriptan, sc in Migraine Attack



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 $P < 0.001$)

Migraine

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

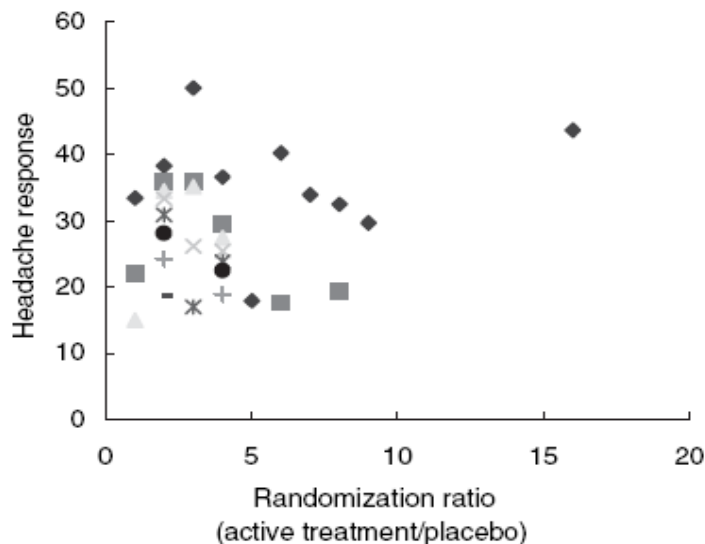


Figure 1 The percentage of patients reporting a headache response 2 h after receiving placebo does not appear to be influenced by patient expectations about the likelihood of receiving placebo. A prior study suggested that patients in studies where most subjects received active treatment (high randomization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

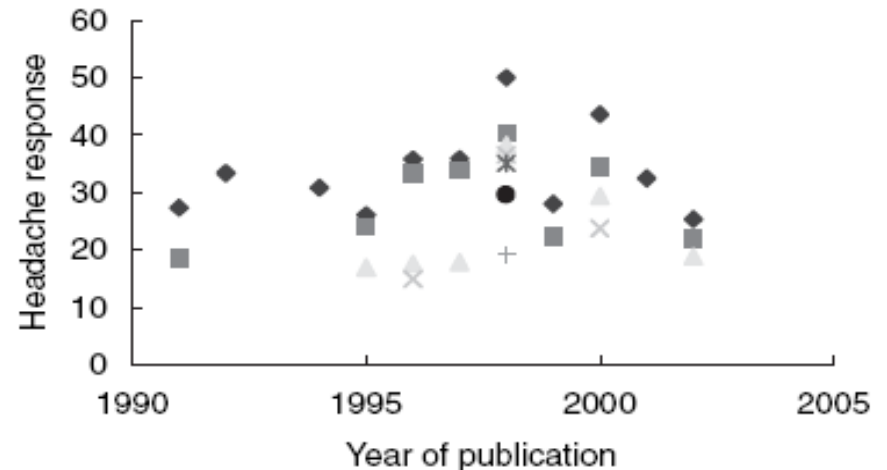


Figure 2 There has been no significant change in the average percentage of patients reporting a headache response to placebo over the period of this study.

Nocebo in Migraine

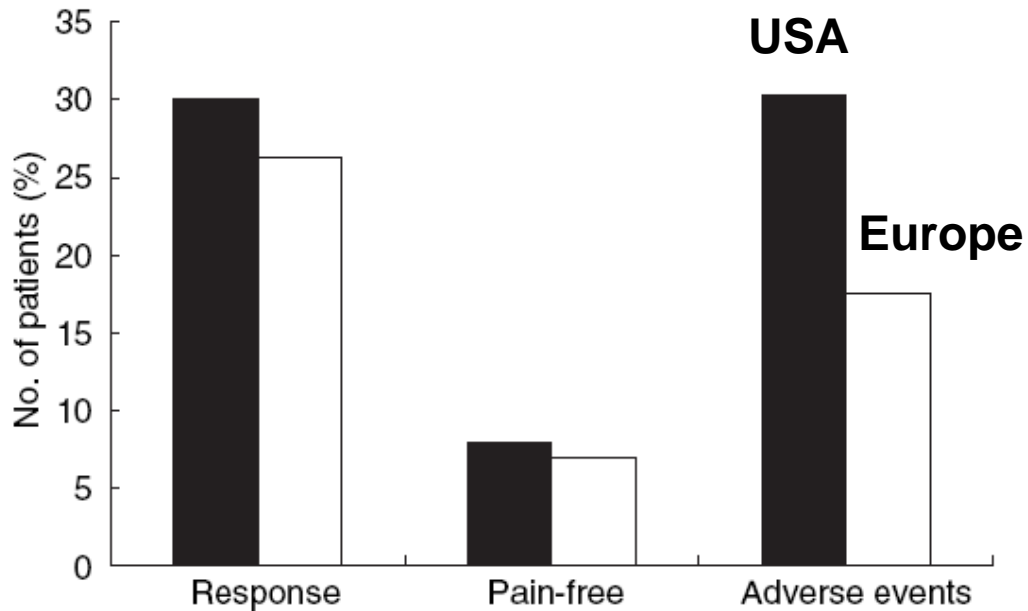


Figure 3 The percentage of patients reporting adverse events two hours after taking placebo is significantly higher in studies performed in North America (■) than in Europe (□). The percentage of patients who are pain-free or report a headache response two hours after taking placebo is not statistically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

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 :

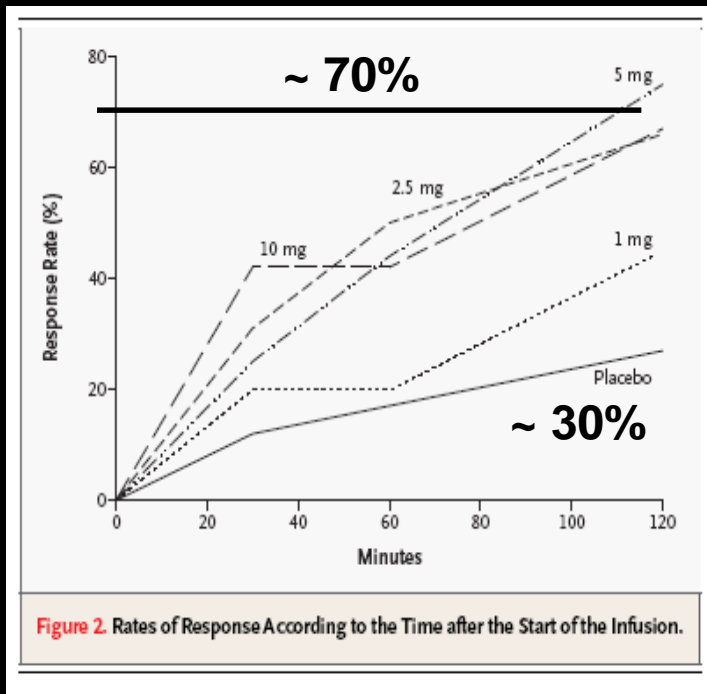
- No open/single blind trials
- Two arms, randomized, placebo-controlled, double blind, parallel
- Cross-over, only in exploratory, proof-of-concept trials
- Three arm (active comparator + placebo) or superiority two arm trial
- Run in period (1 m)

Migraine

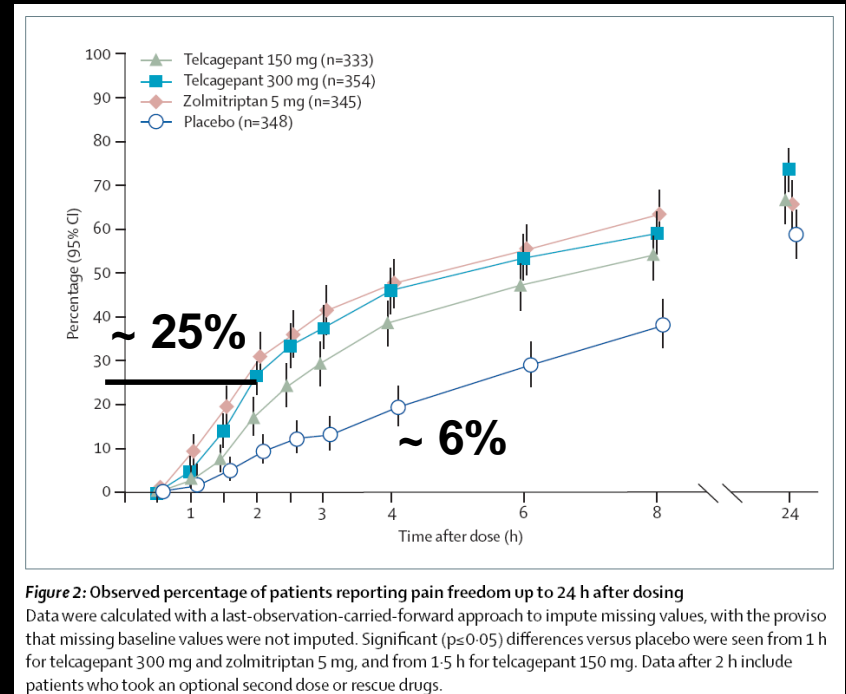
CGRP Receptor Antagonist – Inhibits Neurogenic Vasodilatation

Olesen et al, N Eng J Med, 2004

Ho et al, Lancet, 2008



Olgeceptant
Mild or No Pain



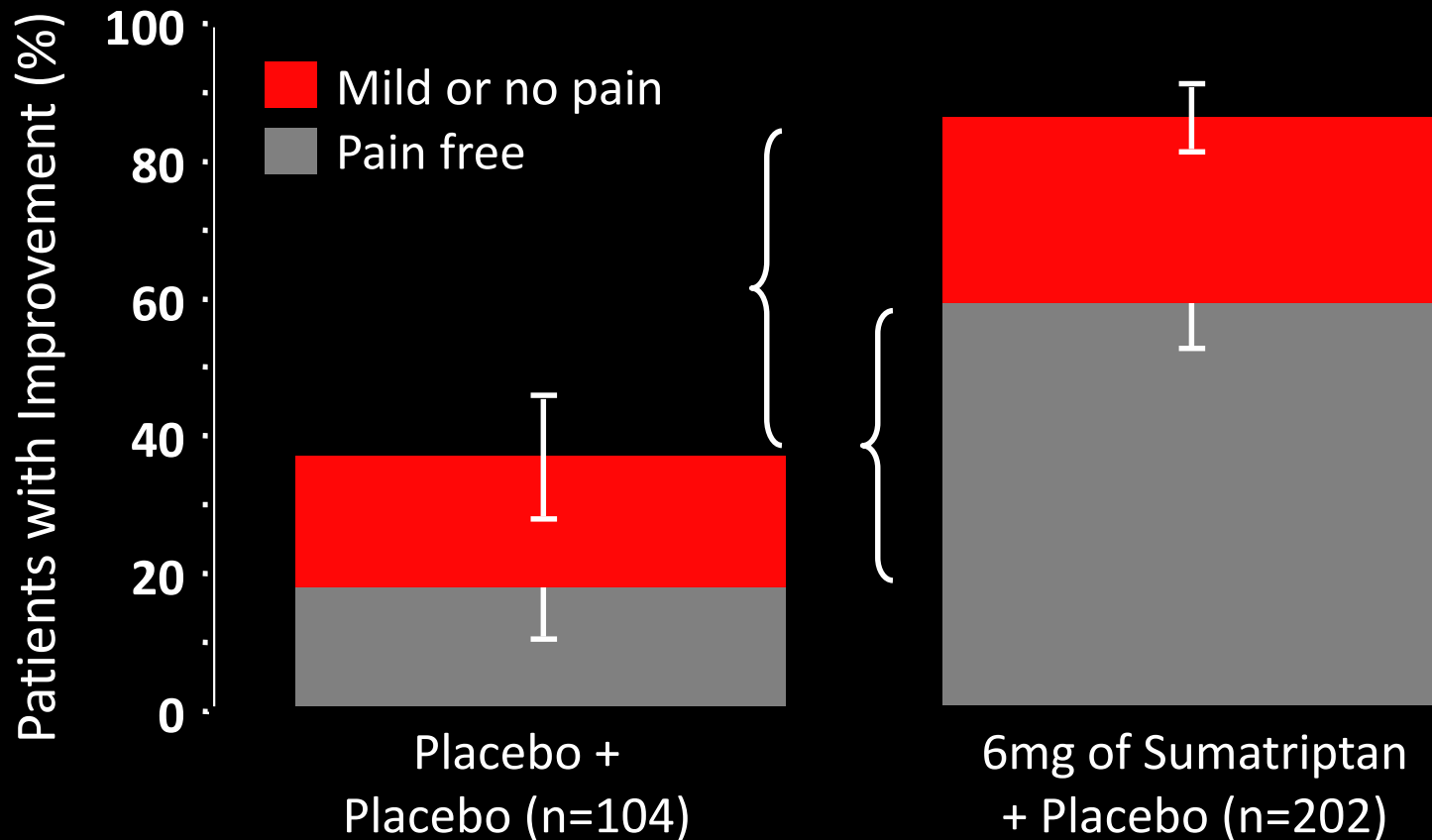
Telgacepant
Pain Free

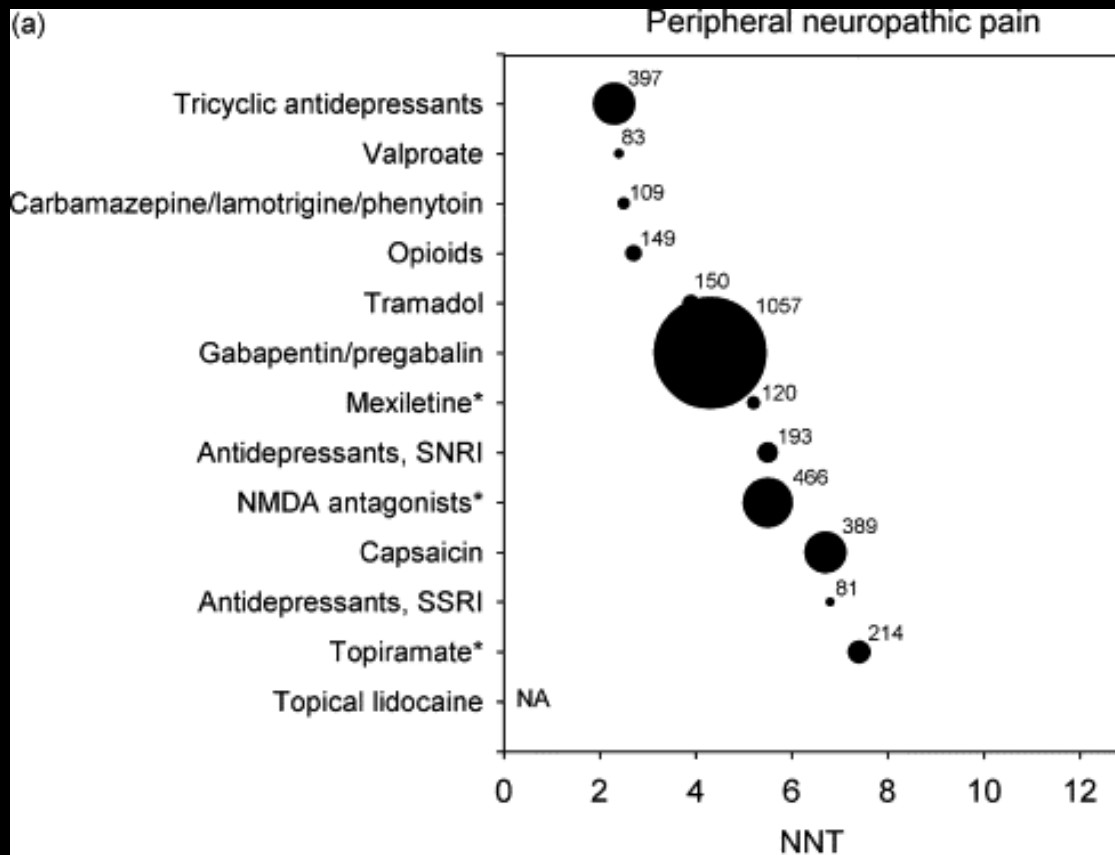
Neuropathic Pain

- Diabetic neuropathy
 - Viral (HIV) neuropathy
 - Post Herpetic Neuralgia
 - Trigeminal Neuralgia, etc.
-
- CNS
 - PNS
-
- Neuropathic Cancer Pain

Sumatriptan, sc NNT ~ 2.5

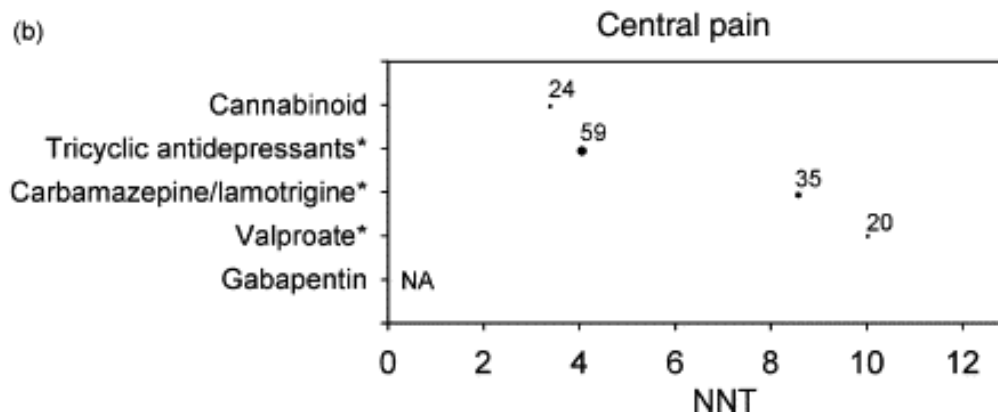
Migraine Attack





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

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

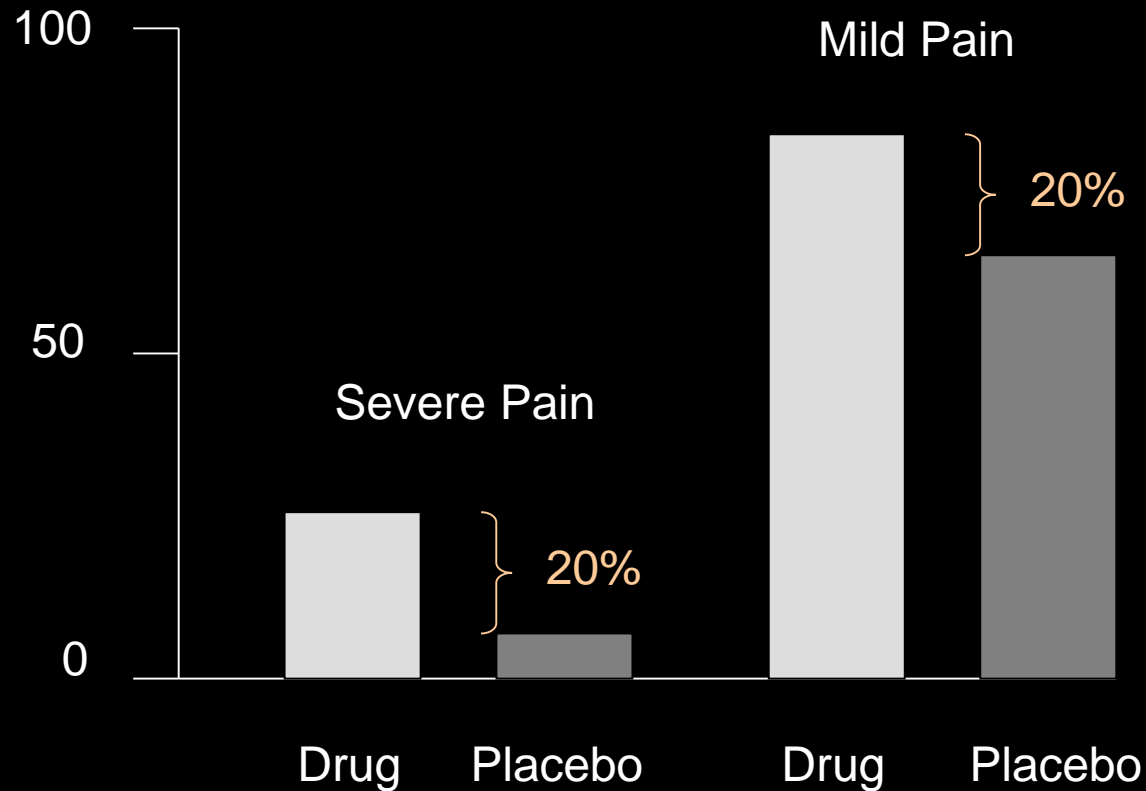


- post-stroke pain,
- pain following spinal cord injury
- multiple sclerosis

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

New evidences in pain control

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

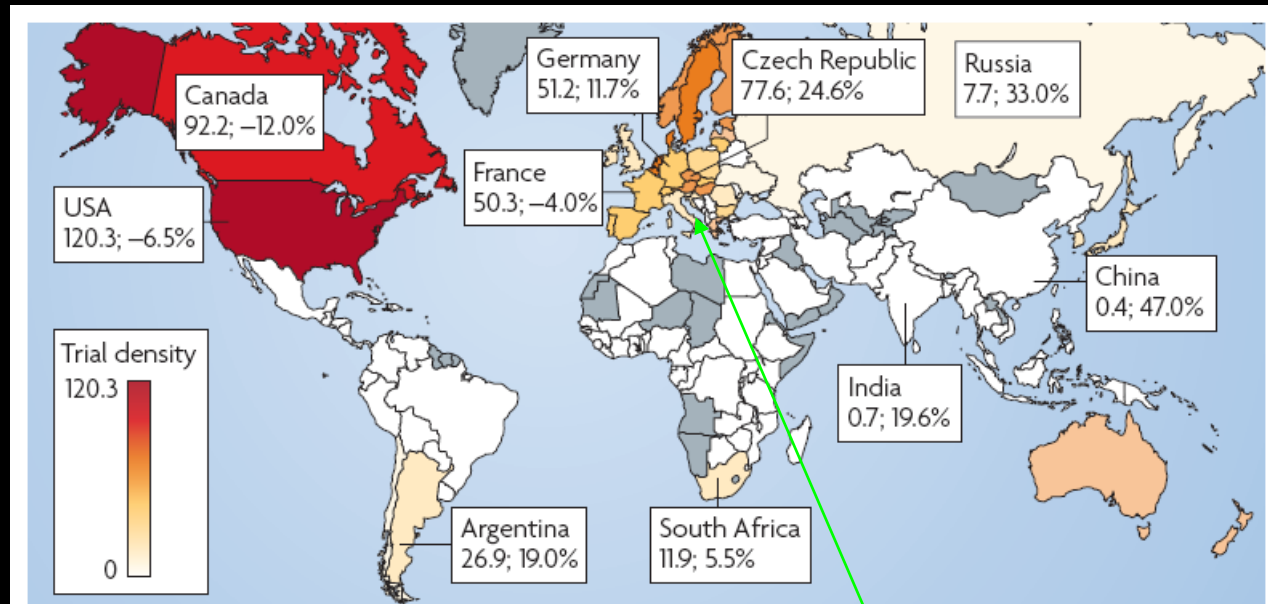


Figure 1 | Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide. Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent 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