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**

- Trigger
  - RN
  - LC
  - 5-HT
  - NA
  - DA
  - COX
  - PGs
  - Neurogenic inflammation

- PAIN
  - Cortex
  - Thalamus
  - CTZ
  - Hypoth.
  - PHOTOPHOBIA
  - PHONOPHOBIA
  - VOMITING

**TRIPTAN: mechanism of action**

- Dura mater
- Blood vessel
- Trigeminal ganglion
- Trigeminal nucleus
- Brainstem

- 5HT1B
- Blood vessel
- Dura mater
- Trigeminal neuron
- Brainstem

- COX
- PGs
Drugs

- Analgesics
- Analgesics + ....
- 5-HT<sub>1B-1D</sub> agonists (triptans)
- Ergots
- Anti-emetics

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: Favorable 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 %)

+ 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.

* 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

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>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</td>
</tr>
<tr>
<td>II</td>
<td>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</td>
</tr>
</tbody>
</table>
| 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:  
(a) Drugs with no severe adverse events  
(b) Unsafe drugs or with complex indications for use (e.g. special diets) or important pharmacological interactions |
| 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.
### Table 1: Drugs for the symptomatic treatment of migraine with a level of recommendation I and II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Level of recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan tablets</td>
<td>6 mg</td>
<td>I</td>
<td>Rapid onset of action compared to the other formulations</td>
</tr>
<tr>
<td>Sumatriptan suppository</td>
<td>65-100 mg</td>
<td>I</td>
<td>Usually oral route is possible due to nausea</td>
</tr>
<tr>
<td>Sumatriptan nasal spray</td>
<td>10 mg</td>
<td>I</td>
<td>Usually oral route is possible due to nausea</td>
</tr>
<tr>
<td>Zolmitriptan tablets</td>
<td>2.5 mg</td>
<td>I</td>
<td>Rapid onset of action</td>
</tr>
<tr>
<td>Zolmitriptan oral suppository</td>
<td>2.5 mg</td>
<td>I</td>
<td>Rapid onset of action</td>
</tr>
<tr>
<td>Ergotamine dihydrochloride</td>
<td>5-10 mg</td>
<td>I</td>
<td>Recommended dosage is 5 mg in patients treated with prophylaxis which increases the plasma concentration of ergotamine</td>
</tr>
<tr>
<td>Ergotamine dihydrochloride</td>
<td>20-40 mg</td>
<td>I</td>
<td>The optimal dosage is 20 mg</td>
</tr>
<tr>
<td>Aserpine tablets</td>
<td>10 mg</td>
<td>I</td>
<td>Good solubility profile</td>
</tr>
<tr>
<td>Aserpine suppository</td>
<td>10 mg</td>
<td>I</td>
<td>Good solubility profile</td>
</tr>
<tr>
<td>Aserpine nasal spray</td>
<td>1-2 mg</td>
<td>II</td>
<td>Believed in the case of frequent migraine attacks risk of abuse and headache chronication</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td>Level of evidence</td>
<td>Scientifically supported</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------------</td>
<td>-------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Naproxen oral</td>
<td>550-1,500 mg</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>Meloxicam oral</td>
<td>500 mg</td>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>Combination analgesics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piroxicam + acetylsalicylic</td>
<td>500 mg + 100 mg + 130 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin + piroxicam</td>
<td>25 mg + 2 mg + 75 mg</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>Ibufrocin + piroxicam</td>
<td>25-50 mg + 4-8 mg + 75-150 mg</td>
<td>II</td>
<td>+</td>
</tr>
<tr>
<td>Piroxicam + codeine per os</td>
<td>400-650 mg + 6-25 mg</td>
<td>II</td>
<td>+</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide i.v.</td>
<td>0.1 mg/kg 1-3 times</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>
Association Analgesic + Antiemetic

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

* In low-frequency migraine
Possible abuse/dependence

NEW MODALITIES
Multimechanistic approach

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Suma</th>
<th>Naproxen</th>
<th>Suma + Naproxen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-hour response</td>
<td>49%</td>
<td>46%</td>
<td>65%*</td>
<td>27%</td>
</tr>
<tr>
<td>24-hour pain relief</td>
<td>29%</td>
<td>25%</td>
<td>46%*</td>
<td>17%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>41%</td>
<td>47%</td>
<td>29% *</td>
<td>38%</td>
</tr>
</tbody>
</table>

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
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.

Establishment of Central Sensitization

Pain Onset (2h min 2 h)

Triptan Pain-Free Efficacy

Ongoing Central Sensitization
The “act when mild” study

Goadsby et al., 2008
EFFICACY AND TIMING OF INTAKE

<table>
<thead>
<tr>
<th>Throbbing pain</th>
<th>PERIPHERAL SENSITIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLodynia</td>
<td>CENTRAL SENSITIZATION</td>
</tr>
</tbody>
</table>

TRIPTANS  
ANALGESICS  
ANALGESICS  
ANALGESICS
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  \( \rightarrow \)  
SP release  \( \rightarrow \)  
NK1 Receptor (endothelial cells)  \( \rightarrow \)  
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


CGRP – data from animal models of migraine

Greco et al., 2008
Calcitonin (thyroid)

Calcitonin Gene
Alternative Splicing
Calcitonin gene related peptide
(nervous system)

CL-R
+ RAMP1

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

Olcegepant

Telgacepant


Electrical stimulation TG

23

126 Patients (18-85 years) 85-41


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.

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.

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.

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