The European Headache School
2012

# ACUTE TREATMENT FOR MIGRAINE

Cristina Tassorelli

Headache Science Centre, IRCCS "Neurological Institute C. Mondino" Foundation - Pavia
University Centre for Adaptive Disorders and Head Pain (UCADH)

Dept. of Public health and Neurosciences, University of Pavia

## Knowing the systems and the mechanisms to find the targets

- Trigeminovascular activation and sterile inflammation
- Chronic sentitization and hyperalgesia
- Spreading depression

## Acute therapy

- Relieves pain and disability

&

- Stops progression once attack has began

## Preventive Therapy

- Taken daily to reduce:

Attack frequency
Severity
Duration

- Patients will likely also use acute medication

## Drugs

- Analgesics
- Analgesics + ….
- 5-$HT_{1B-1D}$ agonists (triptans)
- Ergots
- Anti-emetics

## Migraine Disability

### Frequency of attack

- **Low**: ≤ 2 attacks/month
- **Medium**: 3–5 attacks/month
- **High**: ≥ 6 attacks/month

### Severity of attacks

- **Degree 3**: very severe or fully disabling (no activities, bed rest required)
- **Degree 2**: moderate or partially disabling (restriction of the activities)
- **Degree 1**: Mild or not disabling (activities are possible)

## POSSIBLE CARE APPROACHES TO THE ACUTE TREATMENT OF MIGRAINE

**STEPPED**

**Drugs are escalated, if needed, in subsequent attacks**

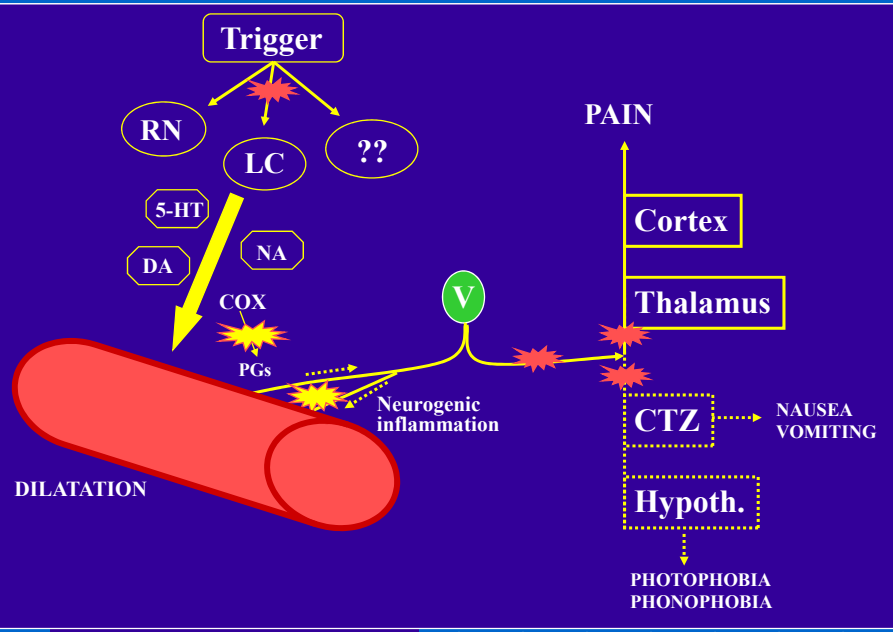
**STRATIFIED**

**Choice of drugs based on migraine-related disability**

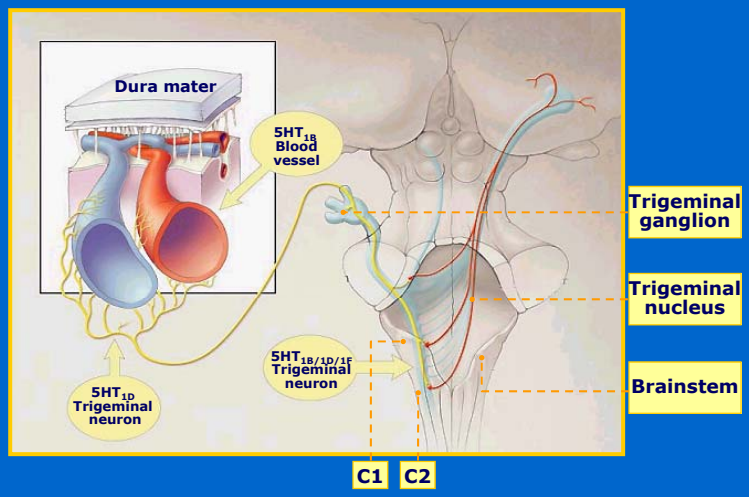
**STAGED**

**Drugs are escalated, if needed, during the same attack**

## NSAIDs: possible sites of action




## TRIPTAN: mechanism of action



## Drugs

- Analgesics
- Analgesics + ….
- 5-$HT_{1B-1D}$ agonists (triptans)
- Ergots
- Anti-emetics

J Headache Pain
DOI 10.1007/s10194-012-0437-6

GUIDELINES

**Italian guidelines for primary headaches: 2012 revised version**

Paola Sarchielli · Franco Granella · Maria Pia Prudenzano · Luigi Alberto Pini · Vincenzo Guidetti · Giorgio Bono · Lorenzo Pinessi · Massimo Alessandri · Fabio Antonaci · Marcello Fanciullacci · Anna Ferrari · Mario Guazzelli · Giuseppe Nappi · Grazia Sances · Giorgio Sandrini · Lidia Savi · Cristina Tassorelli · Giorgio Zanchin

## Levels of evidence

Level A: Two or more clinically controlled, randomize, double-blind studies carried out according to good clinical practice (GCP) versus placebo or versus an active drug for which there is proven evidence of efficacy

Level B: One clinically controlled study according to GCP or more than one controlled case–control study/ies or Cohort study/ies

Level C: Favourable judgement of two-thirds of the Ad Hoc Committee, historical controls, non-randomized studies, case reports

# SCIENTIFIC STRENGTH OF EVIDENCE

| | |
|---|---|
| +++ | The difference in the parameters of efficacy registered in studies compared with placebo or another active drug has a high level of significance ($p < 0.01$; $p < 0.001$; $p < 0.0001$). Adverse events are rare or occasional and not severe |
| ++ | The difference in the parameters of efficacy registered in studies reaches the minimum level of significance ($p < 0.05$) or the minimum clinically significant level (difference in the parameters <15 %)[a] |
| + | The difference in the efficacy parameters between the study drug and placebo or another active drug is not statistically significant |
| 0 | The drug is not efficacious or is characterized by severe adverse events |

[a] Even drugs for which the difference in the efficacy parameters compared with placebo or another active drug is higher than the minimum level of statistical significance, but have frequent, yet no severe adverse events are included in this group

# CLINICAL EFFECTIVENESS

Symptomatic drugs

| | |
|---|---|
| +++ | The majority (>60 %) of the patients had partial or total relief of headache. More than 30 % of them were pain free |
| ++ | Many patients (from 40 to <60 %) had partial or total relief of headache, or 20–29 % of the patients were pain free |
| + | Some of the patients (from 20 to <40 %) had partial or total relief of headache. Up to 20 % were pain free |
| 0 | Less than 20 % of the treated patients received a clinical benefit |
| ? | The members of the Ad Hoc Committee were unable to express any judgement on effectiveness based on their personal clinical impressions |

# LEVELS OF RECOMMENDATION

| | |
|---|---|
| Level I | Drugs with high efficacy supported by statistically significant data (evidence of at least two controlled, randomized studies versus placebo or versus active drugs of proven efficacy) or very high clinical benefit for patients (clinical effectiveness +++) and with no severe adverse events |
| Level II | Drugs whose value of efficacy is statistically of lower significance compared to drugs of group I and with a less significant clinical benefit for patients (clinical effectiveness ++) and no severe adverse events |
| Level III | Drugs showing efficacy from a statistical point of view but not from a clinical point of view (contrasting results or evidence is not conclusive). The drugs belonging to this group were further subdivided into two subgroups:<br>(a) Drugs with no severe adverse events<br>(b) Unsafe drugs or with complex indications for use (e.g. special diets) or important pharmacological interactions |
| Level IV | Drugs of proven efficacy but with frequent and severe adverse events or drugs whose efficacy has not been proven from a clinical or statistical point of view (no difference with respect to placebo). Drugs with unknown clinical patient benefit or statistical significance of efficacy (data unavailable or insufficient) |

# GENERAL RULES

1. A stratified approach, consisting in a different choice of initial treatment based on the severity of the attack (migraine-specific drugs, i.e. triptans, for moderate/severe attacks and non-specific drugs like analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) for mild/moderate attacks) is recommended [7].
2. The most appropriate drug should be taken at the lowest useful dosage as early as possible after the attack begins.
3. As a rule, preparations with only one active principle should be preferred.
4. It is convenient to provide some alternatives for attacks of different severity.
5. Rescue drugs should be provided in case of first-choice medication failure.

REVIEW

**Table 5** Drugs for the symptomatic treatment of migraine with a level of recommendation I and II

| Drug | Dosage | Level of recommendation | Comments |
|---|---|---|---|
| $5HT_{1B/1D}$ agonists | | | |
| Sumatriptan | | | |
| Subcutaneous | 6 mg | | Rapid onset of action compared to the other formulations |
| Tablet | 50–100 mg | I | |
| Suppository | 25 mg | | Useful when oral route is not possible due to nausea |
| Nasal spray | 20 mg | | Useful when oral route is not possible due to nausea |
| Zolmitriptan | | | Rapid onset of action |
| Tablet | 2.5 mg | | |
| Oral disintegrating tablet | 2.5 mg | I | |
| Nasal spray | 2.5–5 mg | | |
| Rizatriptan | | | Rapid onset of action. The optimal dosage is 10 mg |
| Tablet | 5–10 mg | I | |
| Oral disintegrating tablet | 10 mg | | Recommended dosage is 5 mg in patients treated with propranolol which increases the plasma concentration of rizatriptan |
| Eletriptan | | | |
| Tablet | 20, 40 mg | I | The optimal dosage is 40 mg (best efficacy/tolerability ratio) The dosage of 20 mg is recommended in the case of renal or liver failure |
| Almotriptan | | | |
| Tablet | 12.5 mg | I | Good tolerability profile |
| Frovatriptan | | | |
| Tablet | 2.5 mg | I | Long half-life, good tolerability profile |
| Ergot derivatives | | | |
| Ergotamine oral, rectal, subcutaneous | 1–2 mg | II | Indicated in the case of infrequent migraine attacks. Risk of abuse and headache chronification. An excessive use may cause ergotism |

REVISED PROOF

| | | | |
|---|---|---|---|
| NSAIDs | | | |
| Acetylsalicylic acid (ASA) oral | 500–1,000 mg | I | Good efficacy/tolerability profile Gastrointestinal adverse events |
| Lisine acetylsalicylate oral | 500–1,000 mg | I | Good efficacy/tolerability profile Gastrointestinal adverse events |
| Lisine acetylsalycilate i.v. | 1,000 mg | I | To be used in a hospital setting. Risk of bleeding |
| Diclofenac–K+ oral | 100 mg | II | In the case of frequent migraine attacks risk of abuse and headache chronification |
| Diclofenac–Na+ i.m. | 75 mg | II | |
| Flurbiprofen oral | 100–300 mg | II | |
| Ibuprofen oral | 400–1,200 mg | I | |
| Ibuprofen oral | 200 mg | II | |
| Ketoprofen i.m. | 100 mg | II | |
| Ketorolac i.m. or i.v. | 30–60 mg | II | Clinical trials have been performed in particular settings (emergency departments) |
| Metamizole (dipirone) i.v. or oral | 1,000 mg | II | Potential risk of agranulocytosis >0.1 % and hypotension (i.v. formulation) |
| Naproxen oral | 500–1,500 mg | I | |

| | | | |
|---|---|---|---|
| Na + Naproxen oral | 550–1,500 mg | I | |
| Mefenamic acid per os | 500 mg | II | Effective in menstrual migraine attacks |
| Combination analgesics | | | |
| Paracetamol + acetyl salicylic + caffeine suppository | 500 mg + 500 mg + 130 mg | | To be used for attacks of moderate intensity. Effective also in the treatment of menstrual migraine. In the case of frequent migraine attacks, risk of abuse and headache chronification |
| Indomethacin + prochlorperazine + caffeine oral | 25 mg + 2 mg + 75 mg | I | In the case of frequent migraine attacks, risk of abuse and headache chronification |
| Indomethacin + prochlorperazine + caffeine suppository | 25–50 mg + 4–8 mg + 75–150 mg | II | See above |
| Paracetamol + codeine per os | 400–650 mg + 6–25 mg | II | See above |
| Antiemetics | | | |
| Metoclopramide i.v. | 0.1 mg/kg 1–3 times | II | To be used in a hospital setting |

**Table 6** Drugs for symptomatic treatment of migraine with a level of recommendation III and IV

| Drug | Route of administration | Dosage | Level of evidence | Scientific strength of evidence | Clinical effectiveness | Adverse events | Level of recommendation |
|---|---|---|---|---|---|---|---|
| NSAIDs | | | | | | | |
| Indomethacin | os | 25–50 mg | C | + | ++ | Frequent, not severe | III |
| | Rectal | 50–100 mg | C | + | ++ | Frequent, not severe | III |
| Nimesulide | os | 100 mg | C | + | + | Occasional, not severe | IV |
| Paracetamol | os | 650–1,000 mg | B | + | ++ | Rare, not severe | III |
| Piroxicam | Rapid dissolving formulation | 40 mg | B | ++ | + | Frequent, not severe | III |
| Ergot derivatives | | | | | | | |
| Ergotamine + caffeine | os, rectal | 2 + 200 mg | C | + | + | Frequent, not severe | III |
| Combination analgesics | | | | | | | |
| Butalbital + propyphenazone + caffeine | os | 50 + 150 + 125 mg; 175 + 25 + 75 mg | C | 0 | + | Those of each active substance | IV |
| Antiemetics | | | | | | | |
| Metoclopramide | os | 10 mg | C | 0 | 0/+ | Infrequent | IV |
| Prochlorperazine | Rectal | 20 mg | B | ++ | + | Infrequent | III |
| Chlorpromazine | i.m. | 0.1 mg/kg to 3 dosages | C | 0 | + | Occasional | IV |
| | i.v. | 12.5–37.5 mg | B | ++ | ++ | Slight to moderate | III |
| Domperidone | os | 10 mg | C | 0 | + | Rare | IV |
| Opioid analgesics | | | | | | | |
| Meperidine | | 50–100 mg | B | ++ | ++ | Frequent, not severe | III |
| Tramadol | | 100 mg | B | + | + | Occasional, not severe | III |
| Tramadol + paracetamol | | 37.5 + 325 mg | B | + | + | Occasional, not severe | III |
| Other drugs | | | | | | | |
| Lidocaine | Intranasal | 0.4 ml 4 % solution | B | ++ | + | Frequent, potentially severe | III |
| Prednisone | os | 50–100 mg | B | ++ | + | Frequent, potentially severe | III |
| Dexamethasone | i.v. | 10 mg | B | ++ | + | Frequent, potentially severe | III |
| Valproic acid | | 300–800 mg | B | + | ++ | Frequent | III |

REVISED PROOF

## Association Analgesic + Antiemetic

- ✓Acetylsalicilic lisine salt + metoclopramide
- ✓Indomethacin + prochlorperazine + caffeine*

**** In low-frequency migraine***

***Possible abuse/dependence***

## NEW MODALITIES

## Multimechanistic approach

| Parameter | Suma | Naproxen | Suma + Naproxen | Placebo |
|---|---|---|---|---|
| 2-hour response | 49% | 46% | 65%* | 27% |
| 24-hour pain relief | 29% | 25% | 46%* | 17% |
| Recurrence | 41% | 47% | 29% * | 38% |

*Smith et al., 2005*

## Fixed-Dose Sumatriptan and Naproxen in Poor Responders to Triptans With a Short Half-Life

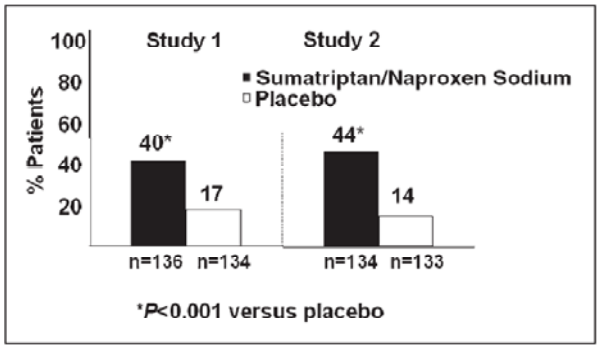
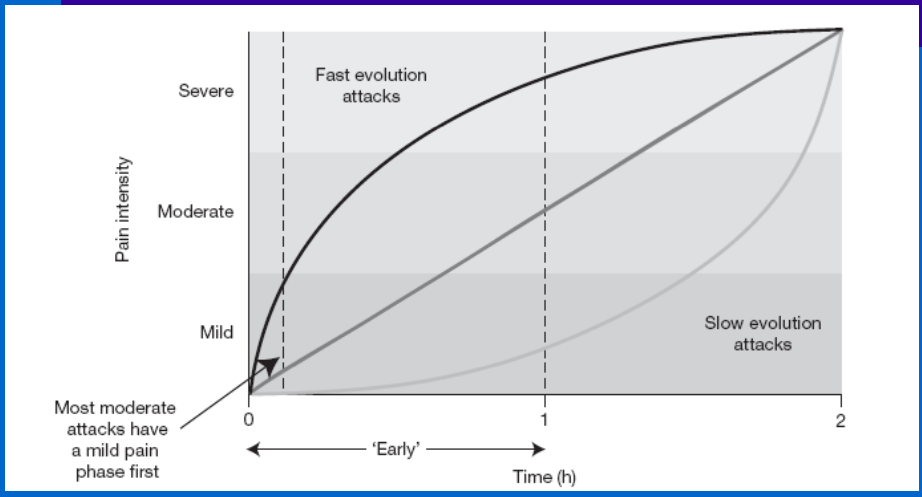
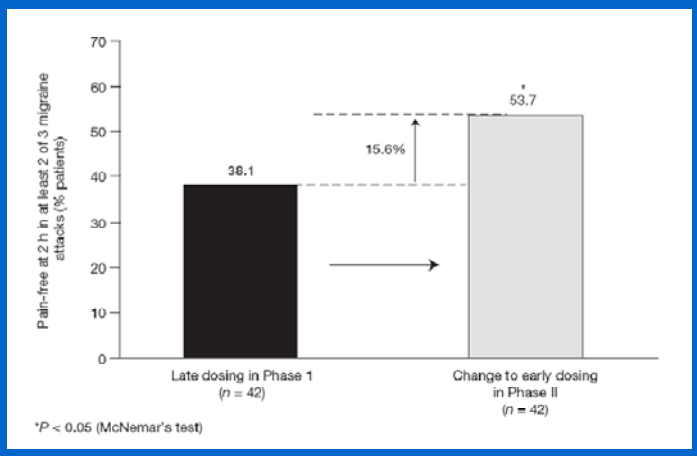



Fig 2.—Percentage of patients with pain-free response 2 hours after treatment of a migraine attack with sumatriptan/naproxen sodium or placebo. Ns differ from those for the intent-to-treat population because not everyone treated their second attack.

Mathew et al., Headache 2009


Severe
Moderate
Mild
Pain intensity
Fast evolution attacks
Slow evolution attacks
Most moderate attacks have a mild pain phase first
0
1
2
'Early'
Time (h)

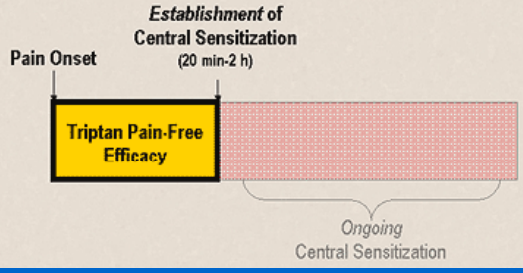
## TEMPO - The Triptans: Efficacy in Migraine after Precocious Oriented

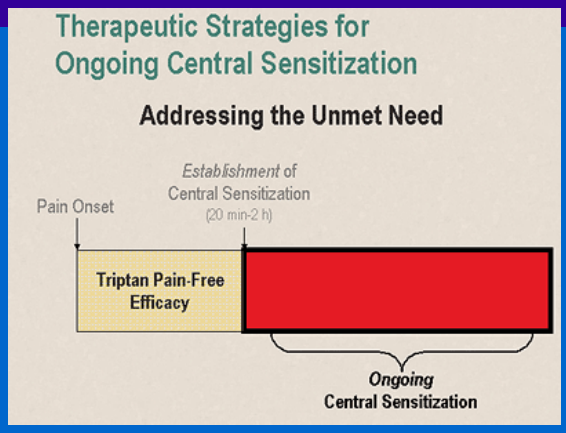



**Within-patient comparison of pain-free rates in patients in TEMPO who treated at least two of three migraine attacks > 1 h after pain onset in Phase I, and switched to an early dosing time (< 1 h after pain onset) in Phase II (26) (reproduced by kind permission of Dr Michel Lantéri-Minet, Pôle Neurosciences Cliniques, Nice, France).**

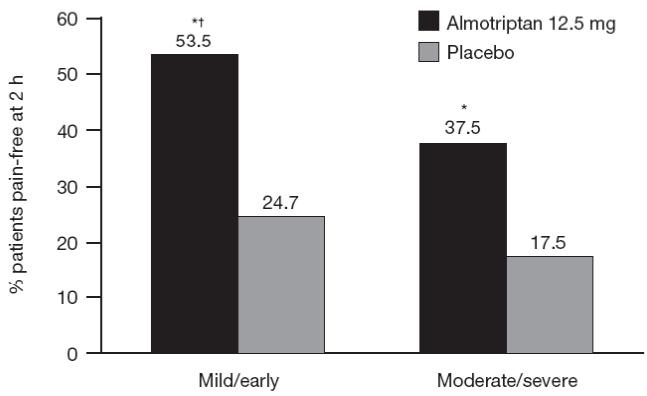
## Triptan Effects Prior to Central Sensitization

- In allodynic migraineurs, triptans are effective during an initial window of time





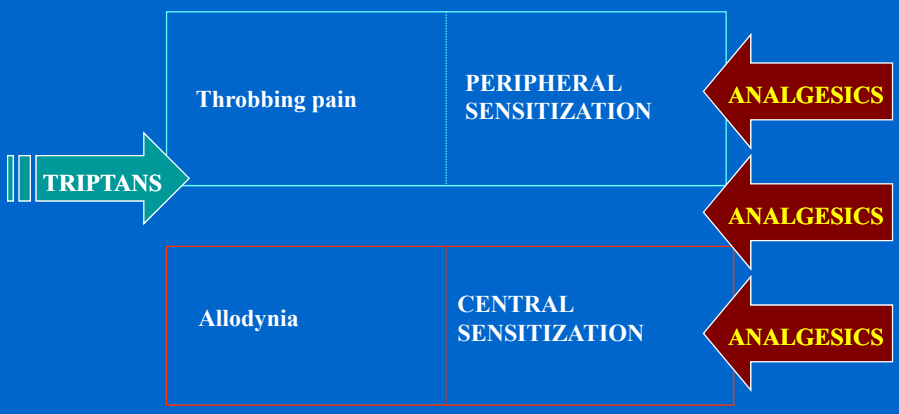

# The "act when mild" study




*$p \leq 0.001$ vs. placebo; †$p = 0.02$ vs. almotriptan moderate/severe

*Goadsby et al., 2008*

# EFFICACY AND TIMING OF INTAKE



Almotriptan and its combination with aceclofenac for migraine attacks: a study of efficacy and the influence of auto-evaluated brush allodynia

*Schoenen et al., 2008*

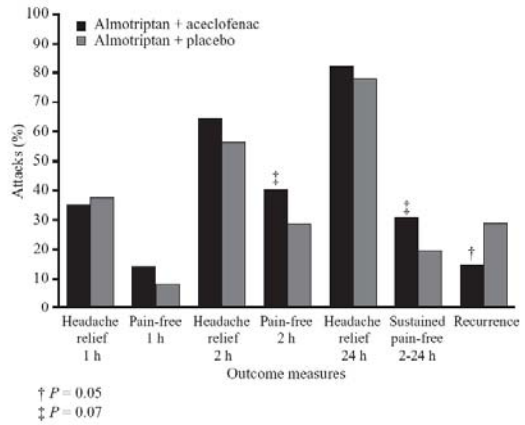
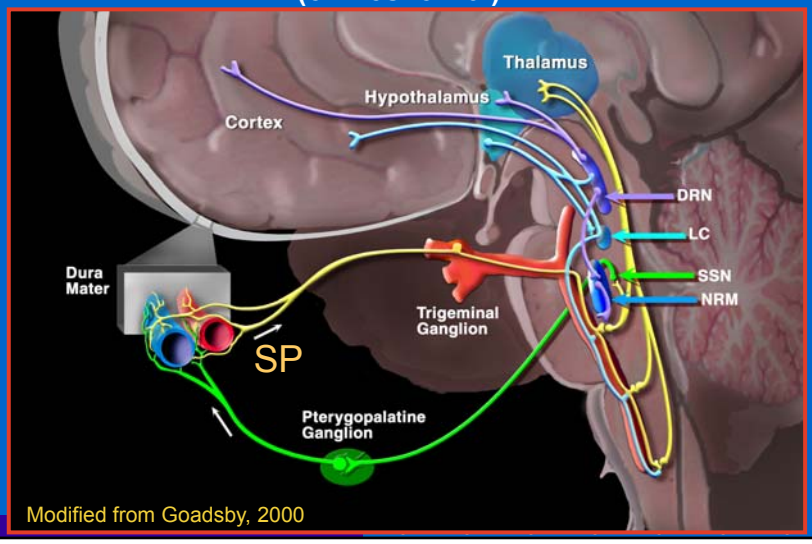



**Figure 4** Treatment efficacy across outcome measures in attacks treated with the almotriptan–aceclofenac (dark bars) or the almotriptan–placebo (light bars) combination.

# NEW POTENTIAL DRUGS

# Trigeminovascular System

(of Moskowitz)




Modified from Goadsby, 2000

# Neurogenic Inflammation

Substance P – SP
Plasma Protein Extravasation

Perivascular trigeminal nerve terminals →
SP release →
NK1 Receptor (endothelial cells) →
Plasma Protein Extravasation (Dura Mater)

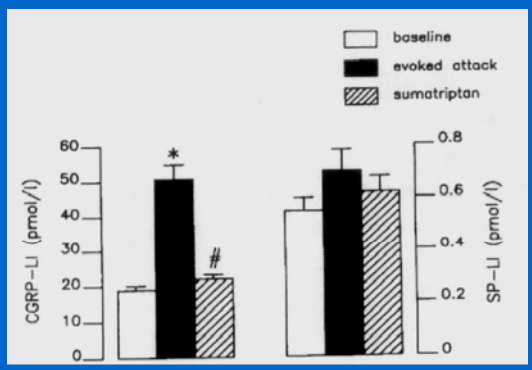
## Clinical Trials in Migraine :

**NK1-R Antagonists** **Failure (n = 4)**

# Neurogenic Inflammation

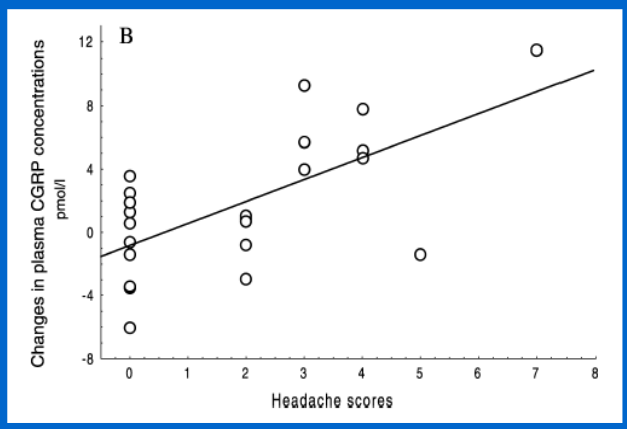
Calcitonin Gene Related Peptide – CGRP
Arterial Vasodilatation

## CGRP-LI in the extracerebral Venous Blood from Cluster Headache Patients During Nitroglycerin-Induced Attack



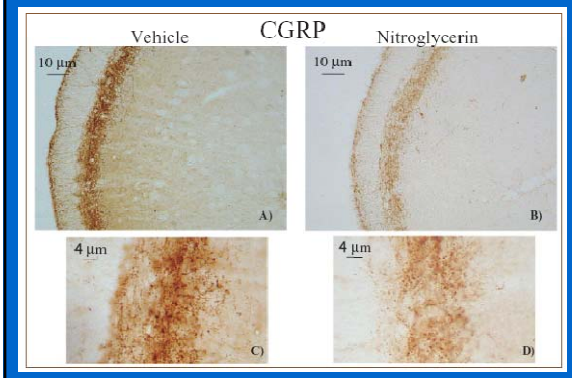

*Fanciullacci et al., Pain 1995; 60:119-23*

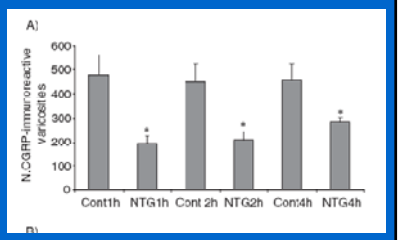
## NO-induced migraine attack: ↑ in plasma CGRP




Juhasz, Pain 106 (2003) 461–470

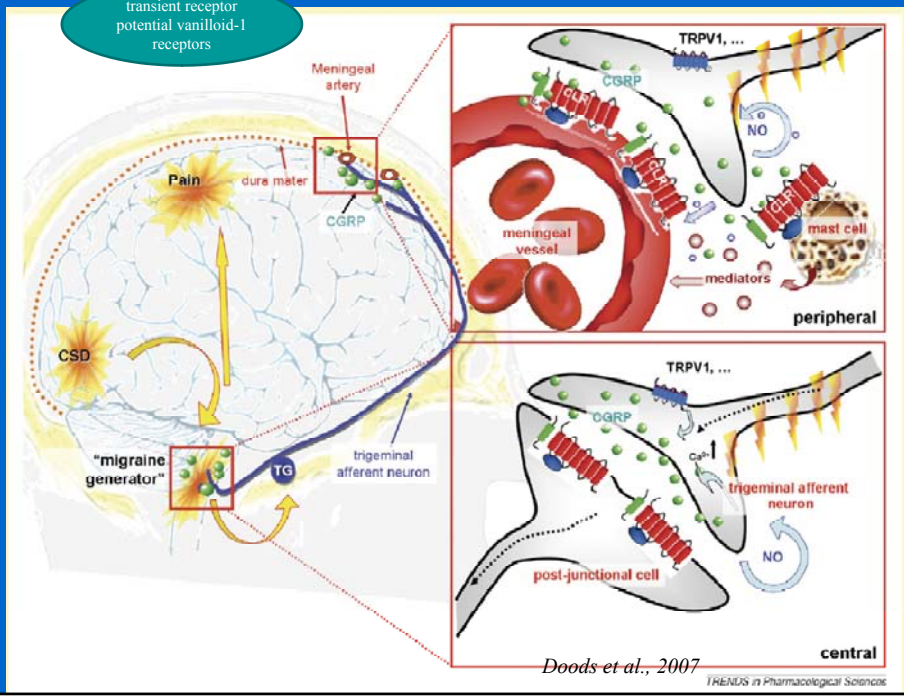
## CGRP – data from animal models of migraine




Greco et al., 2008

transient receptor potential vanilloid-1 receptors




*Doods et al., 2007*

Calcitonin (thyroid)

*Calcitonin Gene*

Alternative Splicing

Calcitonin gene related peptide (nervous system)

+ RAMP1

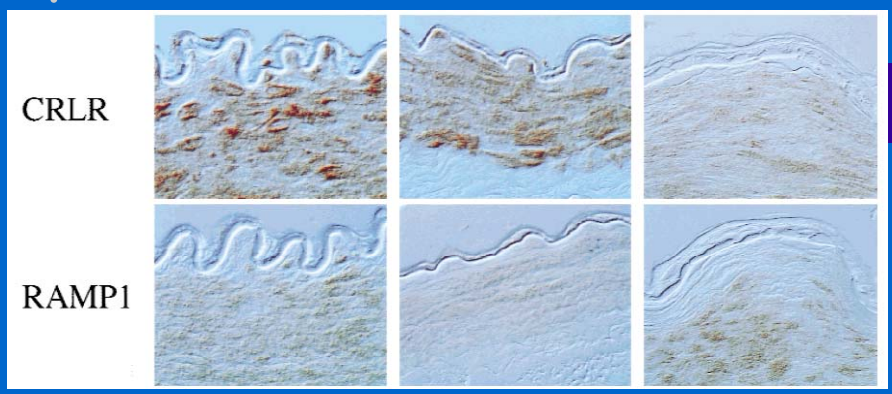
CL-R

receptor activity modifying protein

# CGRP-R (CLR+RAMP1)

- Tunica media (VSMC) of meningal arteries
- Perivascular mast cells
- 32% of TG cell bodies
- Central endings of TG neurons (no staining in Trigeminal Nucleus)

Lennerz et al., 2008

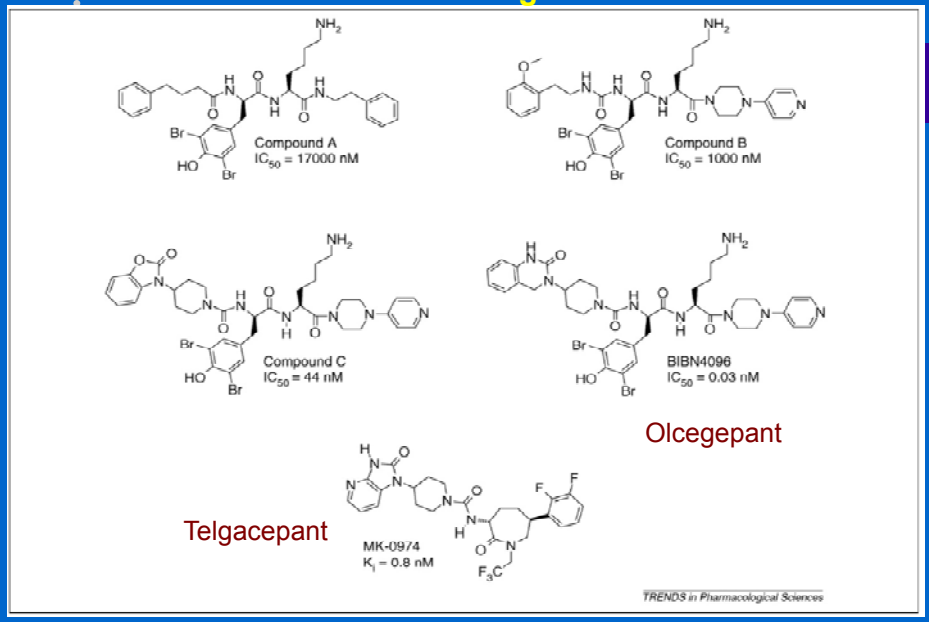



Human Cranial Arteries

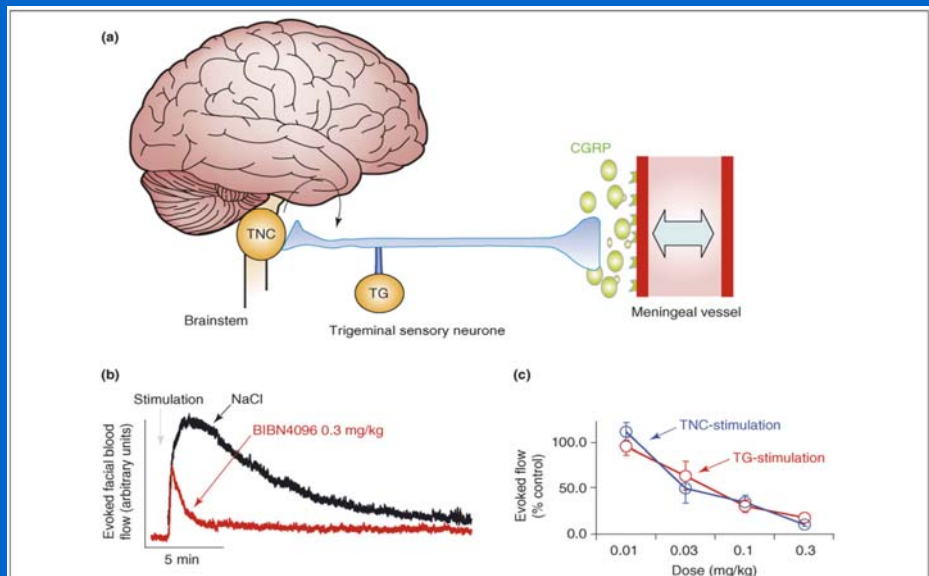
- middle meningeal
- middle cerebral
- pial
- superficial temporal

Oliver et al, 2002

# CGRP- R Antagonists




Doods H et al, Trends Pharmacol Sci. 2007 Nov;28(11):580-7




Electrical stimulation TG

Doods et al, Trends Pharmacol Sci. 2007

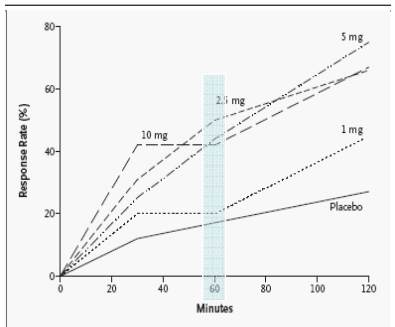



Figure 2. Rates of Response According to the Time after the Start of the Infusion.

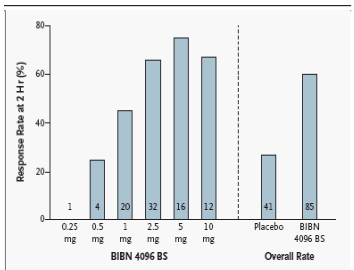



Figure 1. Rates of Response Overall, for Each Dose of BIBN 4096 BS Tested, and for Placebo among Patients with a Moderate or Severe Headache at Base Line.

A response was defined as the absence of a headache or the presence of a mild headache two hours after treatment. The number of patients in each group is shown.

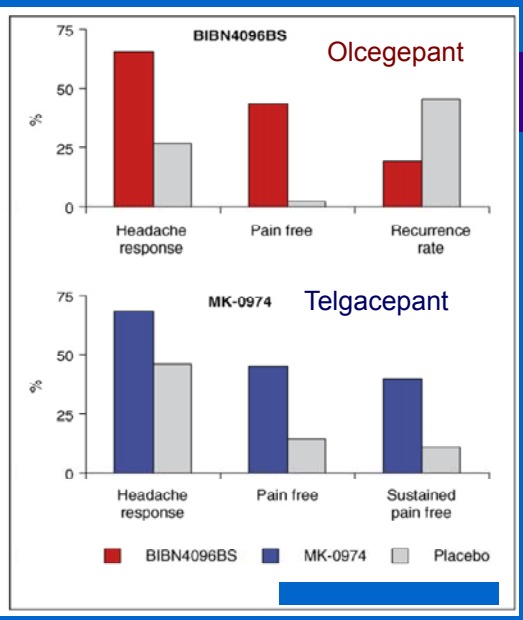
126 Patients (18-85 years) 85-41

Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM;
**BIBN 4096 BS Clinical Proof of Concept Study Group.**
**Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine.**
N Engl J Med 2004, 350:1073-1075

Summary of clinical results demonstrating proof of efficacy for

BIBN4096 (2.5 mg, intravenously) and

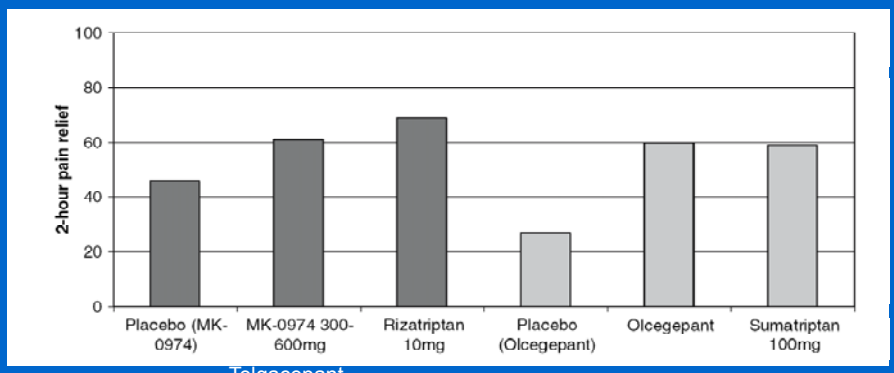
MK-0974 (300 mg, per oral) to relieve headache in migraine patients.




The headache and pain-free response were measured two hours after administration of the drugs.

**Doods et al, TiPS. 2007**

## The anti-migraine effect of MK-0974 and olcegepant or rizatriptan and sumatriptan compared to placebo at 2-h pain relief.

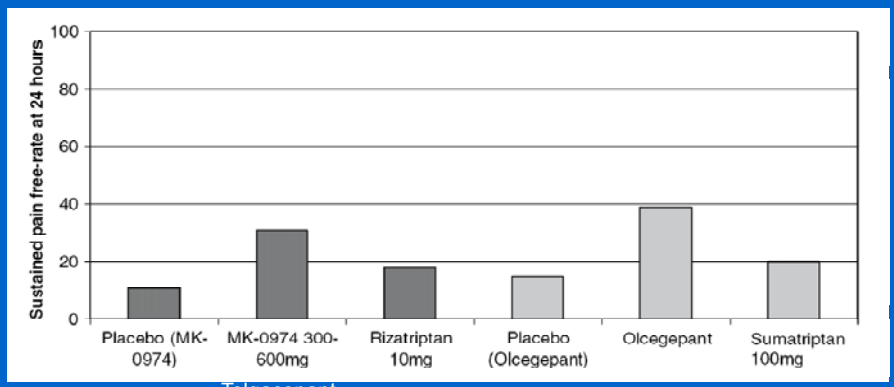



Telgacepant

The overall treatment effect of MK-0974 ($p = 0.015$) and rizatriptan ($p = 0.010$) showed significance versus placebo (left part). A dose of 2.5 mg of olcegepant also showed significant superiority over placebo ($p = 0.001$). Data of sumatriptan from another study were added to demonstrate the similar efficacy of olcegepant compared to triptans

Link et al, J Headache Pain (2008)

## Comparison of the sustained pain free-rate at 24 h of MK-0974 and olcegepant or rizatriptan and sumatriptan, and placebo.




Telgacepant

MK-0974 displayed superior efficacy versus placebo ($p=0.001$). In order to compare the efficacy of olcegepant to a triptan, data of sumatriptan from another study were added

**Link AS et al, J Headache Pain (2008) 9:5–12**

# CGRP Monoclonal Antibodies

- Anti-CGRP antibodies inhibit skin vasodilatation or the increase in MMA diameter likewise CGRP receptor antagonists.
- CGRP antibody treatment had a slower onset of action than the CGRP receptor antagonists. However the inhibition was still evident 1 week after dosing.
- Chronic treatment with anti-CGRP antibodies had no detectable effects on heart rate or blood pressure.

Zeller et al., Br J Pharmacol 2008

LASMIDITAN, a centrally acting, highly selective 5-HT(1F) receptor agonist without vasoconstrictor activity th