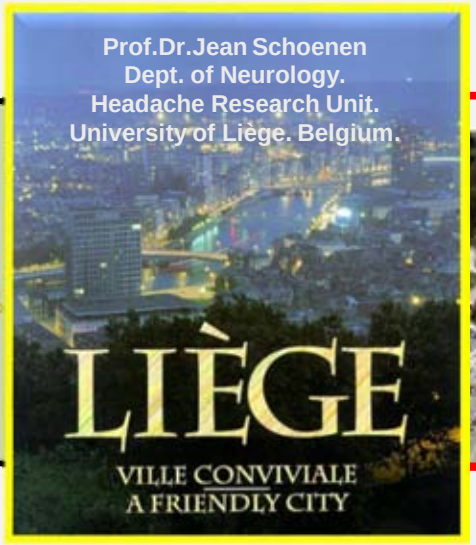
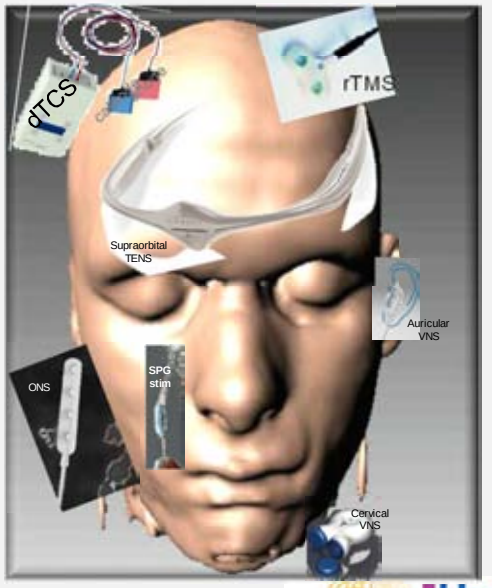
MANAGEMENT of 1 ° HEADACHES



Conflicts of interest:
Investigator/advisor for:
GSK, BMS, Amgen, Richter, Janssen-Cilag, Allergan, Colucid, Boehringer, Merck, Almirall, Pfizer, Medtronic, Coherex, ATI, STX-Med



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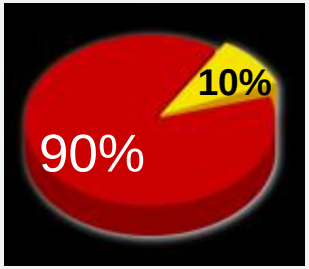
GET IT RIGHT !

1. Get the **relationship** with your patient right !
2. Get the **diagnosis** right !
3. Get the **acute treatment** right !
4. Get the **preventive treatment** right !

Get the relationship with your patient right !

- **L**isten (..to patient's history)
- **A**sk (...the right questions)
- **Q**uestion (...about co-morbidity)
- **E**xamine (...in detail)
- **E**xplain (...the diagnosis)
- **L**isten (...to patient's expectations)
- **E**xplain (...therapeutic options)
- **L**isten (...to patient's preferences)
- **P**ropose & explain (...therapies, life style changes)
- **E**xplain (...headache diary)
- **L**isten (...to patient's questions)
- **A**gree (...on next appointment & interval calls)

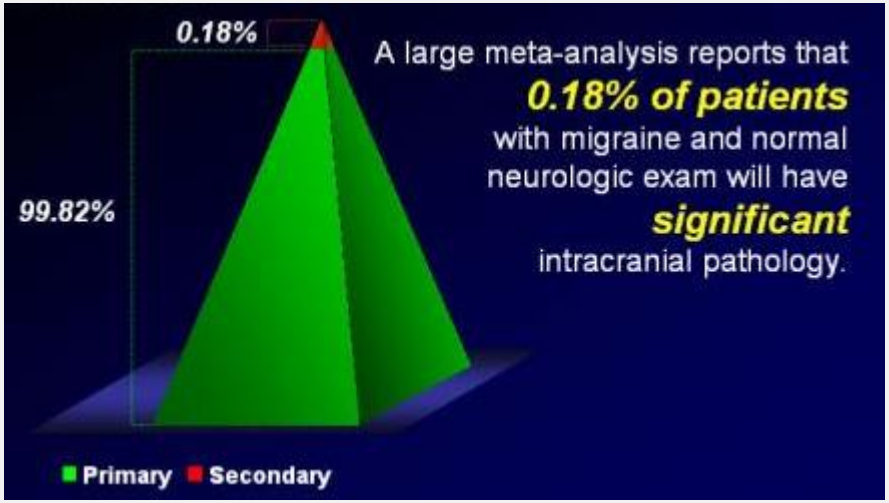
Headache diagnosis



- Primary
  - Migraine
  - Tension-type
  - Cluster
  - Other
- Secondary
  - Infection
  - Hemorrhage
  - Increased ICP
  - Brain tumor

Headache mimickry

- other disorders excluded (crit.E)
- unknown causes, cannot be cured …at present time



- a cause is identified
- can be cured …potentially

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Headache diagnosis

ICHD-3 beta

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
33(9) 629–808

DOI: 10.1177/0333102413485658
cep.sagepub.com

SAGE

Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders, 3rd edition (beta version)

http://www.ihs-headache.org

Primary headaches

Diagnostic criteria
ICHD-II

A:

B:

C:

- 1.
- 2.
- 3.
- 4.

2/4

D:

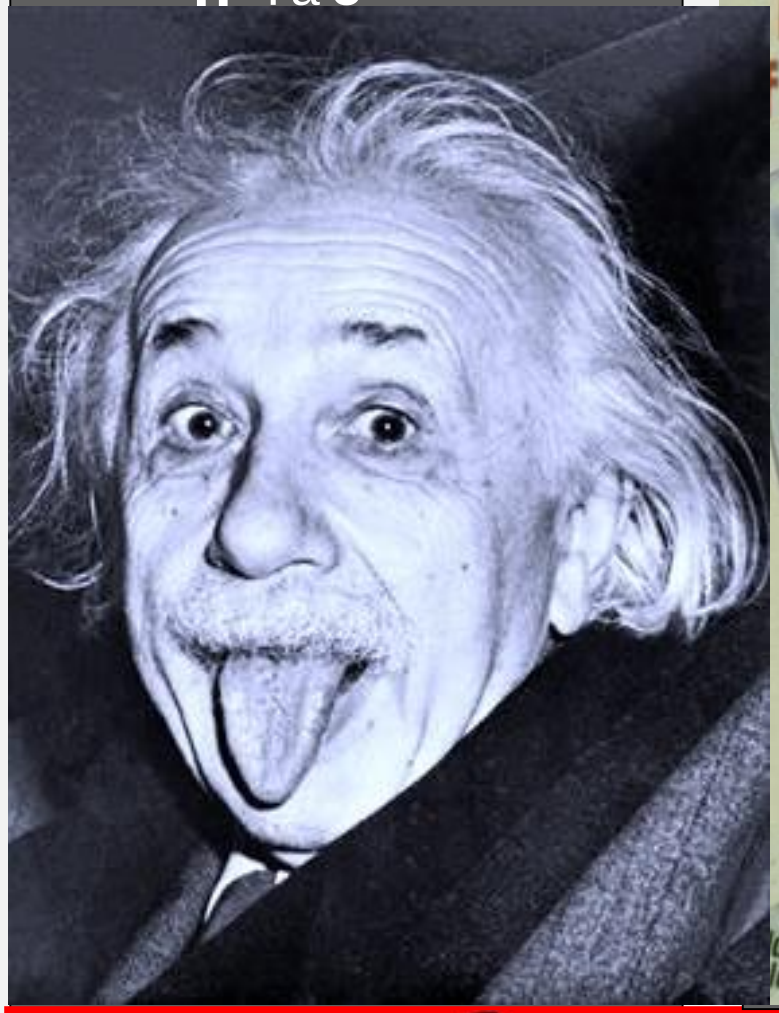
- 1.
- 2.

1/2

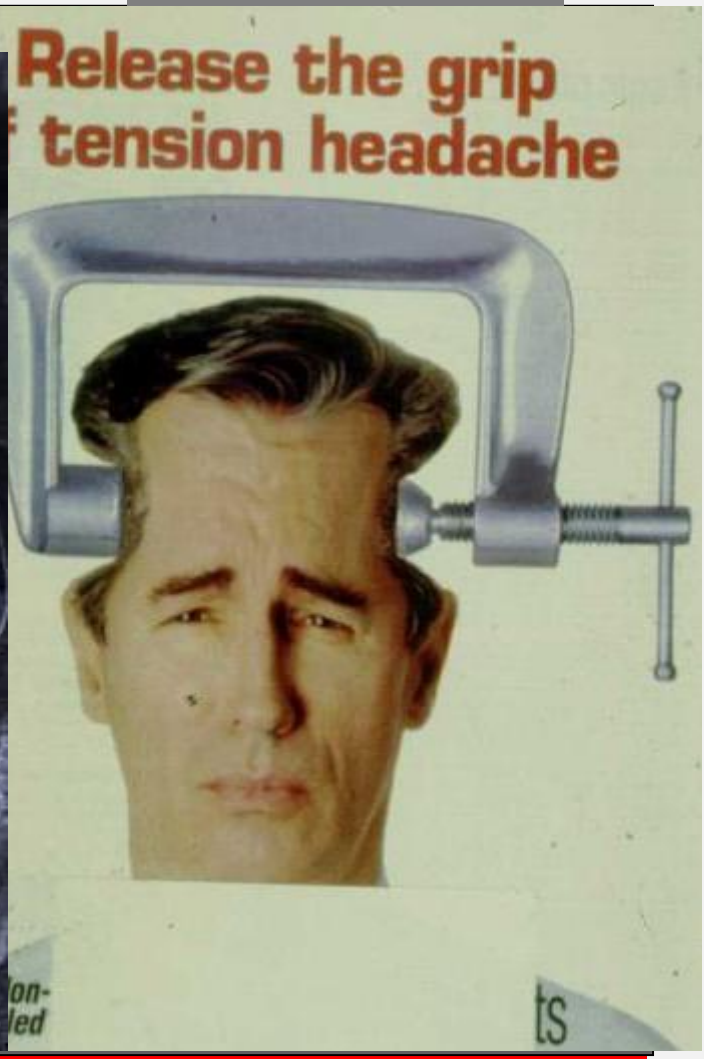
E:

Migraine

n ?á 5



Tension-type

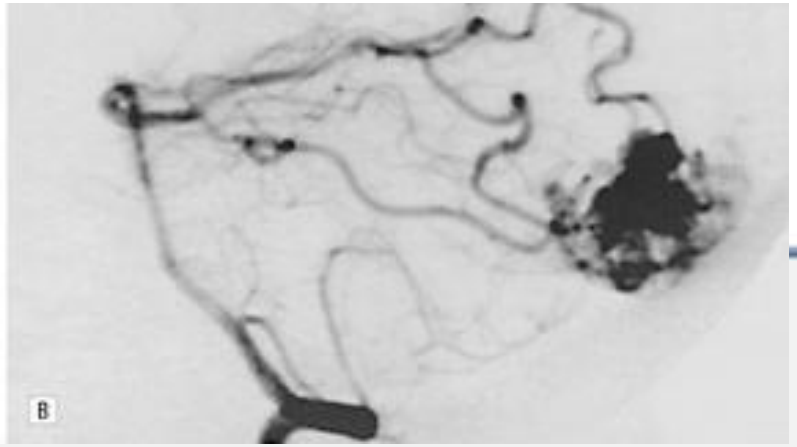


Normal

Case 1

- woman 26 y.o.
- since 3 years, attacks of always right-sided paraesthesias spreading from hand to face, sometimes followed/accompanied by speech disturbance
- exceptionally visual disturbance
- duration: 20-40 min
- followed/accompanied by always left-sided hemicrania, with occasional photophobia, but no GI problems

- **What is your diagnosis ?**



Parieto-occipital angioma

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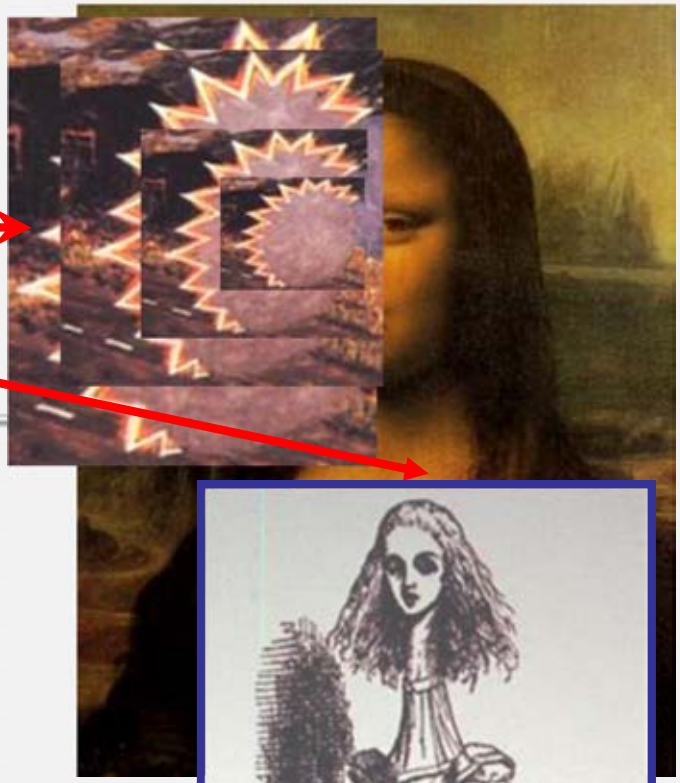
ICHD-II (Cephalalgia 2004)

1.1. Migraine without aura (MO) : 80%

1.2. Migraine with aura (MA) : 20%

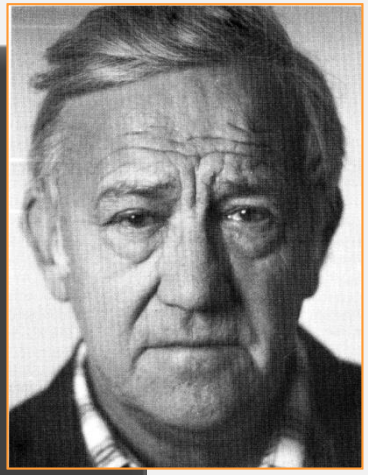


- visual / sensory symptoms both
  - « *positive*» (scintillations/needles) &
  - « *negative*» (scotoma/numbness)
- progressive appearance over ?Ñ5 minutes
- each symptom lasts ?Ñ5 ?Ñ60 minutes
- visual symptoms first: 90%
- visual symptoms are mostly black, gray & white (not coloured)
- the headache starts within 60 min, but can be absent or start before the aura

Dysmorphopsia

"Alice in the Wonderland" Lewis Caroll

Clinical presentation of Cluster Headache



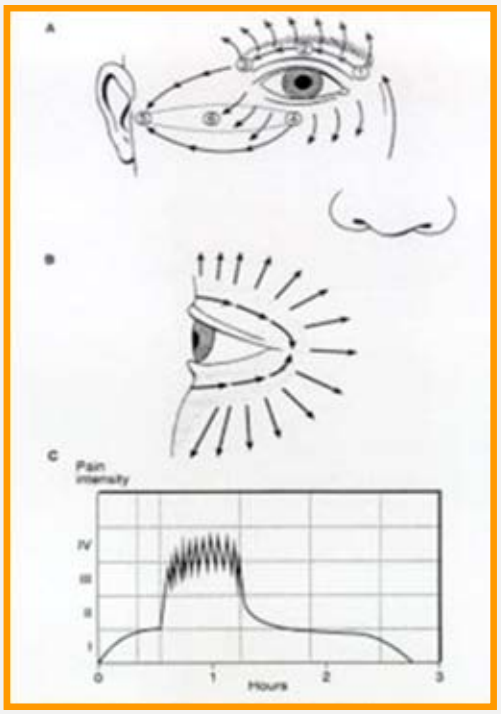
Previously used terms:

- Erythroprosopalgia of Bing,
- Horton's headache,
- histaminic cephalalgia,
- Harris's ciliary or migrainous neuralgia ,
- petrosal neuralgia (Gardner),
- erythromelalgia of the head,
- sphenopalatine, Vidian, Charlin's or Sluder's neuralgia,
- hemicrania periodica neuralgiformis
- "algies vasculaires de la face"

.....

CLUSTER HEADACHE: attack profile

- Unilateral orbital / temporal severe pain intensity
- Rapid onset (min) &
  short duration (15 – 180 min; aver: 45min)
- “Agitated” patient (pacing / restless)
- Cranial autonomic features
  (conj. injection, tearing,
  eye lid edema & ptosis,
  fullness in ear…)
- Attack triggers: alcohol, nitrates..



case 2

- 67 y.o. woman
- since the age of 59 y attacks of fixed right-sided headache
    - temple, orbital
    - on awakening in the morning
    - moderate intensity, non-throbbling, burning
    - no GI symptoms, but sometimes lies down
    - duration : quasi permanent with occasional exacerbations
    - since 3 months : during exacerbations : blurred vision & mild lacrymation
    - past history : possible migraine in adolescence
- family history : nihil
- clinic. exam. : right suboccipital palpation tenderness

Diagnosis : ?

Rp. indomethacine 2 x 75 mg/d : asymptomatic after 4 days

Hemicrania continua

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Trigeminal Autonomic Cephalalgias (TACs)

3.1 Cluster Headache

- 3.1.1 Episodic
- 3.1.2 Chronic

3.2 Paroxysmal Hemicrania

- 3.2.1 Episodic
- 3.2.2 Chronic

3.3 SUN (Short-lasting Unilateral Neuralgiform headache attacks)

- 3.3.1 SUNCT (with Conjunctival injection and Tearing)
- 3.4 SUNA (with cranial Autonomic symptoms)

3.5 Hemicrania continua

3.6 Probable TAC

(Cephalalgia 2004; 24[Suppl 1]: 1-160; *Goadsby & Lipton Brain 1997;120:193)

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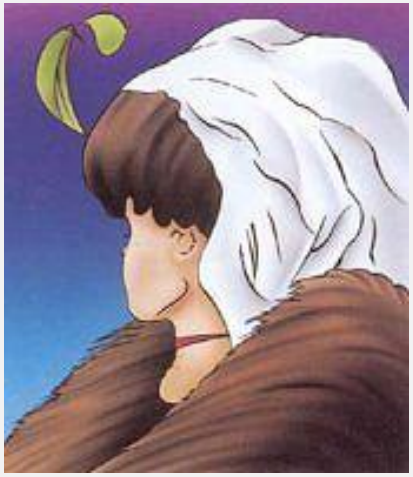
MIGRAINE THERAPY : 2 faces of a coin



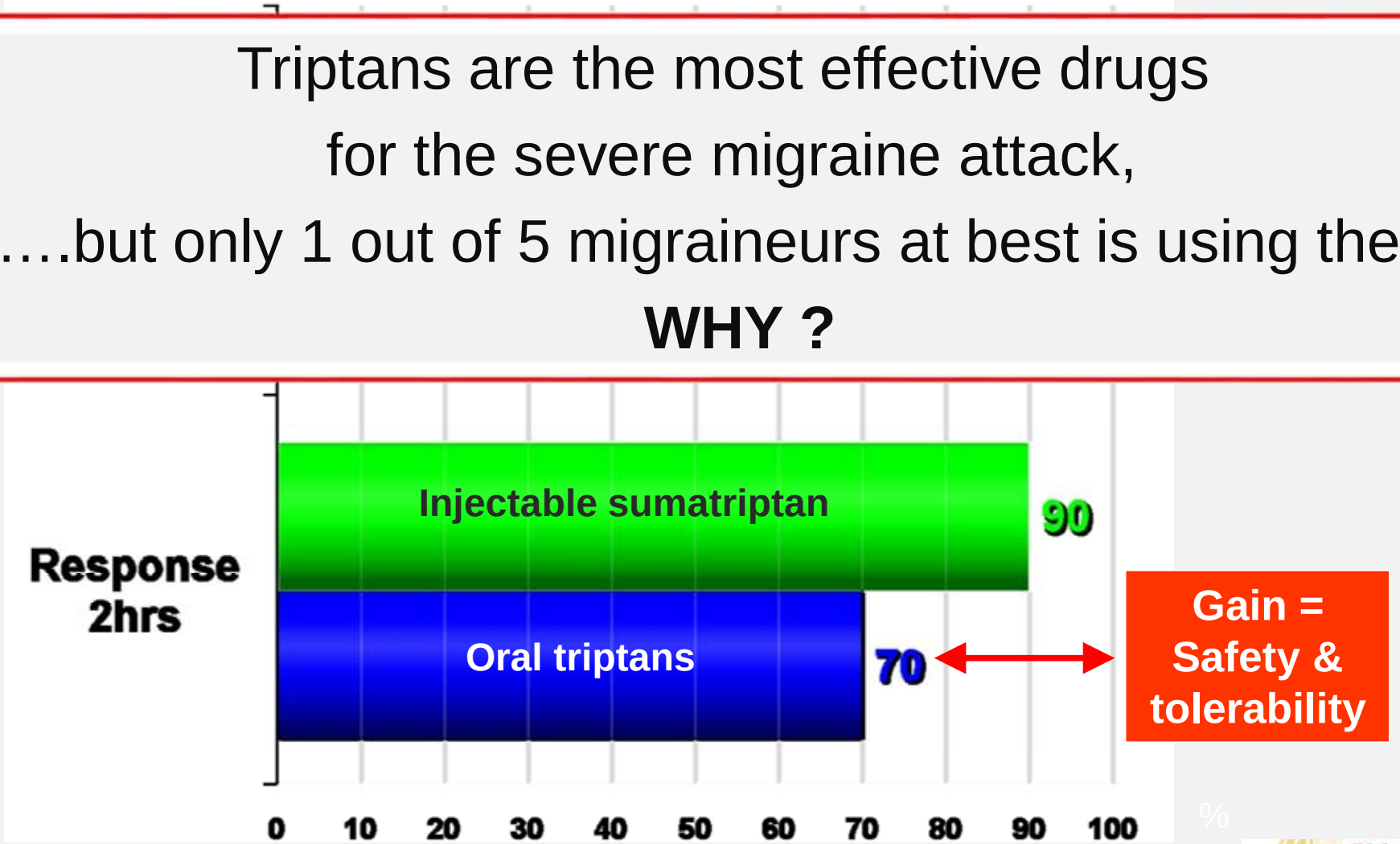
1. **What causes the migraine attack ?**
   → **Acute therapy**

2. **What causes the repetition of attacks ?**
   → **Preventive therapy**
   - **What is available ?**
   - **How to improve ?**

Acute Migraine Therapy

Overall absolute efficacy rates of triptans (%)

Triptans are the most effective drugs
for the severe migraine attack,
….but only 1 out of 5 migraineurs at best is using them.
WHY ?



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Case 3

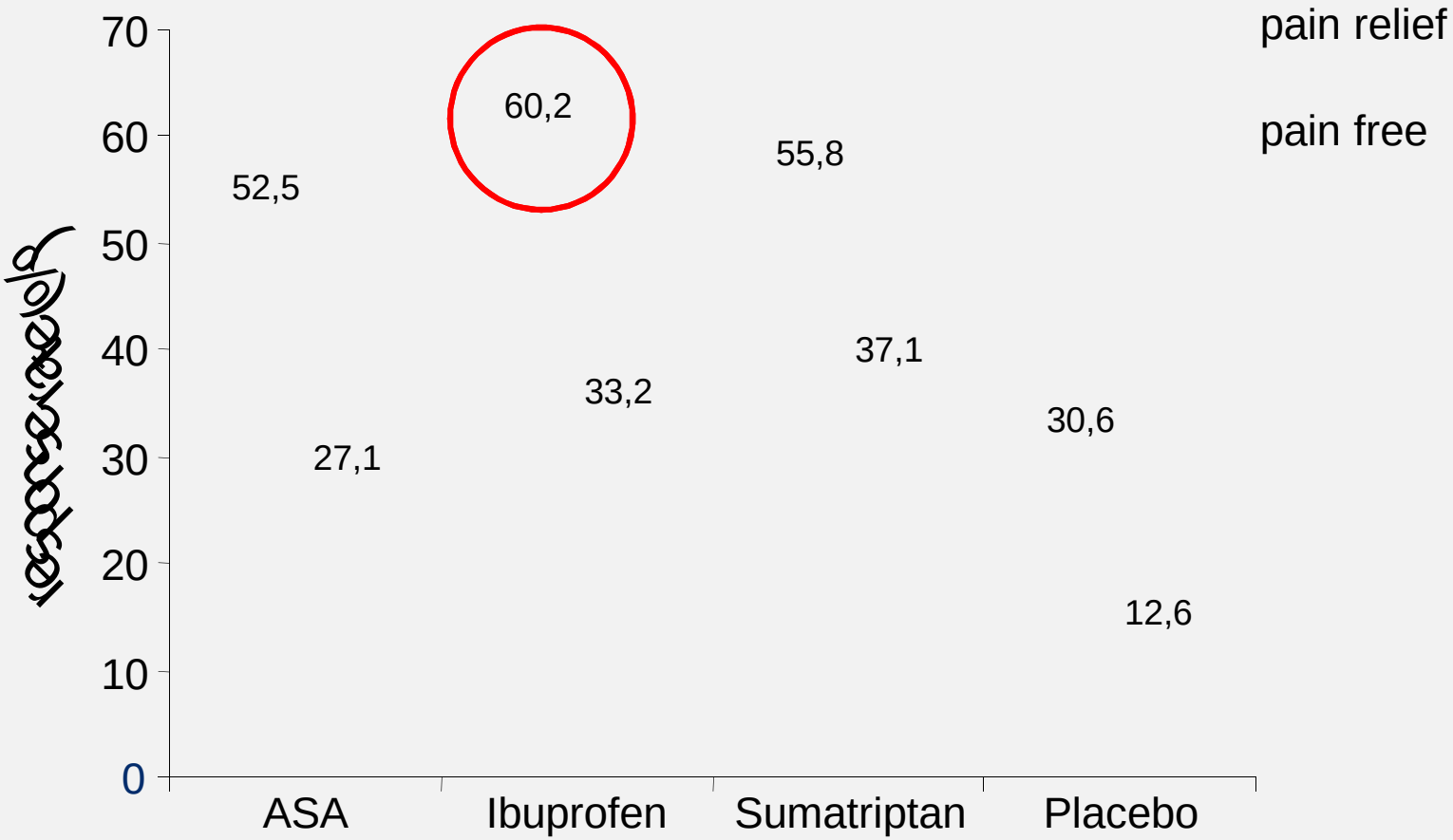
- Mrs A… 37 y.o. has migraine with visual aura since adolescence. She has on average 8-10 attacks per year.
- She had been using an ergotamine tartrate-caffeine preparation immediately at attack onset. Headache usually disappeared after 1 hour, but she had each time severe nausea, sometimes followed by vomiting.
- She has tried sumatriptan tablets 100 mg twice and injection once without success and seeks a more efficient treatment.

What went wrong ?

NSAIDs are effective, in particular for mild attacks !

Comparison of ASA (1000 mg), sumatriptan (50 mg) and ibuprofen (400 mg)

The EMSASI* Study Group. Cephalalgia 2004.



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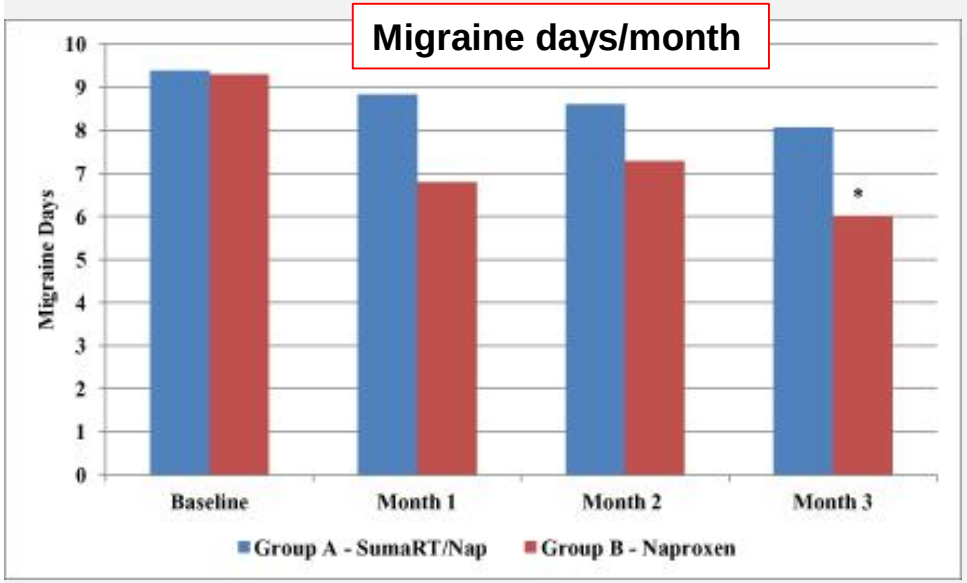
NSAIDs in migraine

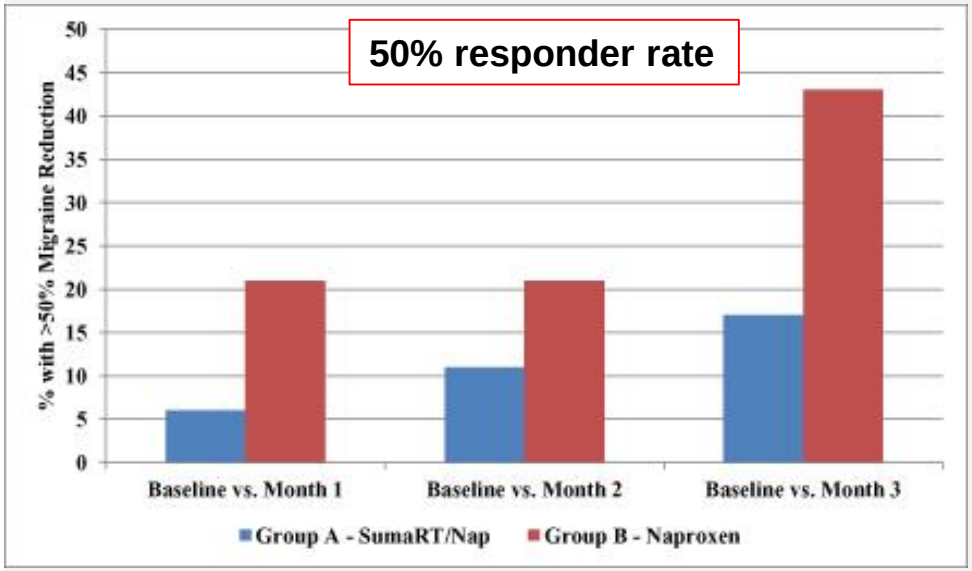
- **First choice** in most guidelines : NSAIDs (including paracetamol, aspirin...)
- **Evidence of efficacy** for
  - ASA (**!**)
  - paracetamol
  - ibuprofen (**!**)
  - diclofenac (**!**)
  - naproxen
  - metamizol
  - tolfenamic acid (**!**)
  - phenazone
  - combination (ASA, paracetamol, caffeine)
- **No superiority** of a specific NSAID (except combination with caffeine), but watch the **dose**

! = not inferior to a triptan in controlled trials

SumaRT/Nap vs Naproxen Sodium in Migraine Treatment

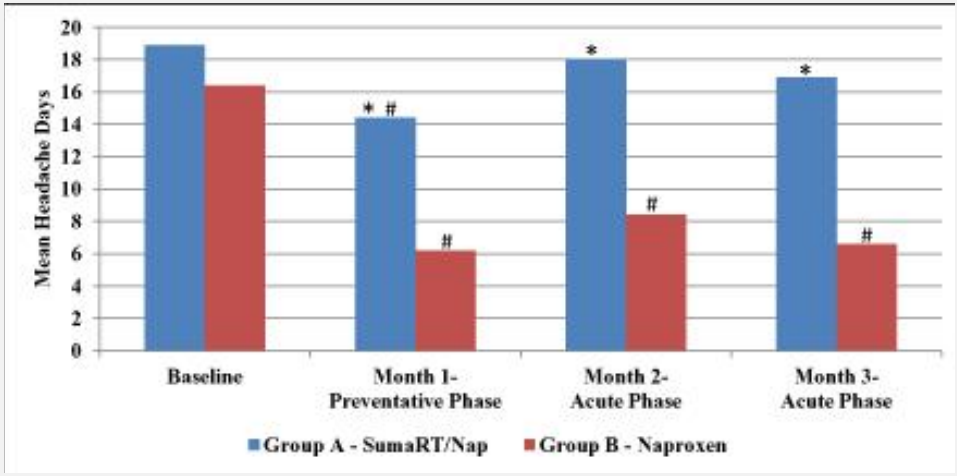
Episodic Migraine

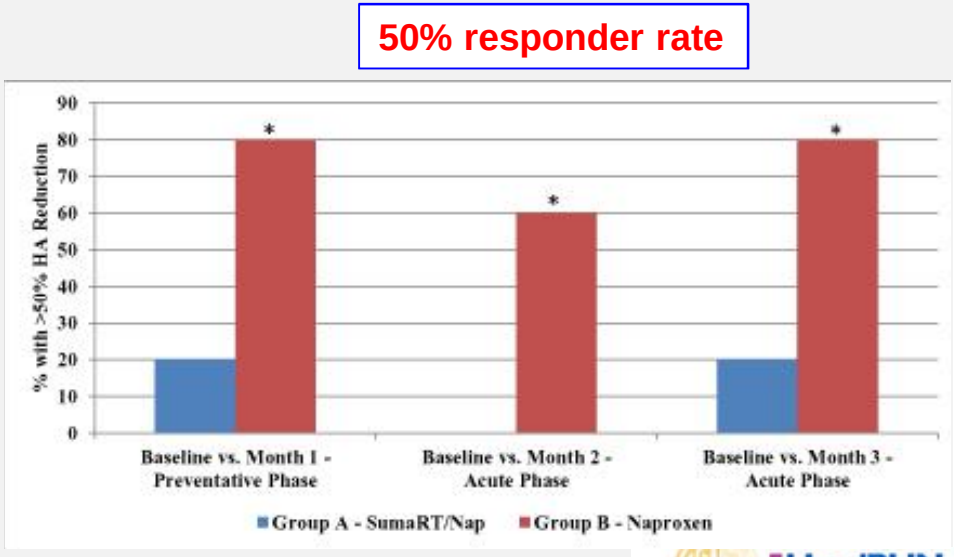




SumaRT/Nap vs Naproxen Sodium in Treatment and Disease Modification of Migraine: A Pilot Study. Cady et al. Headache 2013

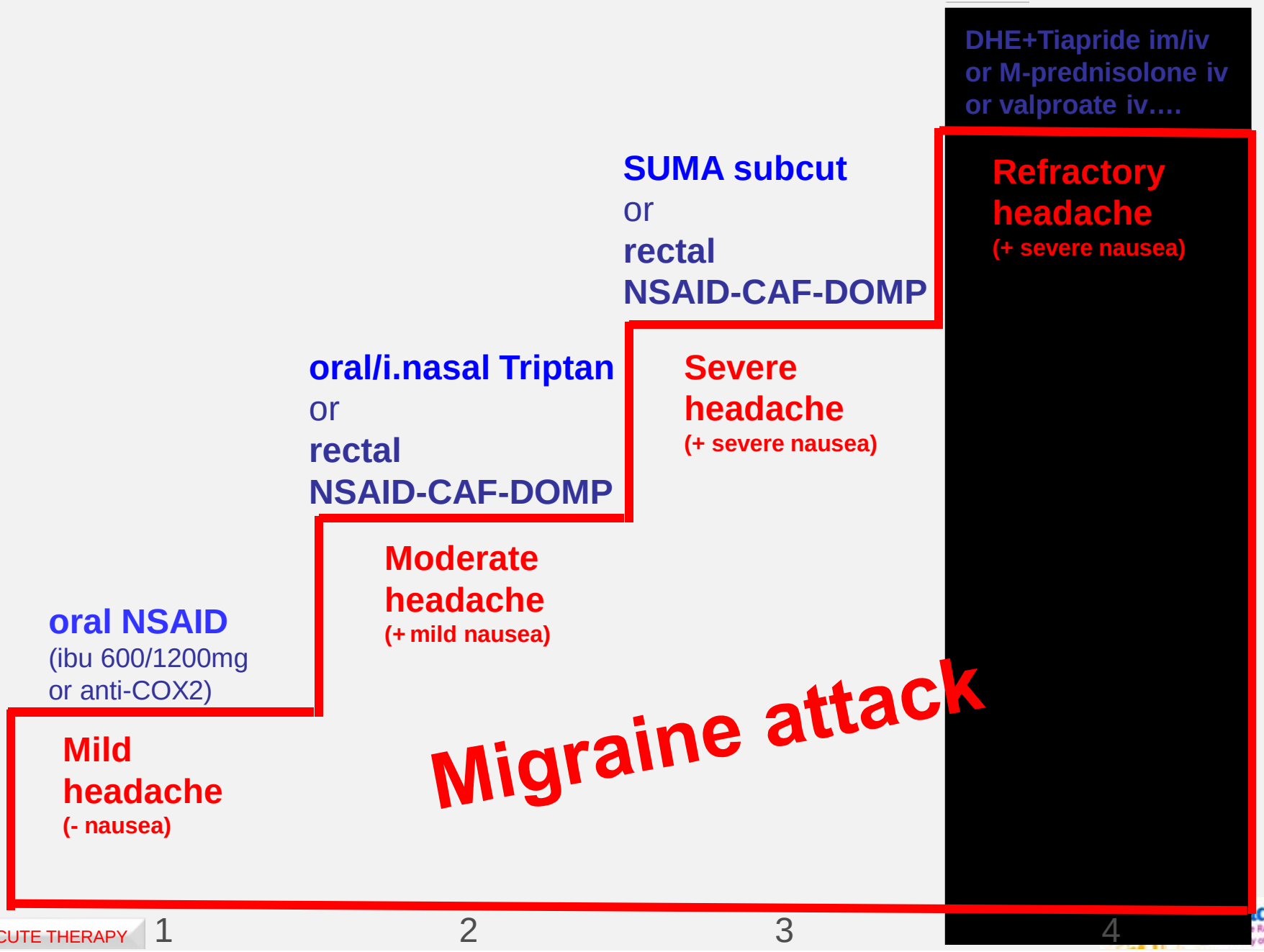
Chronic Migraine





Treatment of Chronic Migraine: A 3-Month Comparator Study of Naproxen Sodium vs SumaRT/Nap. Cady et al. Headache 2013 DOI: 10.1111/head.12210

Step-wise strategy within attacks



Acute migraine therapy: perspectives

Near future

- **CGRP**rec antagonists: the “gepants”
  (development halted because of hepatotoxicity)
- **CGRP** antibodies
- **5-HT1F** agonists: the “ditans”

No vascular effects

Far future

- mGluR antagonists
- *adenosine* A1 rec agonist; *vanilloid* (VR1) rec antagonist; *somatostatin* rec agonist
- *nociceptin* and NOP receptor; *cannabinoid* rec CB1; *orexin* A

ACUTE MEDICATION OVERUSE

PREVENT !!

If more than

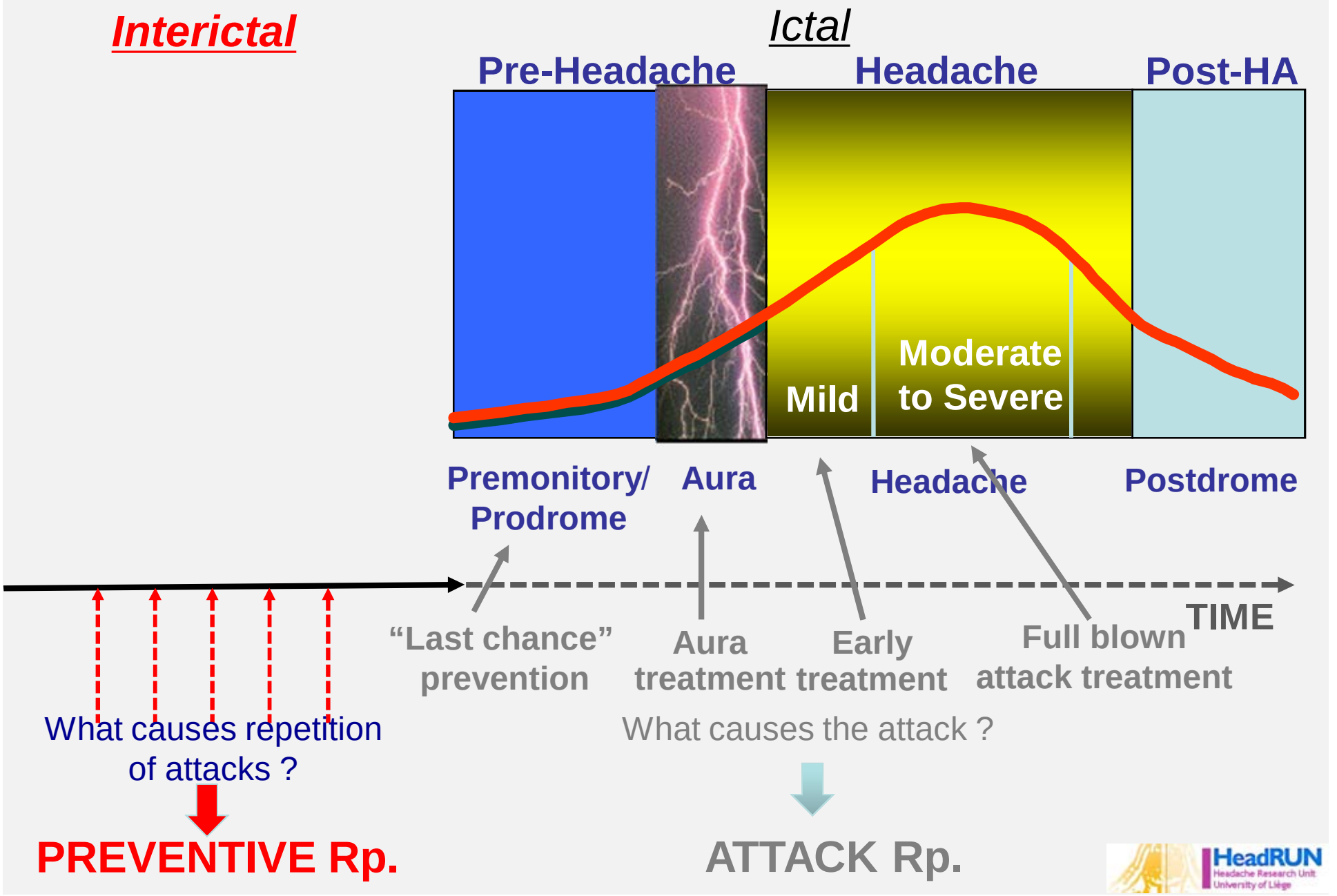
10 days per month

Intake of acute
headache medication

NSAIDs

over combination
analgesics/triptans

Migraine = repetition of migraine attacks



Case 4

- this 40 yo woman has migraine without aura since adolescence.
- she consults because she has since 2 years weekly migraine attacks which she treats with an oral triptan.
- Her attacks usually start on awakening.
- This aggravation has coincided with increased socio-professional stress which, she thinks, is the culprit.

Do you think that's correct ?

- taking history, she drinks 5-6 espresso coffees per day and 3-4 cola drinks, an estimated daily caffeine intake of 800-1000mg
- 3 months after having switched to decaf (except 1 or 2 espressos/day), she has on average 1 moderate menstrual migraine attack per month

Manage aggravating factors

- Chemicals (caffeine, ? Aspartame…)
- Hormones (OCP, post-menopausal substitution..)
- Acute medication overuse
- Lack of physical exercise
- Comorbid psychiatric disorders
- stress accumulation (daily hazzles
- ....

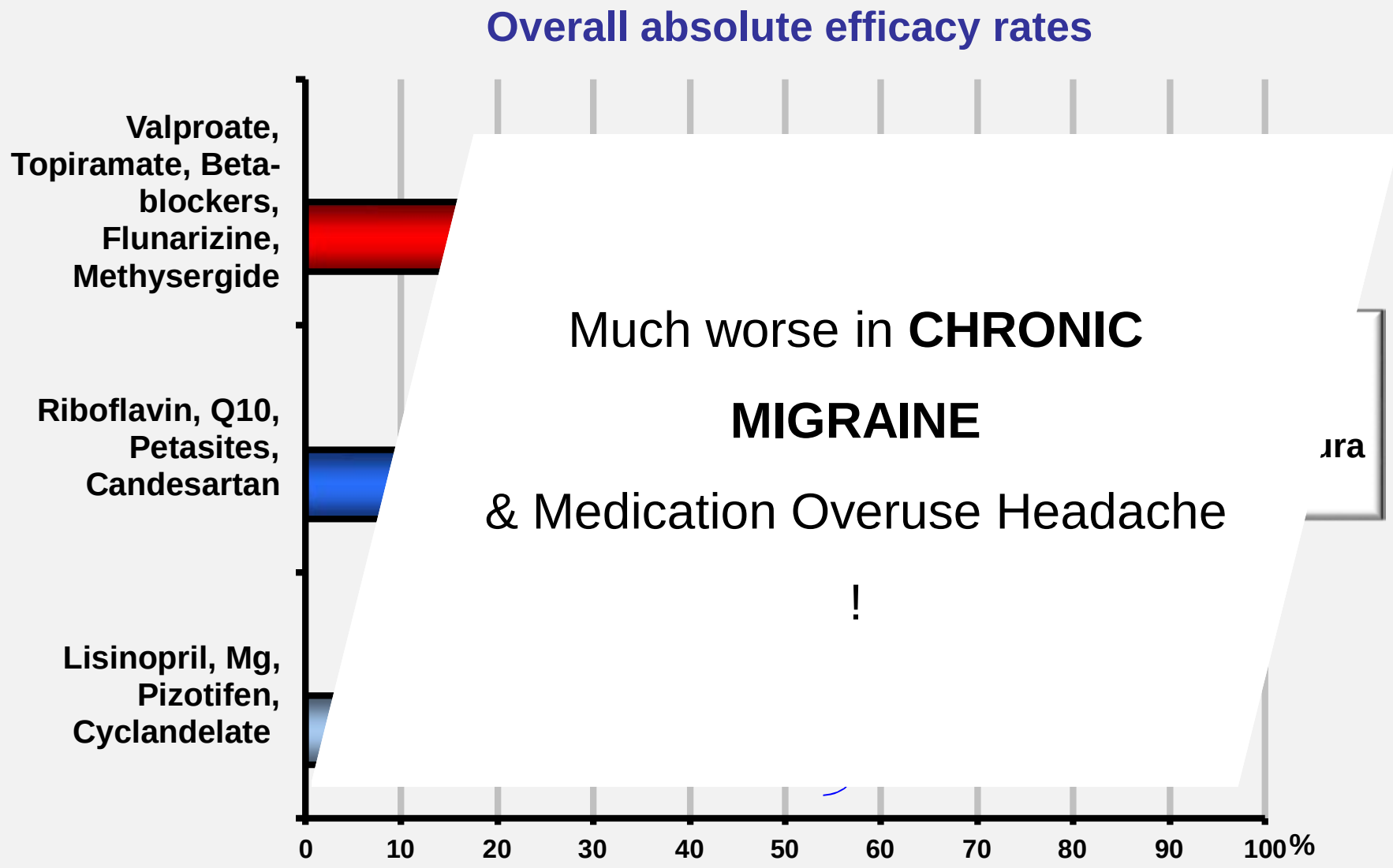
Trigger factors (..of an attack)

- Alcohol
- Post-stress relaxation
- Plasma estrogen decrease
- Intense sensory stimuli
- Missing meals / lack of sleep
- …..

Consider Prevention When..

1. **High disability**:
   migraine significantly interferes with patients' daily routine, despite acute treatment
2. **High frequency**:
   attacks >1/week with risk of CM or MOH
3. **Acute medications not satisfactory**:
   inefficiency, recurrence, contraindications, troublesome AEs, or overconsumption
4. **Patient preference**
5. **Uncommon migraine conditions**
   Hemiplegic Migraine, Basilar Migraine,
   Migraine with Prolonged Aura, Migrainous Infarction

Preventive Anti-Migraine Drugs have limited efficiency



Chronic Migraine : ICHD-IIIb classification

New appendix criteria open for a broader concept of chronic migraine.
Headache Classification Committee. Cephalalgia 2006; 26: 742-746

1.5. Complications of Migraine

A1.5.1. Chronic Migraine

A. Headache (tension-type and/or migraine) on ?á15 days per month for at least 3 months

B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for 1.1 ***Migraine with or without aura***

C. On ?á8 days per month for at least 3 months headache has fulfilled C1 and/or C2 below,

1. typical criteria for **migraine without aura**
2. **treated and relieved** by triptan(s) or ergot **before the expected development of C1** above

D. No medication overuse and not attributed to another causative disorder

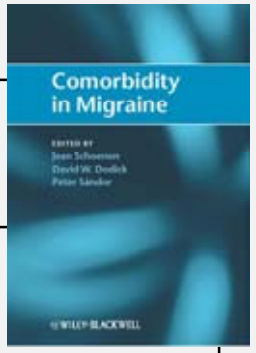
How to improve outcome ?

Novel more effective preventive drugs ? **NONE IN SIGHT**

1. Combine preventive drugs ?
2. **Manage comorbidity**!
3. Use botulinum toxin ?
4. Try non-drug treatments ?
5. **Go for neurostimulation?**
6. **Consider multimodal therapy** ?

2. MANAGING MIGRAINE & COMORBID DISORDER THERAPIES

(In « Comorbidity in Migraine » 2011. Eds Schoenen, Dodick, Sàndor)



Therapeutic strategies based on the reciprocal effects of migraine and comorbid disorder therapies			
Effect of migraine therapy on *comorbid* disorder	Effect of *comorbid disorder* therapy on migraine		
	+	=	-
+	1 THERAPY may suffice	MIG THER (add *COMORD THER* if necessary)	MIG THER and Change *COMORB THER*
=	*COMORB THER* (add MIG THER if necessary)	MIG THER and *COMORB THER*	Change *COMORB THER*
-	*COMORBID THER* and Change MIG THER	Change MIG THER	Change MIG and *COMORBID THER*

Case 5: the difficult headache patient

- 40 yo woman has migraine since age 14
- 3 to 4 disabling attacks per week: 80% without aura (1 disabling perimenstrual att); 20% with strictly visual aura lasting 30-45 min
- she has hypertension since age 30, treated with *amlodipine* and *hydrochlorothiazide*
- she is depressed since 4 years and takes *fluoxetine*
- for chronic low back pain she takes *paracetamol* 1g x 4/wk
- her BMI is 32, waist circumference 105 cm
- she has 3 children, takes an OCP and smokes 20 cig/day
- on TCD she has a grade 2 R-L shunt on Valsalva manoeuvre

Topiramate

Sartan
(cande-, telmi-)

SNRI (Venlafaxine)
or NDRI (bupropion)

Physiotherapy
Reduce analgesics

Dietary counselling

Stop OCP and/or smoking; consider progestin only pill

No closure !

NEUROSTIMULATION METHODS FOR HEADACHES

- deep brain stimulation _ *Rp/ CH*
  (hypothalamic)
- **occipital nerve stimulation** (ONS) _ *Rp/* ***CH + MIG***
  (percutaneous)
- sphenopalatine ganglion stimulation _ Rp/ CH (MIG)
  (pergingival)
- vagus nerve stimulation (VNS) _ *Rp/ pilot*
  (transcutaneous)
- **supraorbital nerve stimulation** (Cefaly®) _ *Rp/* ***MIG***
  (transcutaneous)
- *transcranial* magnetic (TMS) & direct current stimulation (tDCS) _ *Rp/ MIG*

ONS in refractory Migraine

(Magis & Schoenen. Lancet Neurology 2012)

Authors	Number of patients	Follow-up time (months)	Results	Side effects
Popeney & Alo. 2003	25	18.3	64% patients improved by at least 50%	Lead migration Infection
Matharu et al. 2004	8	18	100% of patients improved by at least 50%	Abdominal haematoma Lead migration
Schwedt et al. 2007	8	19	50% of patients improved by at least 50%	Lead migration
Lipton et al. 2009 (A) (PRISM)	125	3	No difference vs. sham	Infection Site pain Sensory symptoms
Marchioretto & Serra 2010 (A)	34	12	Overall 56% frequency reduction	Light
Saper et al. 2011	66	3	39% of patients improved by at least 50% not powered for efficacy	Lead migration Infection
Silberstein et al. 2011 (A)	157	3	Reduction in headache days by 36% the 1° endpoint not met	Infection
Reed et al.2009, 2011 (A) ONS+SNS	44	13	Overall 57% frequency reduction	
Narouze et al. 2011 (A)	12	13	Overall 81% frequency reduction	Slight lead migration
Linder & Reed 2011 (A) ONS+SNS	13	?	Overall 80% frequency reduction (60% pain free)	
Total	500		?%-66% improvement, but not in RCTs	

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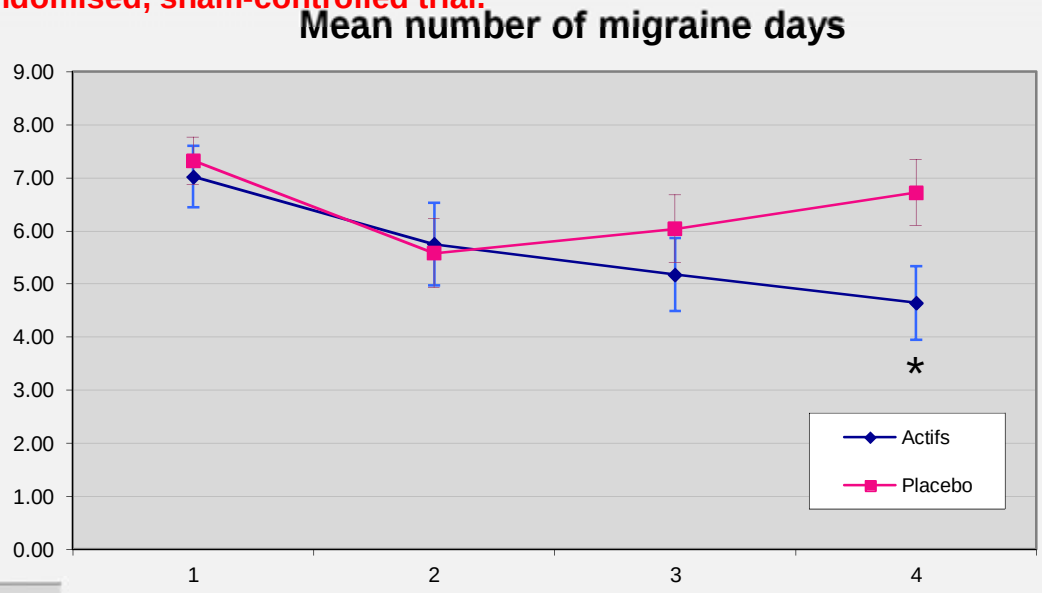
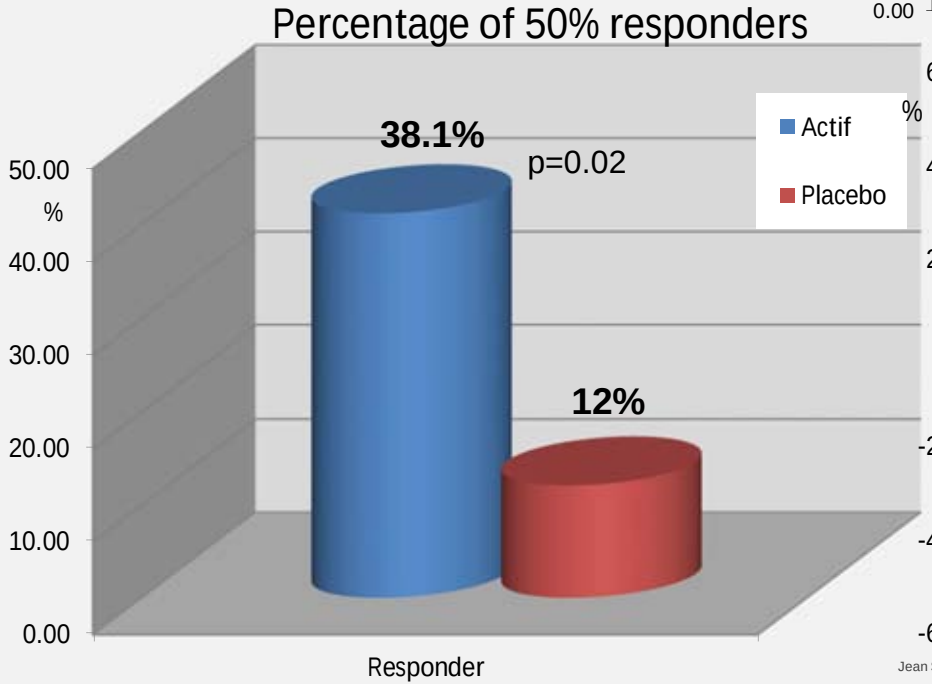
Prevention of (EPISODIC) Migraine by supraorbital transcutaneous neurostimulation using the Cefaly® device (PREMICE):

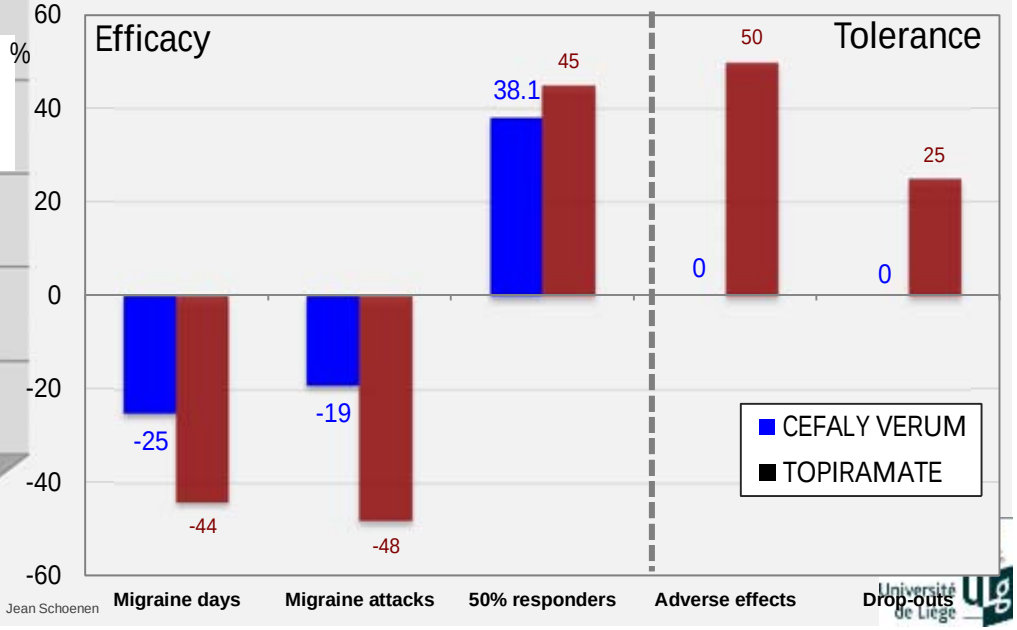
a multi-centre, randomised, sham-controlled trial.

(square pulse, 60Hz, 300?sec, max 14.99 mA, 20 min)

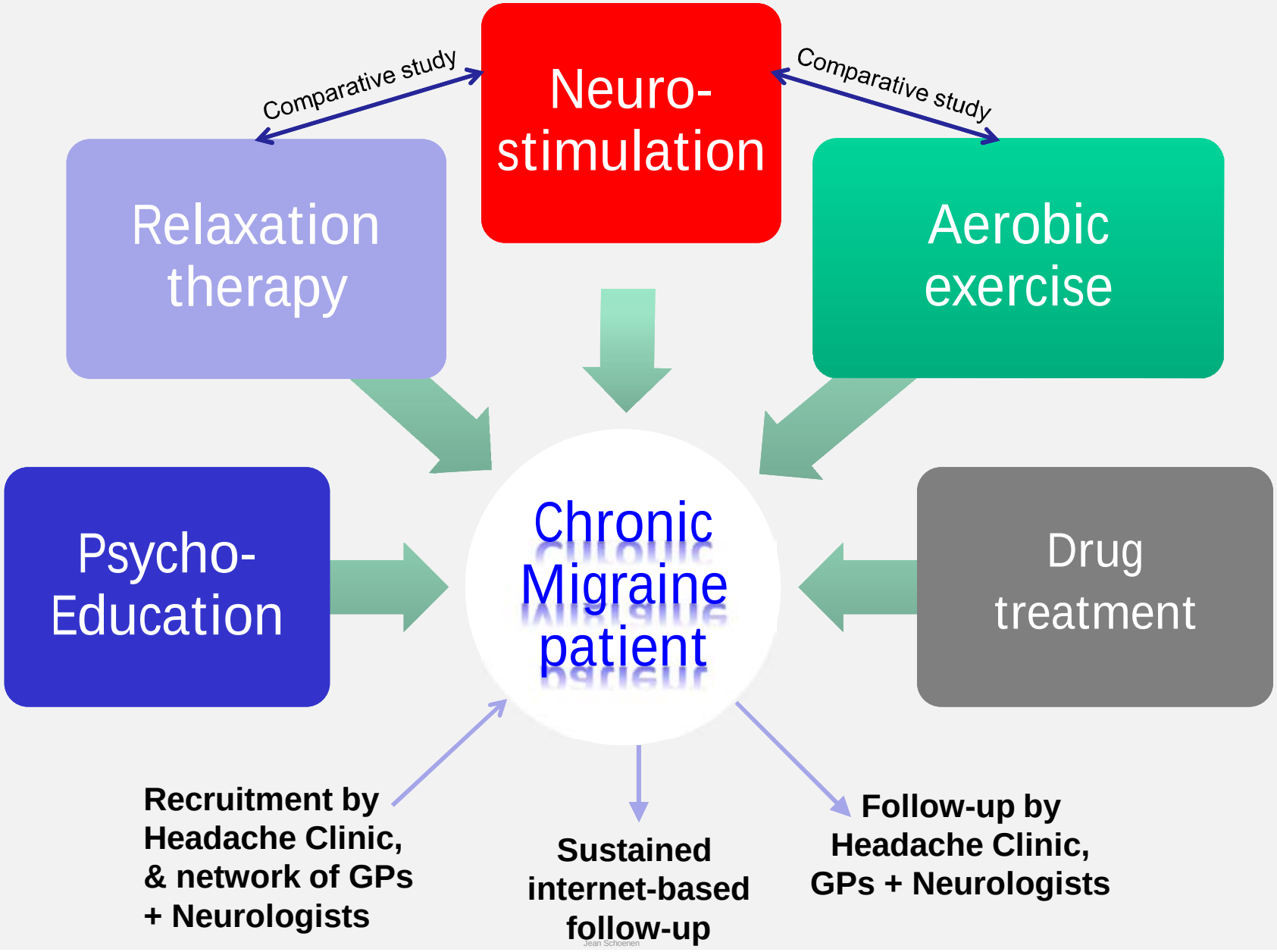
- Migraine without aura: 2-8 attacks/mth
- N= 5 centres (Belgian Headache Society)
- N= 34 active stimulation
- N= 33 sham stimulation
- Duration: 1 month baseline
  +3 months Cefaly °
- Sponsored by STX-Med







Day Clinic for Multimodal Headache Treatment (ULg)



J Headache Pain
DOI 10.1007/s10194-011-0348-y

ORIGINAL

Clinical outcome of a headache-specific multidisciplinary treatment program and adherence to treatment recommendations in a tertiary headache center: an observational study

Charly Gaul · Christina van Doorn · Nadine Webering · Martha Dlugaj · Zaza Katsarava · Hans-Christoph Diener · Günther Fritsche

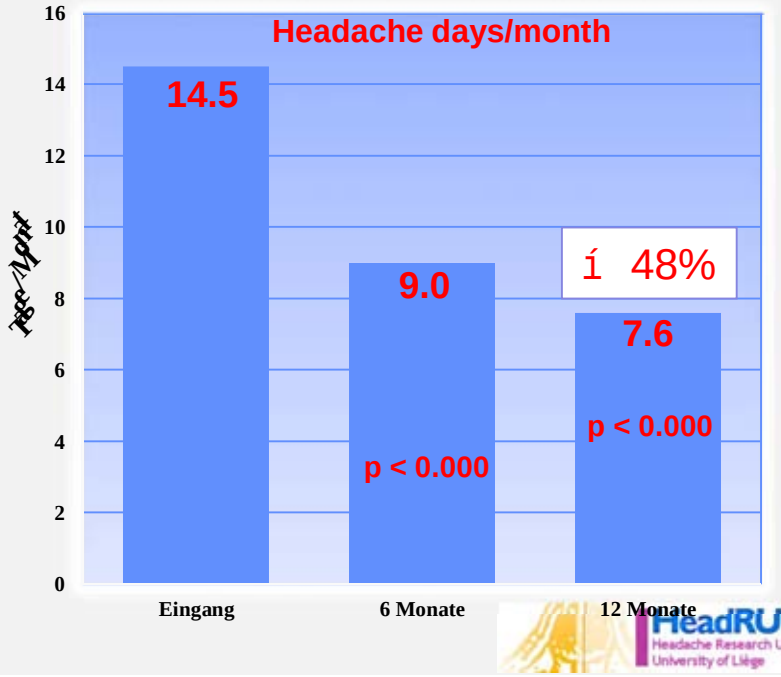
5-day headache specific multidisciplinary treatment programme (MTP)

N= 295 → 210 Mig, 17 TTH, 68 Mig+TTH → 56 MOH

- Headache frequency:
  13.4 days/mth è 8.8 days/mth (**- 34%**)
- ?Q50% reduction (responders) : **43%**
- Mig = TTH > Mig+TTH (OR 3.136)
- Favorable predictors:
  high headache frequency,
  adherence to lifestyle modifications
- Adherence to pharmacotherapy: 35%,
  relaxation: 61%,
  aerobic exercise: 72%

Jean Schoenen

KOPFSCHMERZKLINIK BERLIN
(Wallasch T.)



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Tension-type Headache

= a featureless headache

TTH: from pathophysiology to therapy

Combination

Stress management

Relaxation therapies
(EMG Biofeedback…)

Tricyclics

Physical therapy

CNS
- stress coping
- depressive mood
- central dysnociception
- central sensitisation

PNS
- muscle strain
- myofascial factors
- peripheral sensitisation

Acupuncture (?)

Botulinum toxin: **not effective**

Acute pharmacotherapy

CLUSTER HEADACHE: natural history

Cluster headache

Episodic (90%)

Chronic (10%)

- Cluster period lasts for more than one year without remission or remission lasts less than 1 month

Episodic → Chronic 13%

Chronic → Episodic 33%
(Manzoni)

Cluster-free intervals
1.1 yr → 3.5 yr *(Igarashi)*

Manzoni GC et al. *Cephalalgia*. 1991.
Igarashi H, Sakai F. *Cephalalgia*. 1996.

ICHD-II Cephalalgia. 2004.

1-2% treatment-resistant ?

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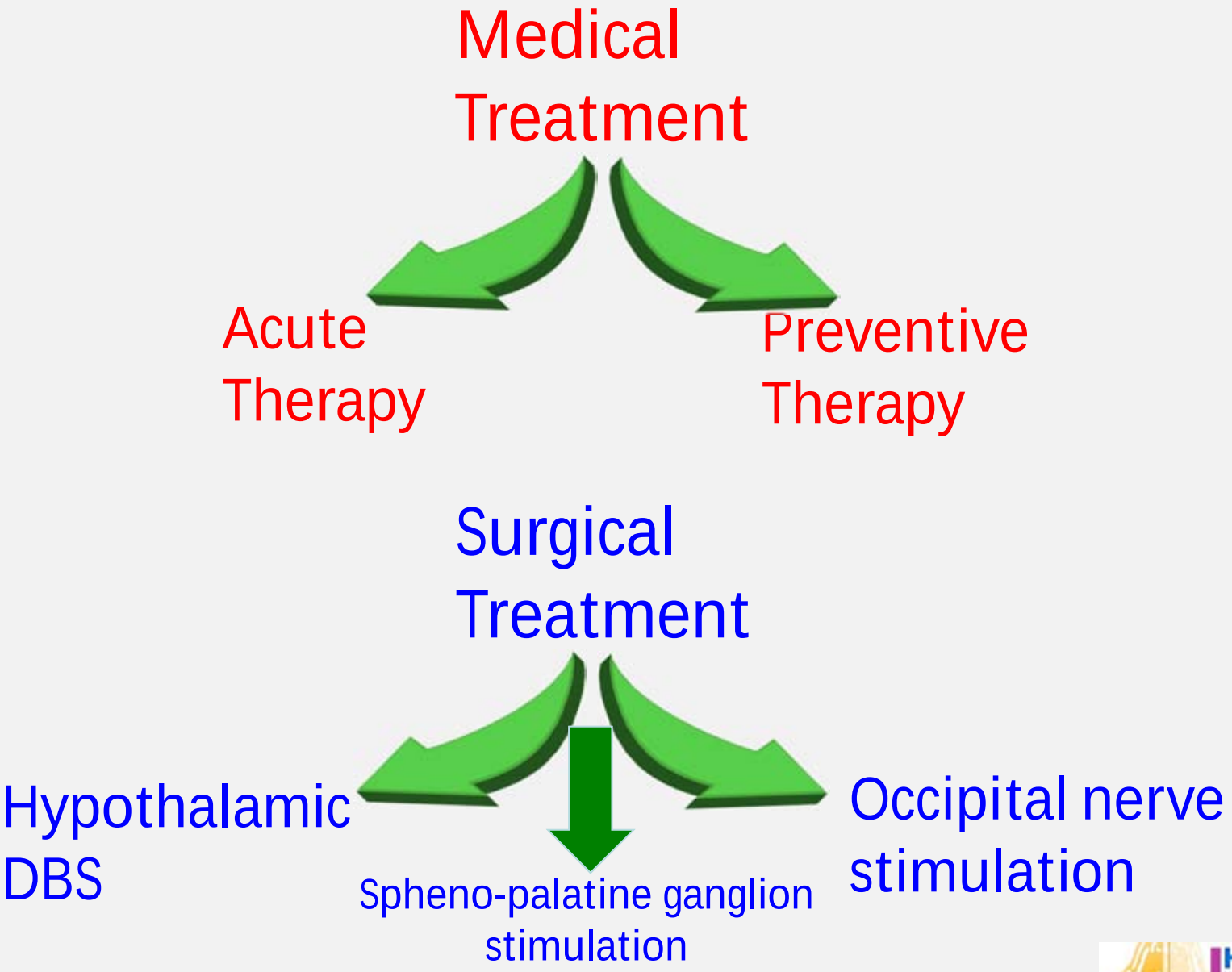
CLUSTER HEADACHE: management

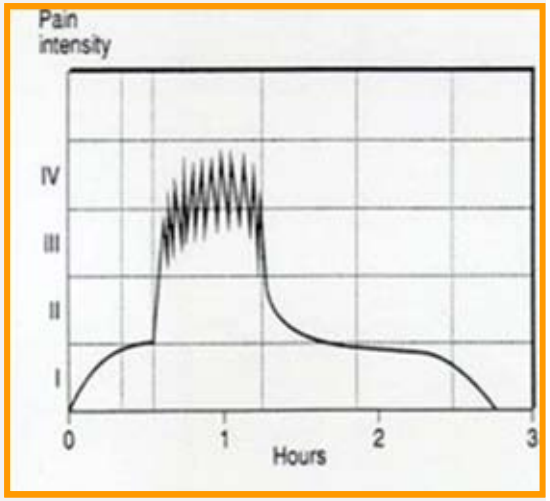


CLUSTER HEADACHE: management

Acute Therapy

Established

- Oxygen: 100% @ 10-12 L/min, mask
- Sumatriptan: 6mg subcut. inj.
- Dihydroergotamine mesylate IV/IM/SQ 0.5 – 1.0 mg
- Zolmitriptan 10mg nasal spray
- Lignocaine intranasal (4-6%)
- Bonain's solution intranasal (cocaïne, menthol, phenol) (Guerrier 1984)
- DHE nasal spray (2-4mg)



Promising

- CGRP antagonists?

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CLUSTER HEADACHE: management

Preventive Therapy

Transitional

- Long-acting steroid + Lidocaine (2%-0.3-1 ml)
- Responder rate: 60% (1,2)
- AEs: -local discomfort
  - alopecia (1%) (3) = avoidable by deep injections

Steroids

- **Suboccipital** : long acting steroid
- Oral : Prednisone 60 mg daily for 3 days, then 10 mg decrements every 3 days

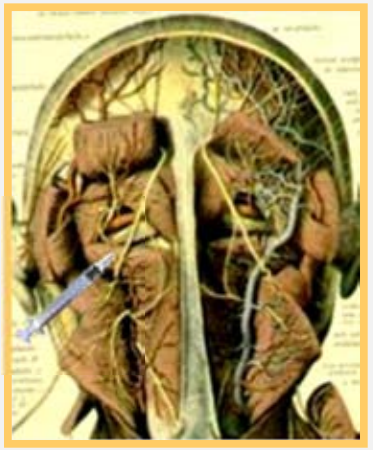
Ergotamine tartrate

(1 – 2 mg po / suppository daily)

Dihydroergotamine

(0.5 – 1.0 mg sc / im q 8 – 12 hrs)

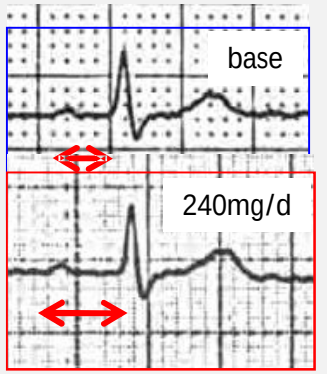
1. Ambrosini et al Cephalalgia 2003
2. Afridi et al., Pain 2006;122:126
3. Shields et al., Neurology 2004;63:2193



CLUSTER HEADACHE: management

Preventive Therapy

Maintenance



(Cohen *et al*. 2007)

Verapamil (480 – 720 mg / day)

(ECG 10ds after dose change after 240mg daily)

Lithium carbonate (150 – 300 mg tid; serum level: 0.8-1 mEq/l)

Combination of verapamil & lithium

Methysergide (2 mg tid; up to 12 mg daily)

Anticonvulsant (topiramate..)

Melatonin

NEUROSTIMULATION METHODS FOR HEADACHES

- **deep brain stimulation** _ *Rp/ CH*
  (hypothalamic)
- **occipital nerve stimulation** (ONS) _ *Rp/* ***CH + MIG***
  (percutaneous)
- sphenopalatine ganglion stimulation _ Rp/ CH (MIG)
  (pergingival)
- vagus nerve stimulation (VNS) _ *Rp/ pilot*
  (transcutaneous)
- supraorbital nerve stimulation (Cefaly®) _ Rp/ MIG
  (transcutaneous)
- *transcranial* magnetic (TMS) & direct current stimulation (tDCS) _ *Rp/ MIG*

ONS trials in drCCH

(Magis & Schoenen. Lancet Neurology 2012)

Authors	Number of patients	Follow-up (months)	Results : number of patients with ?50% improvement	Adverse effects
Magis et al. 2007 & 2011	14	36.8	12	Empty battery
Burns et al. 2007& 2009	14	17.5	5	Empty battery Electrode migration Infection
Proietti Cecchini et al. 2009 (A)	13	21	8	Empty battery
Lara Lara et al. 2009 (A)	6	6-15	4	
De Quintana et al. 2010	4	6	4	
Salomet al. 2010 (A)	14	?	7	Infection
Müller et al. 2010	10	12	9	Infection
Fontaine et al. 2011	13	14.6	10	Empty battery
Strand et al. 2011	3	12	2	
TOTAL	91		61 (67%)	

1st sham-controlled trial (ICON) = ongoing (Wilbrink et al. Cephalalgia 2013)

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Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study

Cephalalgia
0(0) 1–15
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DOI: 10.1177/0333102412473667
cep.sagepub.com
SAGE

Jean Schoenen[1], Rigmor Højland Jensen[2], Michel Lantéri-Minet[3], Miguel JA Láinez[4], Charly Gaul[5], Amy M Goodman[6], Anthony Caparso[6] and Arne May[7]

Study designed to investigate the safety and efficacy of the ATI Neurostimulation System™ for SPG stimulation for the treatment of chronic cluster headache.

- On-demand, patient-controlled therapy via Remote Controller

2a

Remote Controller

ATI Neurostimulation System™

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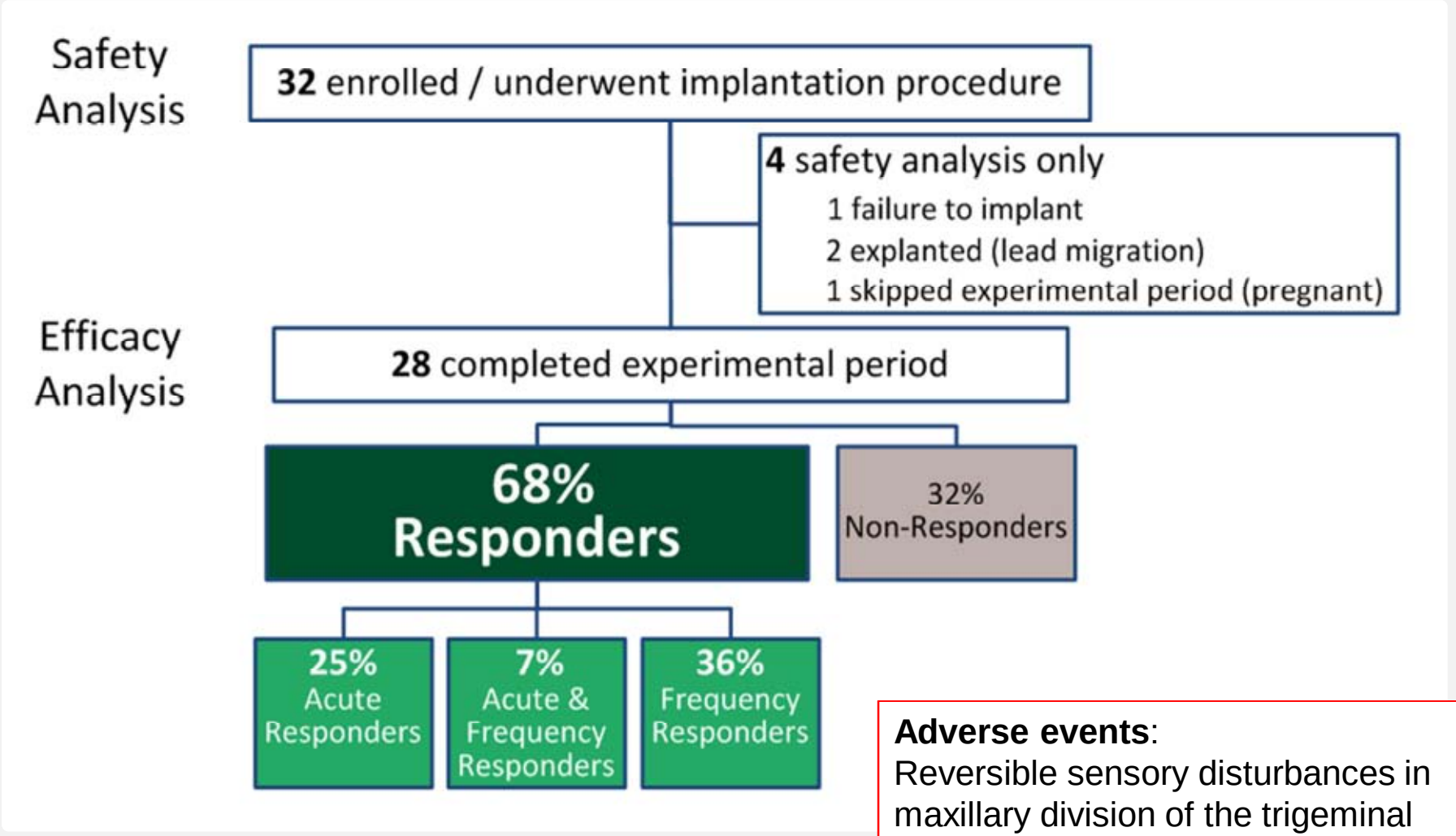
Pathway CH-I: **RESPONDERS**



Adverse events:
Reversible sensory disturbances in maxillary division of the trigeminal nerve
(81% of patients)

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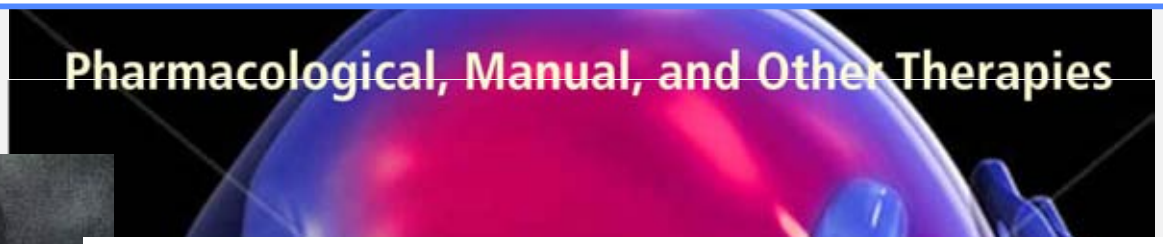
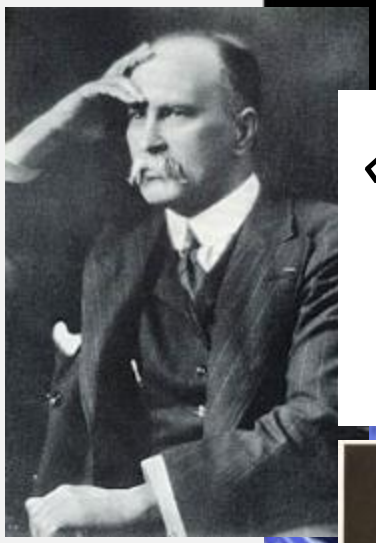
César Fernández de las Peñas | Leon Chaitow | Jean Schoenen

More research needed…

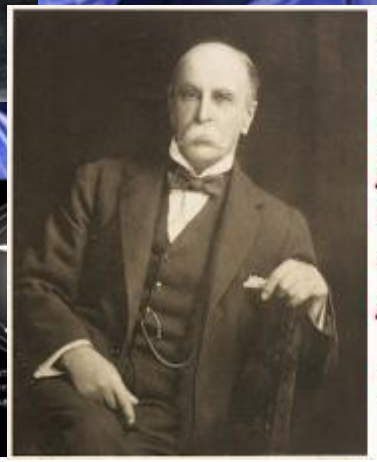
- to provide scientific evidence for therapies
- to customize treatment to individual patients





« You recognize a good doctor by the way he manages a headache patient. »

(Sir William Osler)



"It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has."

William Osler

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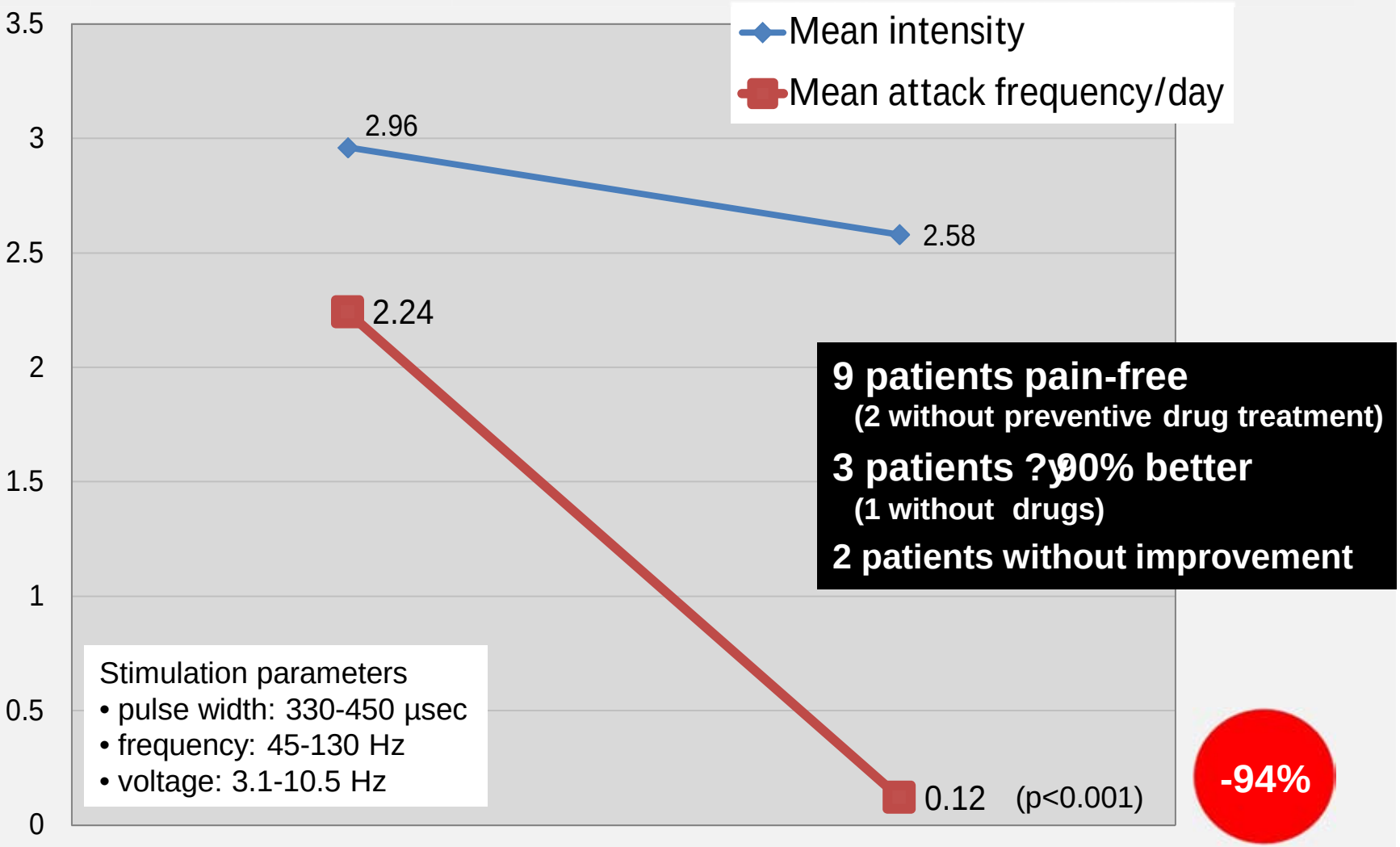
ONS in drCCH: long term outcome

(Magis et al. Headache 2011 in press)



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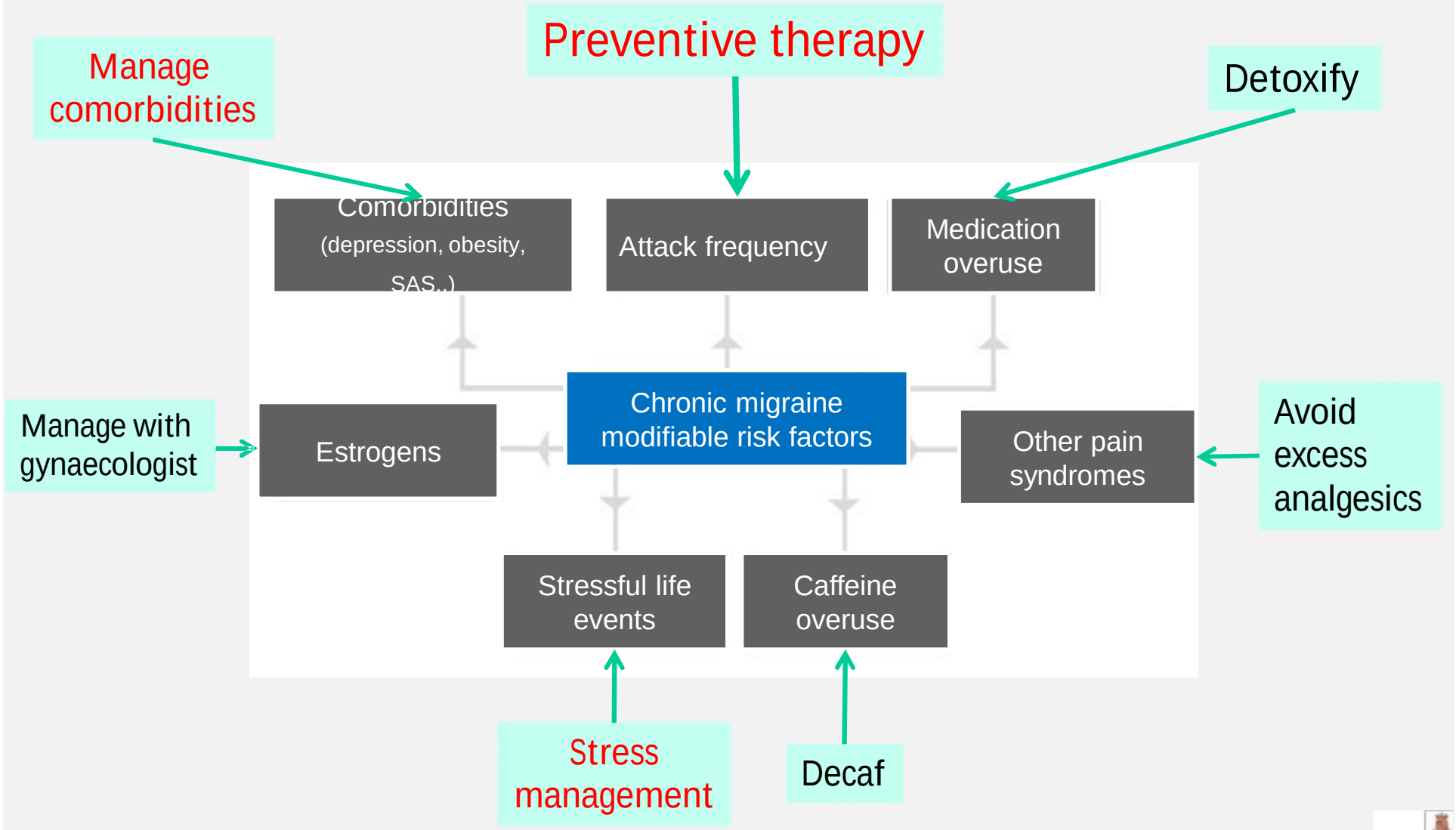
Modifiable risk factors
for progression to chronic migraine and their possible management



Mofified after Bigal E *et al*. *Curr Opin Neurol* 2009;22:269–276.

What is refractory cluster headache ?

(Towards a de?nition of intractable headache for use in clinical practice and trials

PJ Goadsby, J Schoenen, MD Ferrari, SD Silberstein, D Dodick. Cephalalgia 2006)

In cluster headache, failure of at least four classes, where two should come from 1–3

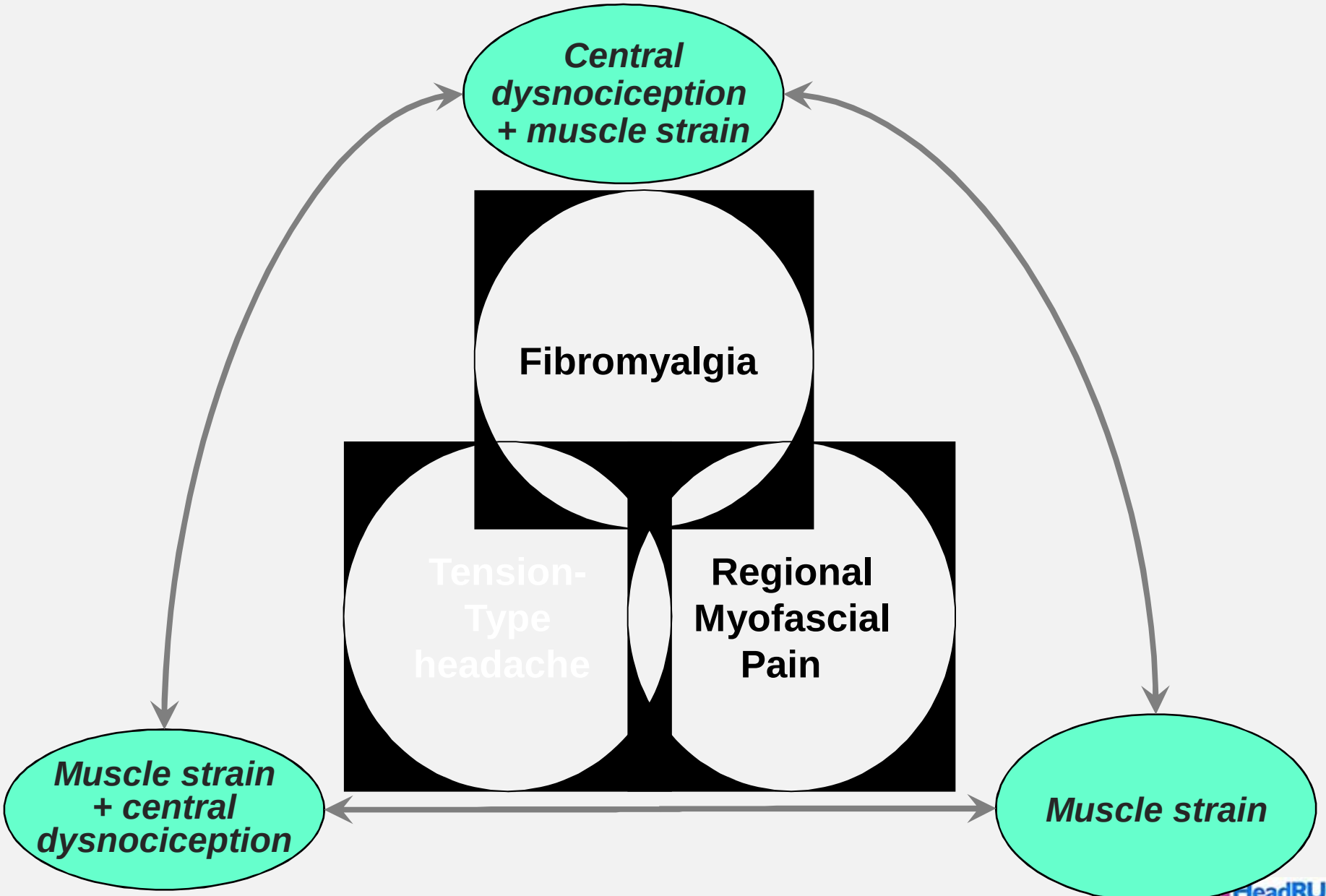
1 Verapamil
2 Lithium
3 Methysergide
4 Melatonin
5 Topiramate
6 Gabapentin

+ suboccipital injection of Diprophos ° -lidocaïne
(Ambrosini et al. Pain 2005)

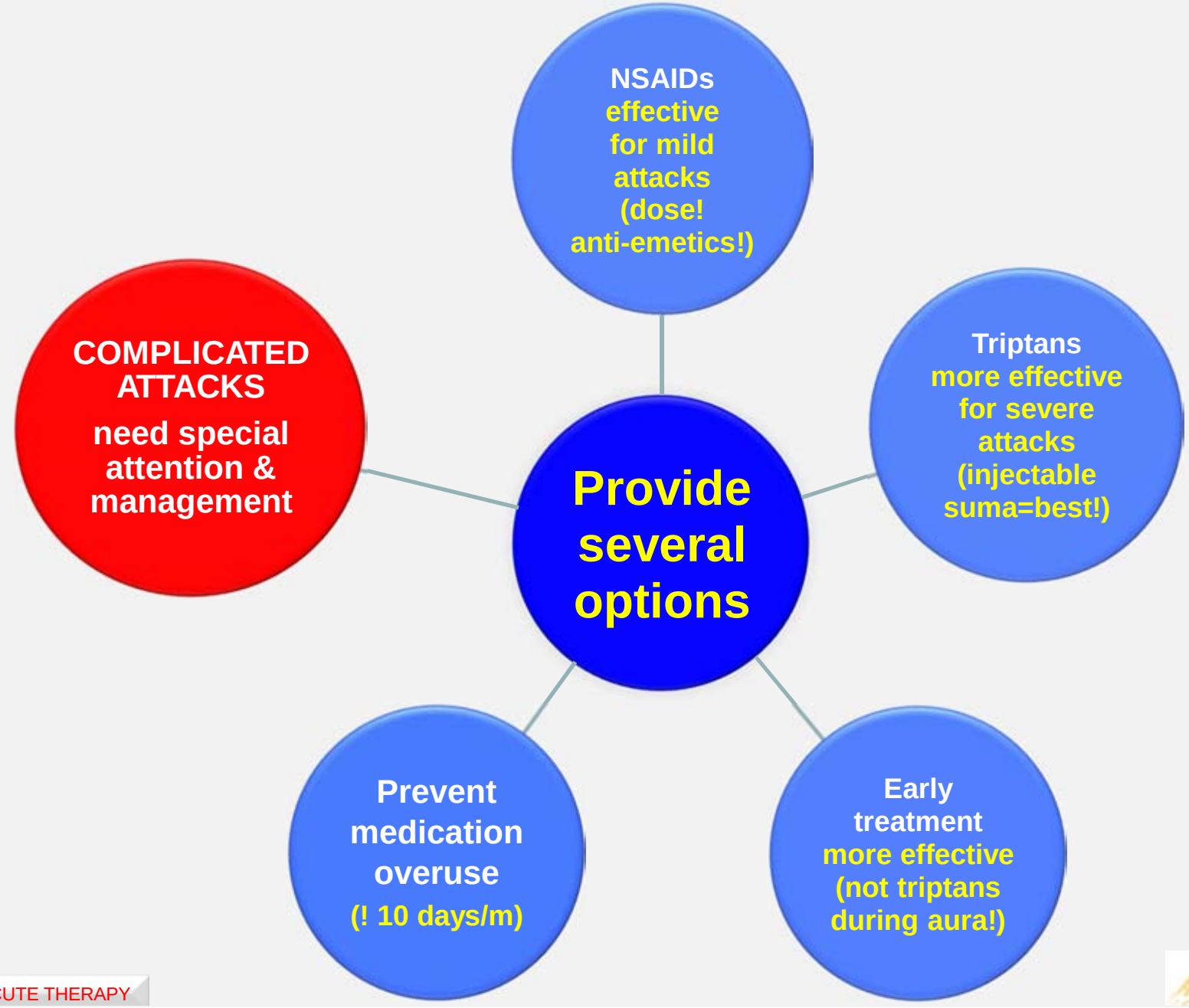
DD paroxysmal focal neurological signs / symptoms

	TIA	EPILEPSY	MIGRAINE
Begin	sudden	sudden	slow
Progression	none	fast	slow
Different symptoms	simultaneous	in sequence	in sequence
Quality	negative	positive	negative+positive
if visual		couloured	black & white
Territory	vascular	cortical	cortical
Duration	short (10-15 min.)	short (min.)	long(ish) (1/2-1 h)

The nosographic matrix of TTH



Acute Migraine Therapy: take home messages



Case 7

- 40 yo woman has migraine since age 14
- 3 to 4 disabling attacks per week: 80% without aura; 20% with strictly visual aura lasting 30-45 min
- she has hypertension since age 30, treated with *amlodipine* and *hydrochlorothiazide*
- she is depressed since 4 years and takes *fluoxetine*
- for chronic low back pain she takes *paracetamol* 1g x 4-6d/wk
- her BMI is 32, waist circumference 105 cm
- she has 3 children, takes an OCP and smokes 20 cig/day
- on TCD she has a grade 2 R-L shunt on Valsalva manoeuvre

What to do ?

Case 6

• this 32 yo woman has migraine without aura and 4 attacks per month. She was not improved by a preventive treatment with beta-blockers and put on topiramate: 50mg/d for 1 week, then 100mg/d…….

• she abandoned topiramate because of fatigue, „manque de mot“ and paresthesias after 10 days.

• as she also had overweight, we tried topiramate again on the following schedule: 25mg nocte for 2 weeks, then 2x25mg/day.
The patient is happy : 1 mild attack/month, but.. she didn‘t loose weight

Go slow and low,…but also long enough !!

Novel devices for non-invasive transcutaneous Vagus Nerve Stimulation

NEUROCORE

INVESTIGATIONAL PLAN

NONINVASIVE NEUROSTIMULATION OF THE VAGUS NERVE WITH THE GAMMACORE™ DEVICE FOR THE RELIEF OF PAIN, NAUSEA AND RELATED SYMPTOMS ASSOCIATED WITH MIGRAINE

No evidence yet !

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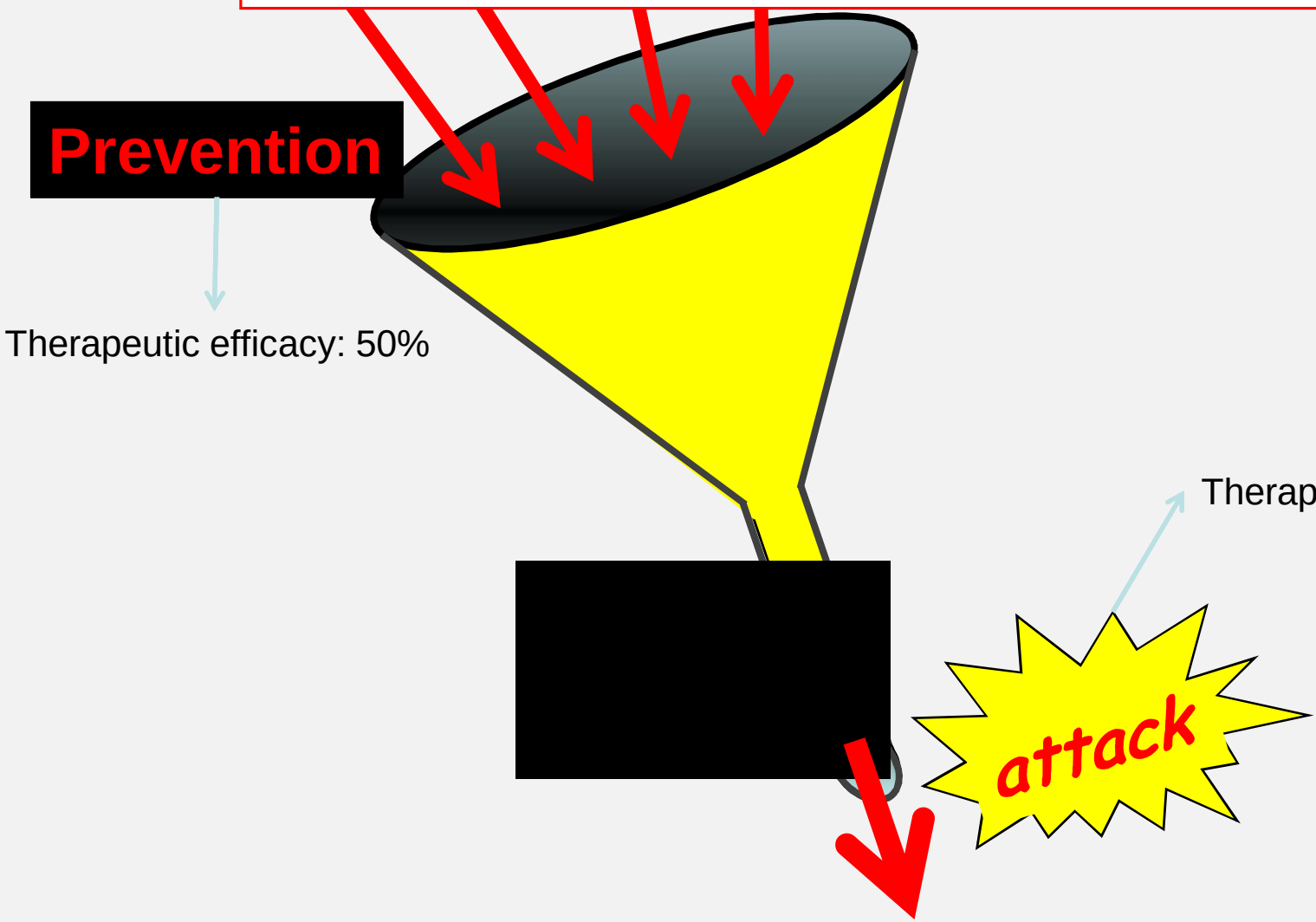
Goals of Preventive Treatment

- Reduce attack frequency, severity, and duration
- Improve responsiveness to Rx of acute attacks
- Improve function, QoL and reduce disability
- Prevent disease chronification
- Reduce costs
- ??Prevent brain lesions (MRI)
- ??Prevent stroke risk increase in MA

The « funnel model » of migraine

Migraine has a complex pathophysiology

- **genotypes : multiple genes, variable penetrance...**
- **epigenetic factors : hormonal, psychological...**



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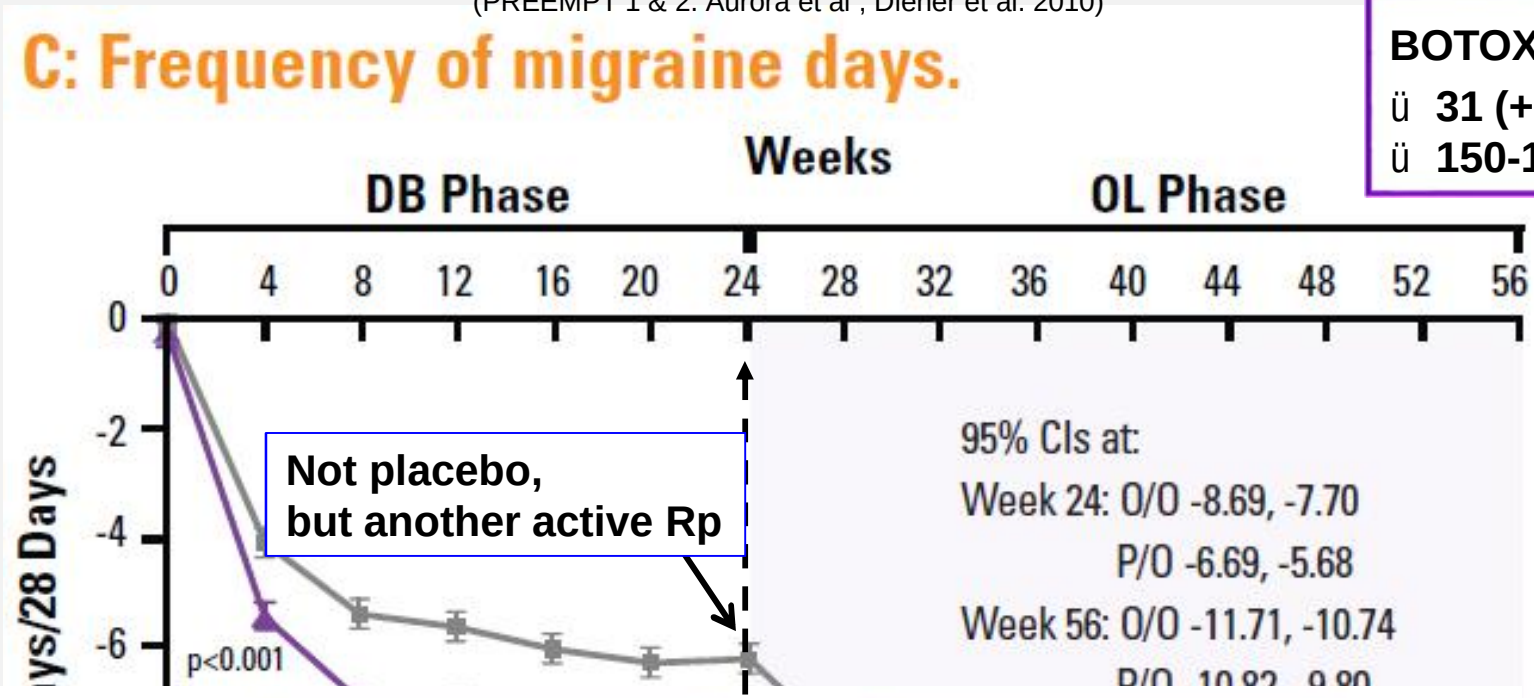
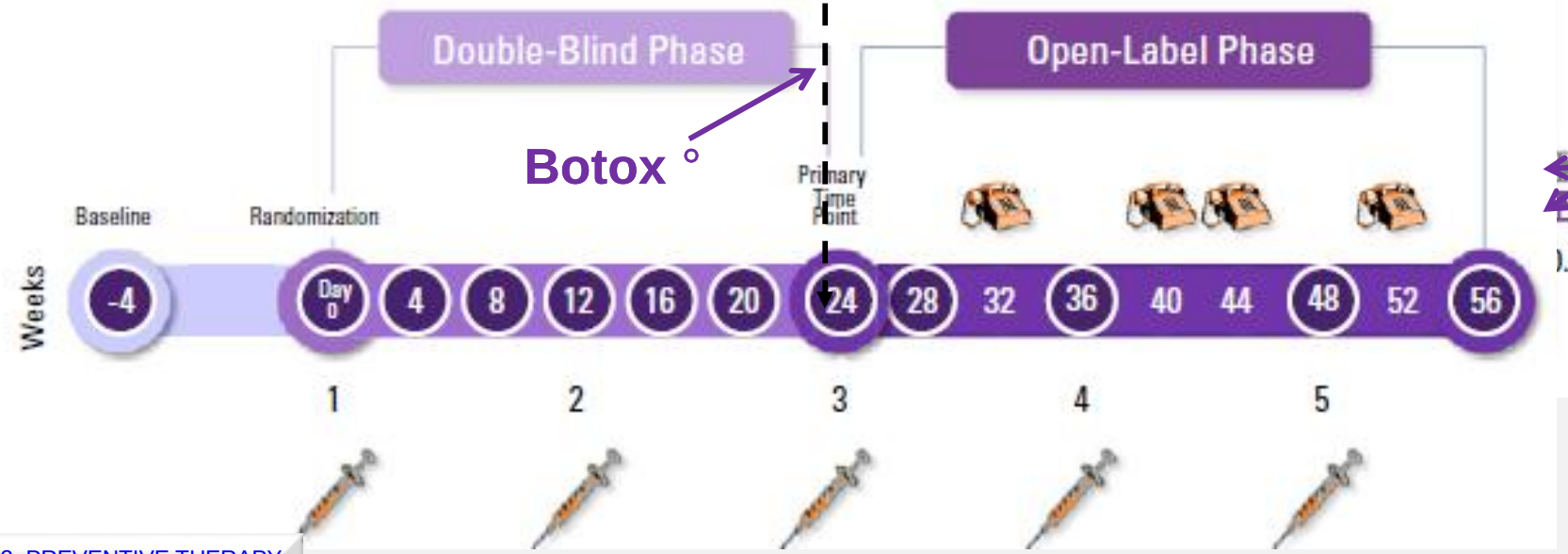
Effect of onabotulinumtoxinA (Botox °) in CHRONIC Migraine

(PREEMPT 1 & 2. Aurora et al , Diener et al. 2010)

BOTOX °

- ü **31 (+8) inj sites**
- ü **150-195 U**

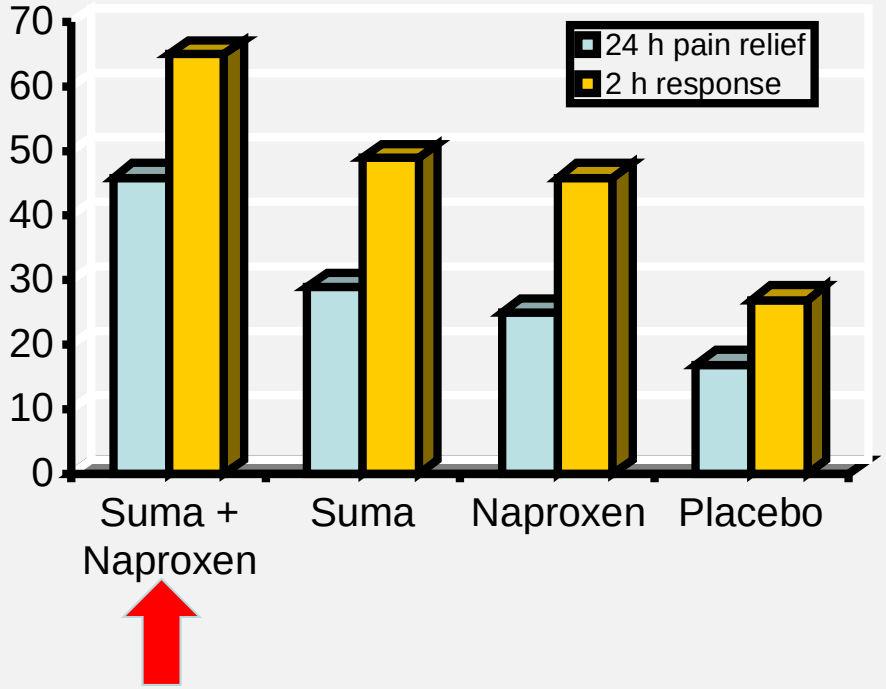




Improving efficacy by combining a triptan to an NSAID

Treximet ° (Suma+naproxen)

(Brandes et al, JAMA 2007)

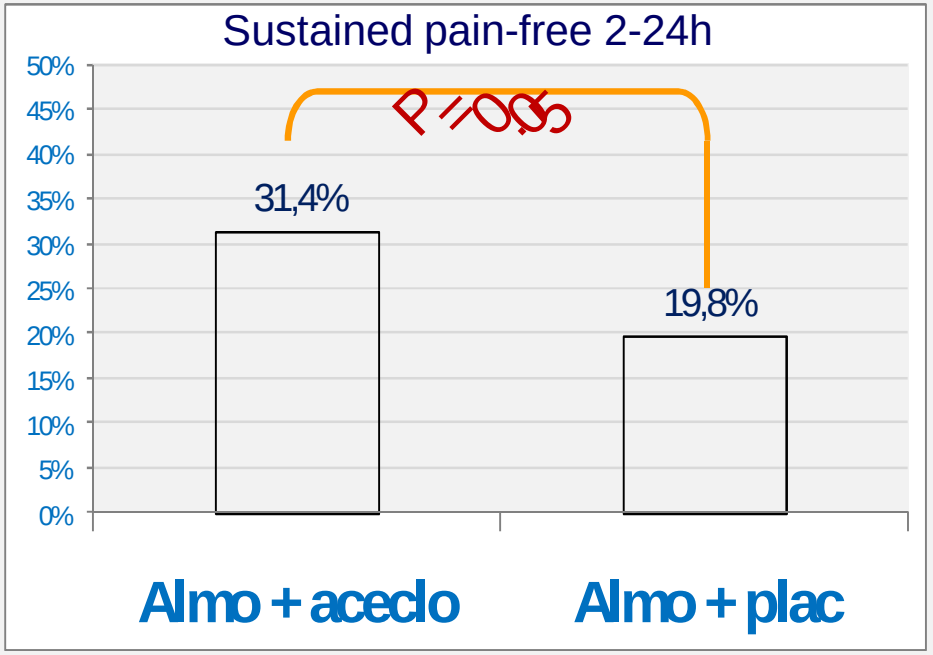


Others:

- Rizatriptan + paracetamol (phase III compl)
- Rizatriptan + caffeine (phase III compl)

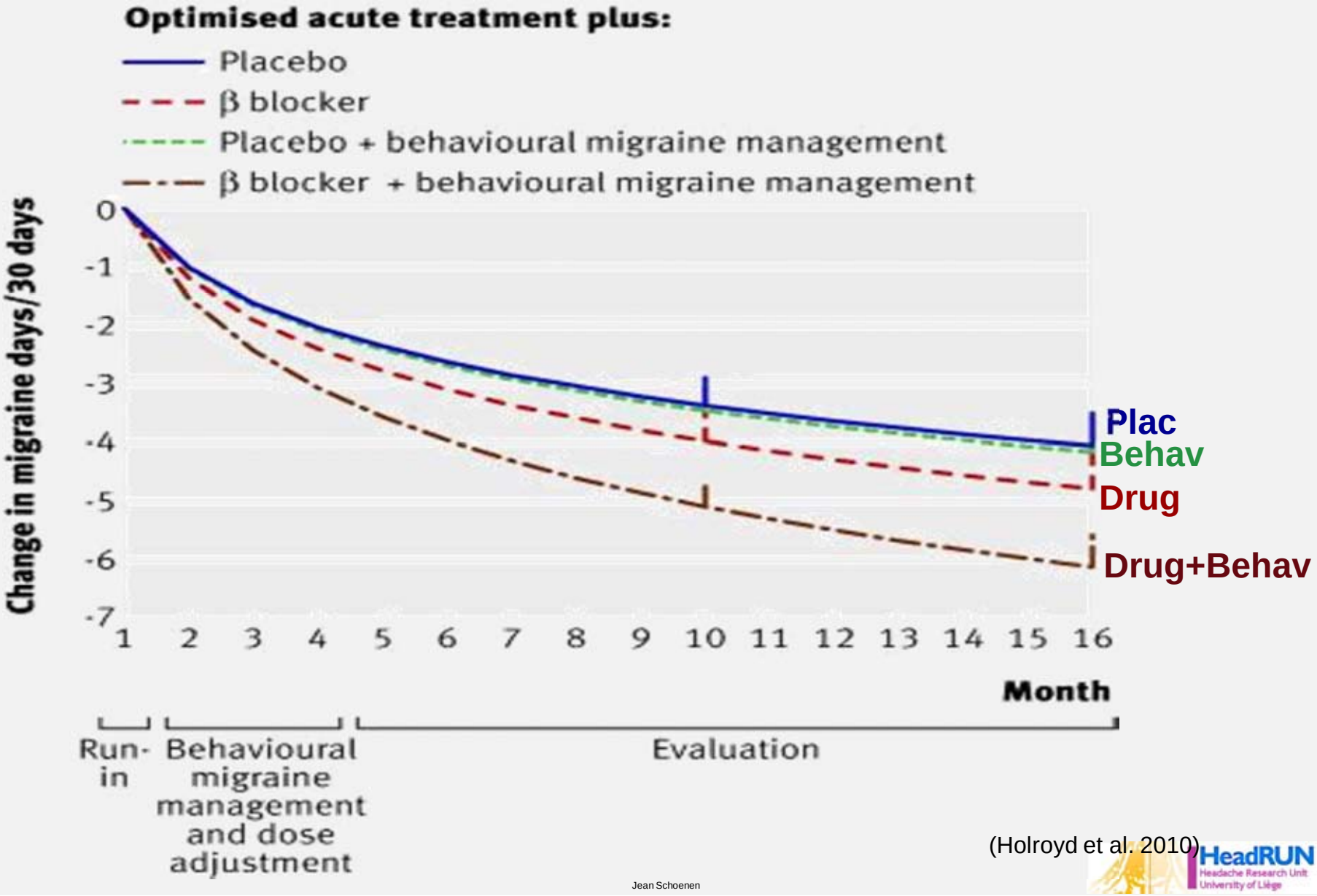
Almotriptan and aceclofenac

(Schoenen et al. Cephalalgia 2008)



Combining drug and non-drug teatments

(beta-blocker + behavioural therapy)



(Holroyd et al. 2010)

NEUROSTIMULATION FOR MIGRAINES

- **occipital nerve stimulation (ONS)**
- sphenopalatine ganglion stimulation
- vagus nerve stimulation (VNS)
- **transcutaneous stimulation (Cefaly?)T**
- transcranial magnetic stimulation (TMS) & direct current transcranial stim. (dTCS)

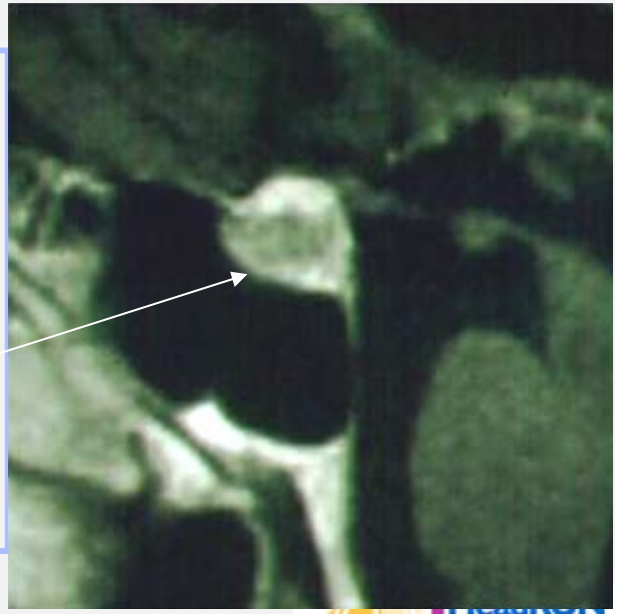
Case 2

- 57 y.o. male has since 10 years attacks of right supraorbital pain
- pain is of moderate intensity, lasts +/- 2 hrs and occurs 2-3 times/week
- it is associated with ipsilateral conjunctival injection, tearing and stuffy nose
- attacks can be precipitated by alcohol

• previous diagnoses : «trigeminal neuralgia», « cluster headache »

- CT scan : pituitary adenoma
- blood chemistry : increased prolactin
- disappearance of attacks shortly after starting treatment with bromocryptine

• diagnosis : macroprolactinoma



Fixed unilateral headaches

1. Trigeminal autonomic cephalalgias (TACs) -
   Hemicrania continua (ICHD-IIIb 3.4)
2. Chronic migraine (ICHD-IIIb 1.3)
3. Nummular headache (ICHD-IIIb 4.8)
4. Secondary headaches
   Cervicogenic headache, occipital neuralgia, ENT.....

Chronic headaches : ICHD-III beta

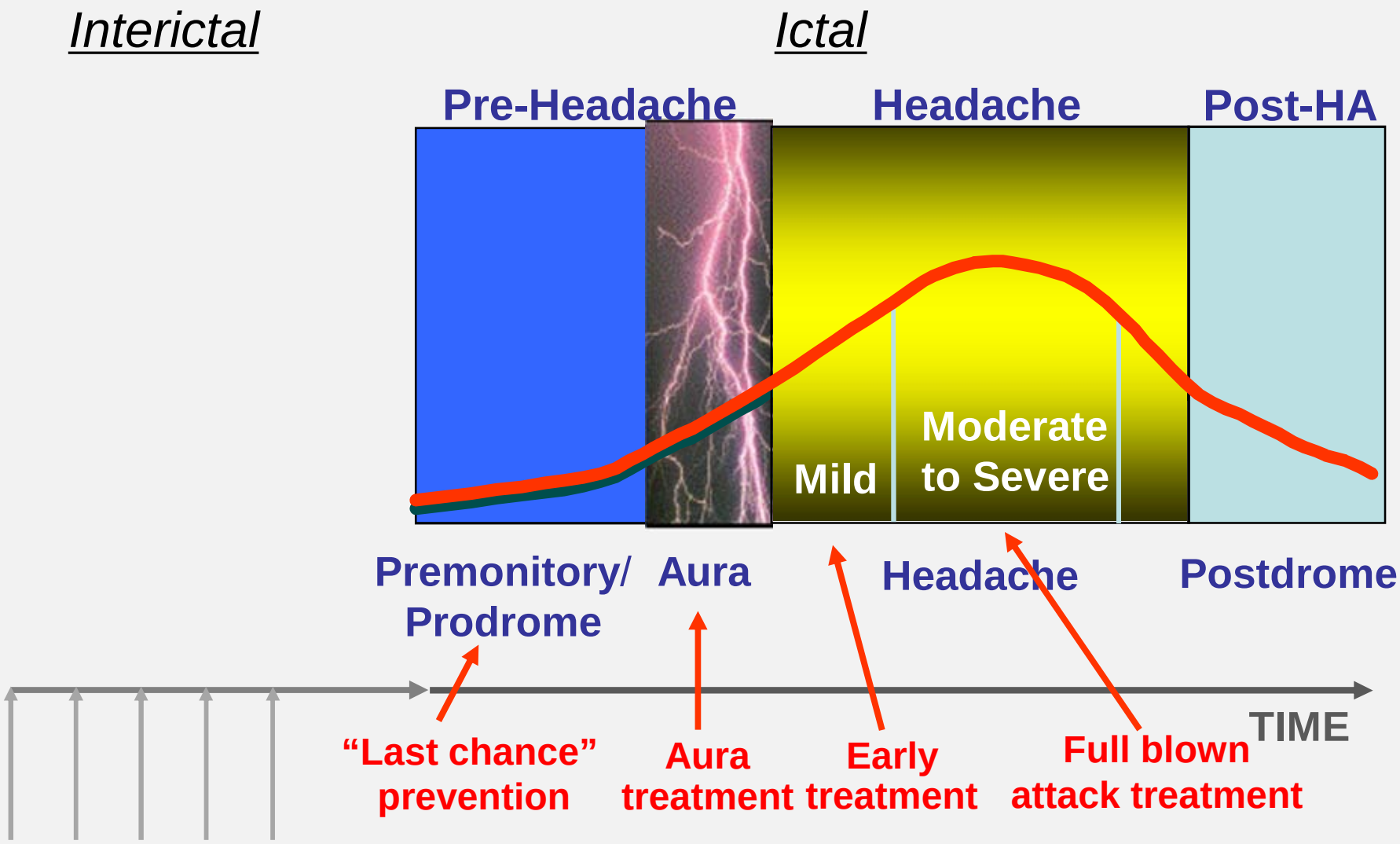
Primary headaches

1. Chronic migraine (ICHD-III 1.3)
2. Chronic tension-type headache
   (ICHD-III 2.3 but with previous history of episodic TTH)
3. Trigeminal autonomic cephalalgias (ICHD-II 3.2)
4. Hemicrania continua (ICHD-III 3.4)

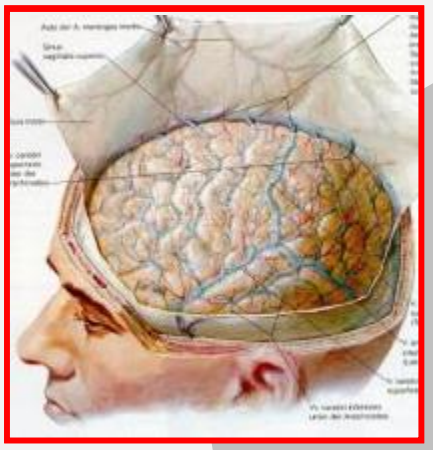
Secondary headaches

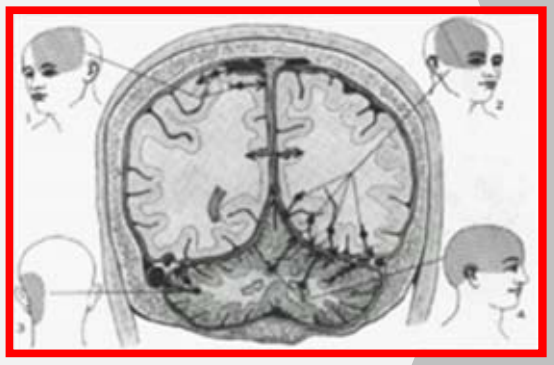
1. Medication overuse headache (ICHD-III 8.2)
2. Cervicogenic headache (ICHD-III 11.2.1)
3. Post-traumatic headache (ICHD-III 5.)

Migraine Attacks are multi-stage sequential processes



Where do acute anti-migraine drugs act ?





MIGRAINE-like HEADACHE

PAG

face

V_{1} som.

5-HT1F

5-HT1B/D

pial / dural vessel

NO

CGRP

V_{1} visc

NO

CGRP

Trigeminal nucleus caudalis

neck

C_{2} som

BRAIN STEM

Ditans ì

Gepants î

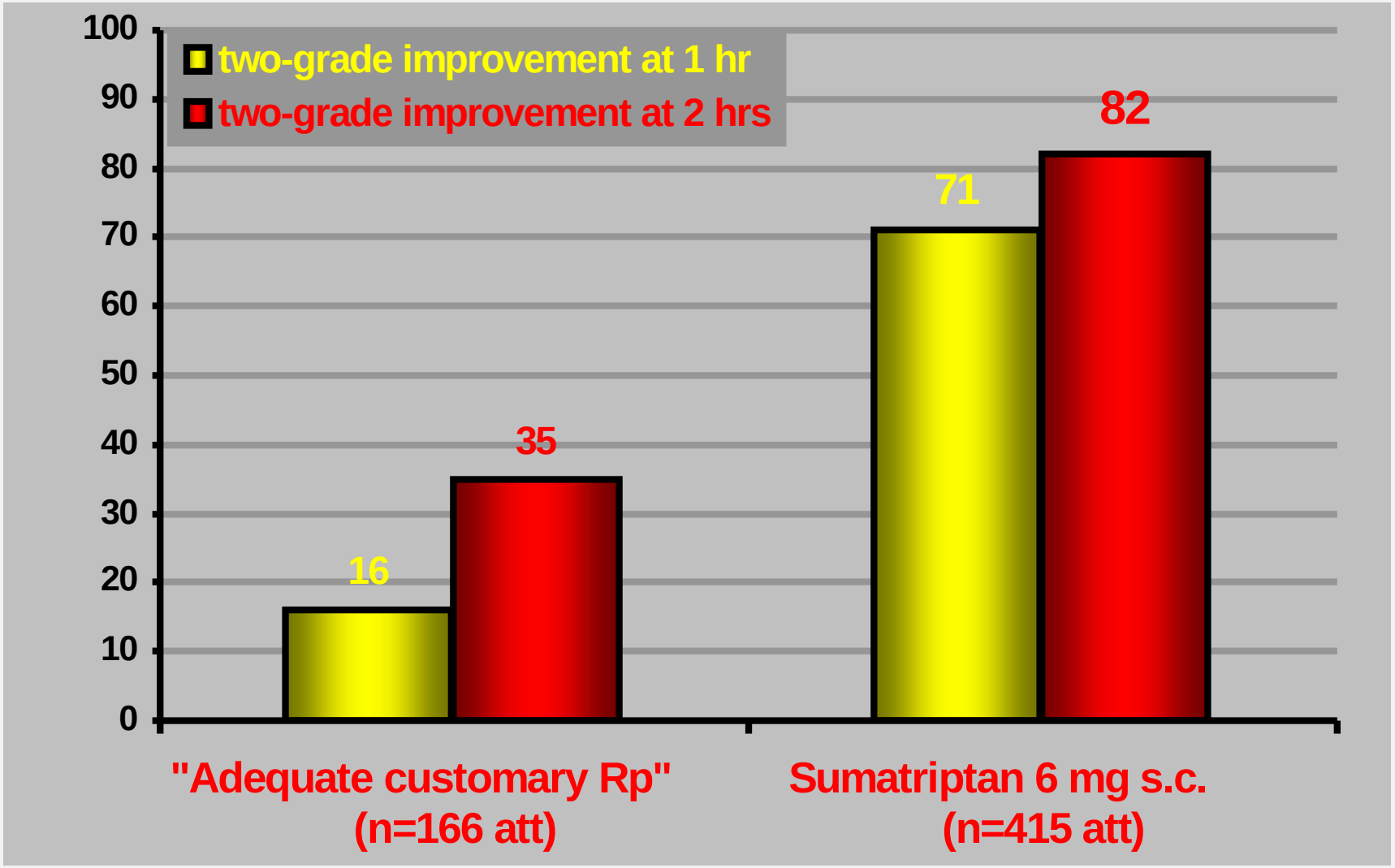
Triptans

Receptors
- glutamatergic
- vanilloid
- cannabinoid
- adenosine
- nociceptin
- ..

The TRIGEMINOVASCULAR SYSTEM :
the main pain-signalling system of the viscera brain

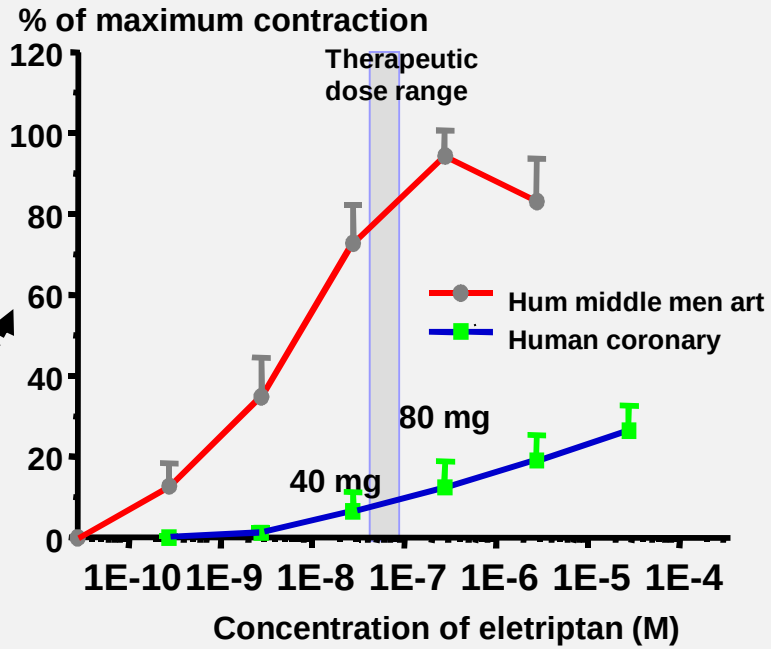
Two-grade improvement at 1 and 2 hrs : « adequate » customary treatment vs Sumatriptan 6mg s.c.

(Schoenen et al. Cephalalgia 1994; 14: 55-63)



Shortcomings of triptans

- Incomplete efficacy
- High recurrence rate
- Triptan-specific side effects
- Propensity to induce MOH
- Cardiovascular safety



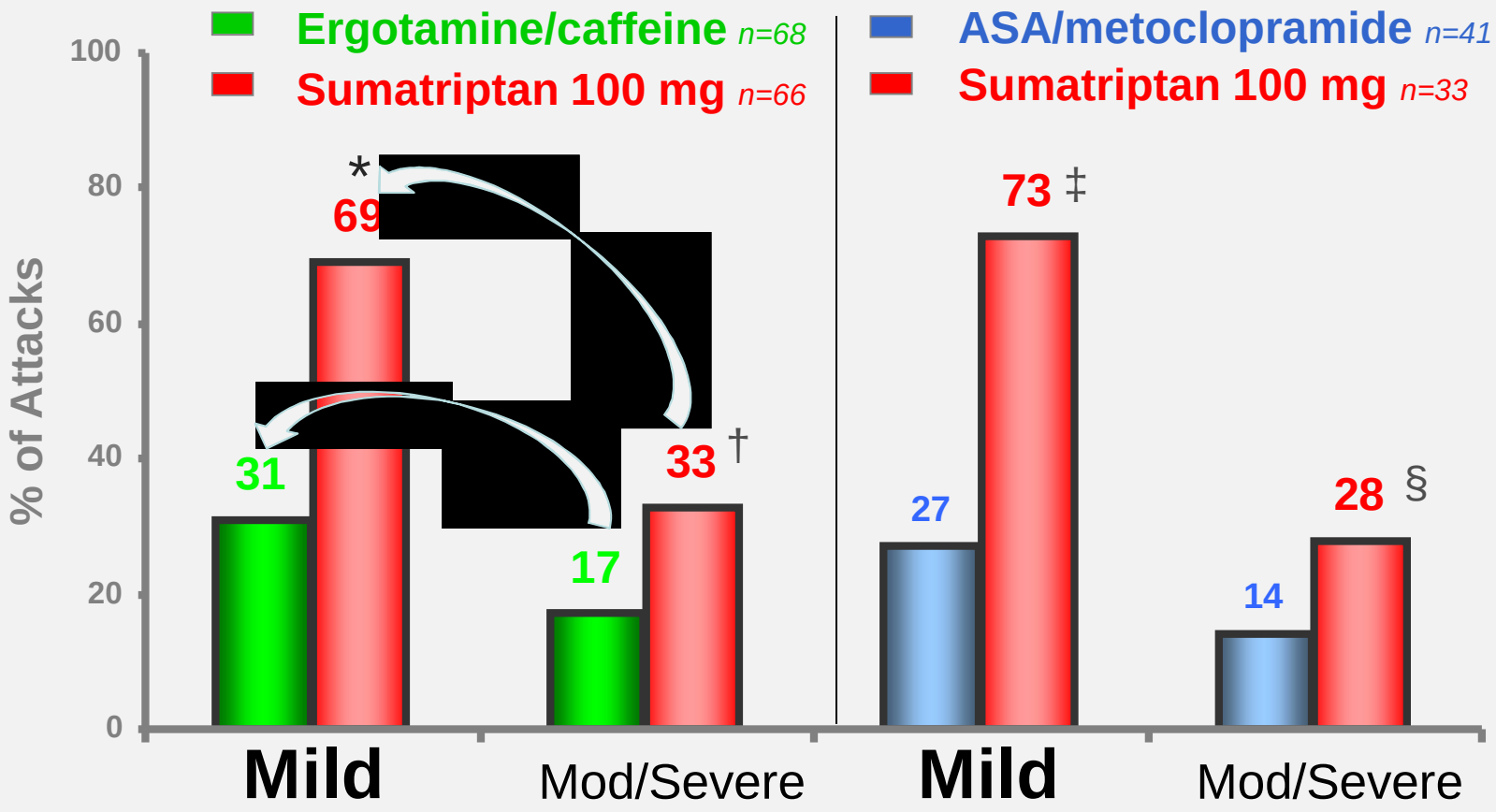
- no association between triptan prescription and stroke (HR 1.13; 95% CI 0.78, 1.65) or myocardial infarction (HR 0.93; 95% CI 0.60, 1.43)

"patients with vascular risk factors were less likely to receive a triptan!"

(GC Hall et al, Neurology 2004;62:563–568)

Pain-free response at 2 hours

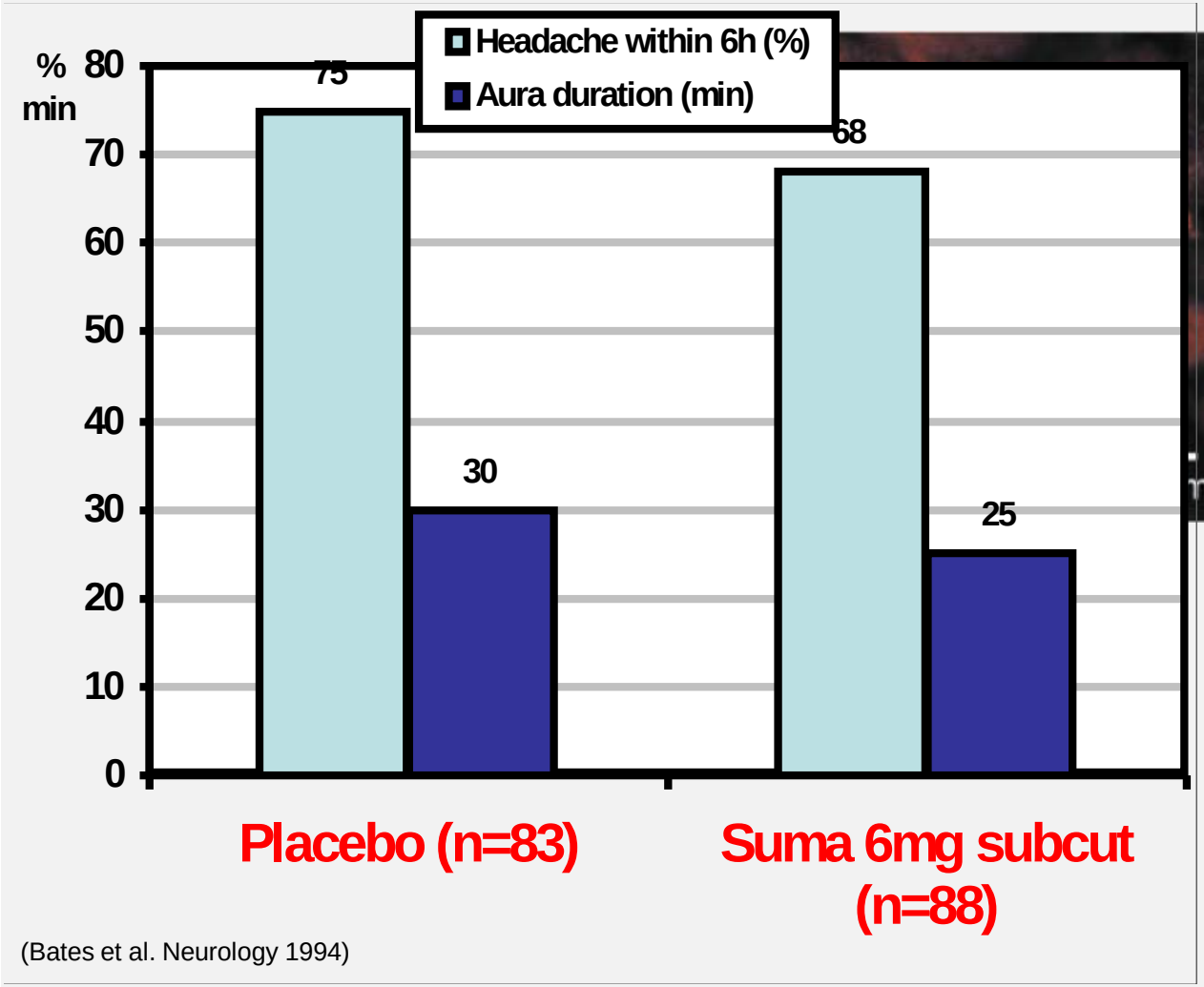
Suma comparative trials with Cafergot (Eur Neurol 1991) & ASA+MCP (Eur Neurol 1992)



* OR =4.4, p<0.0001
† OR =2.5, p<0.0001

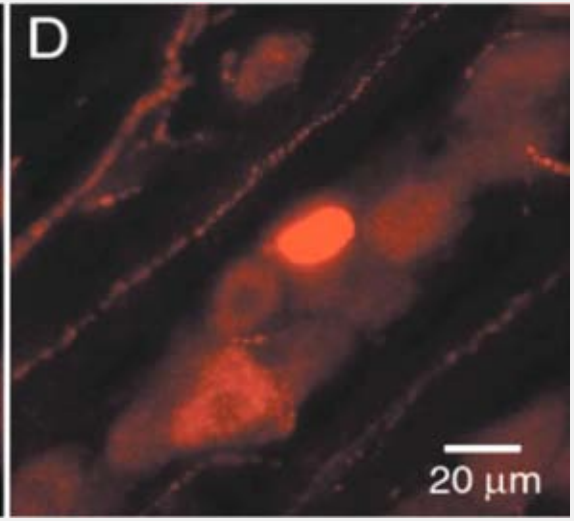
‡ OR =7.4, p=0.0001
§ OR =3.4, p=0.0004

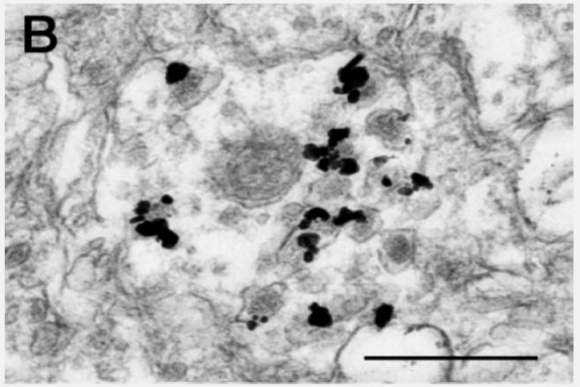
Triptans have poor efficacy when given during the aura.



(Bates et al. Neurology 1994)

Externalisation of receptors needed ?





5-HT1D receptors are localised within dense core vesicles

(Potrebic et al. J Neurosci 2003)

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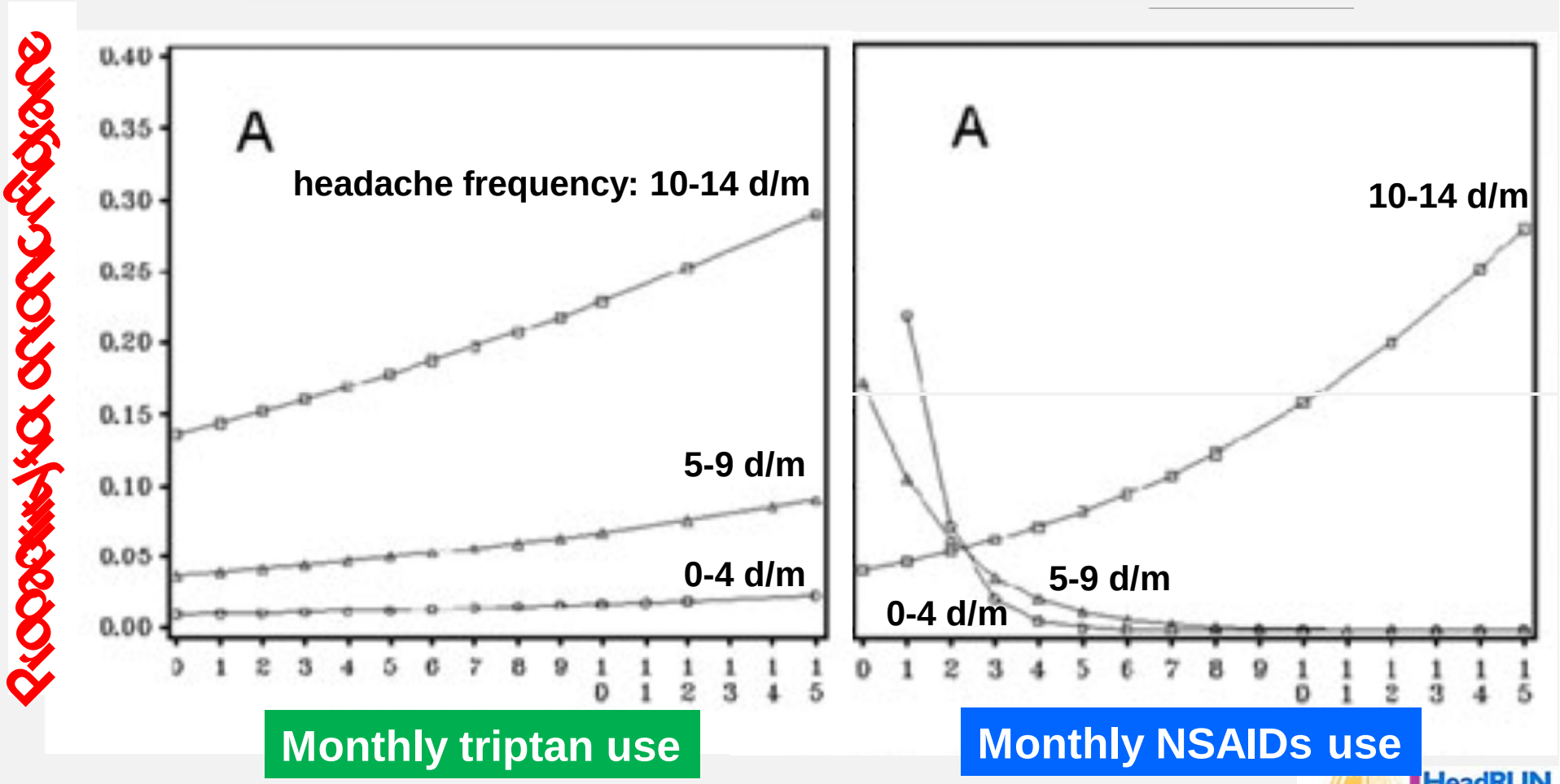
An advantage of NSAIDs

Probability of developing chronic migraine is greater with triptans than with NSAIDs

(Bigal et al. Headache 2008)



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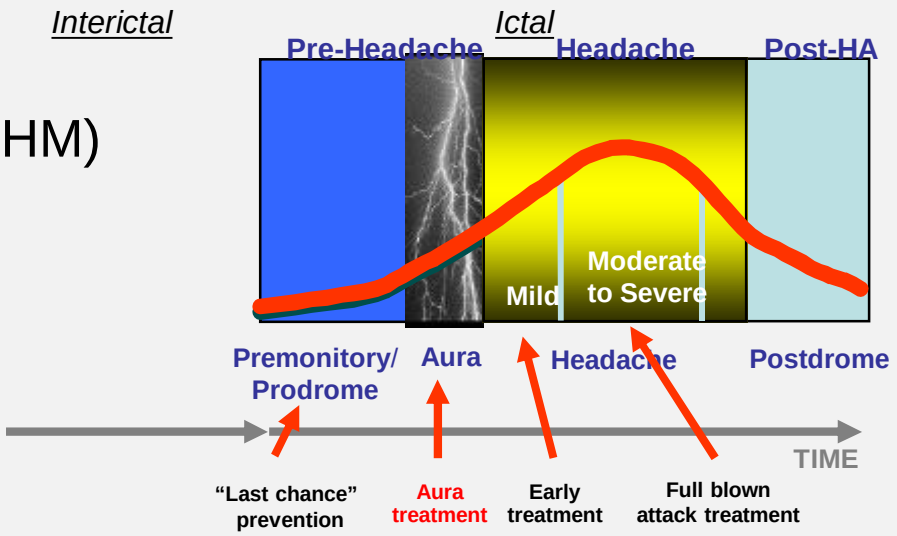
Treatment options for prolonged migraine attacks & status migrainosus

- **Daily i.m. injections of DHE (1mg) and tiapride (100mg)** (OUT-patients: 5-10 days)
- The i.v. dihydroergotamine (DHE) + metoclopramide program (IN)
- NSAIDs (+ anti-emetics) i.m. or i.v.(OUT)
- Steroïds i.v. : (methyl)prednisolone/ dexamethasone, (OUT/IN)
- **Valproate i.v.** or **levetiracetam i.v**. (IN)
- Neuroleptics i.v. : haloperidol, prochlorperazine, chlorpromazine..(IN)
- **Tricyclics i.v. : clomipramine**..(IN).
- Opioïds & tradonal (IN/OUT)

Treatment options for persistent aura and aura status

- Naloxone i.v.
  (Sicuteri et al. 1983)
- Ketamine i.n. 25mg (*FHM*)
  (Kaube et al. 2000)
- Methylprednisolone 100mg/d (FHM)
  (Sanchez-Albisua et al. 2013)
- Furosemide i.v. 20mg
  (Rozen et al. 2000)
- **Acetazolamide p.o. 500mg**
  (Haan et al. 2000; De Simone et al. 2005)
- Phenytoïn
  (Merims & Kuritzky 2000)
- Valproate i.v.
  (Edwards et al. 2001)
- **Lamotrigine p.o. 50-100mg**
  (D'Andrea et al. 1999; Pascual et al. 2004; Bisdorff 2004; Bogdanov et al. 2011)
  ……



What causes the repetition of migraine attacks ?

Migraine is a complex genetic disorder

PREVENTIVE Rp

Genes A+B+C

Migraine threshold

Genes B+C

Genes A+C

Gene B

Gene A

Aggravating factors

Stress
Comorbid Psy
Hormones...

GENE FUNCTIONS
- **neuronal excitability**
- **neurotransmission**
- **neuronal metabolism**
- hormones
- inflammation

EPIGENETICS !!!

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Other preventive treatments

With proven evidence of benefit

- butterbur root (Petasites)

With possible evidence of benefit

- **feverfew**
- **cannabis**
- **pyridoxine (B6)**
- **hydroxycobalamin (B12)**
- **S-adenosyl-methionine (SAM-e)**
- **peppermint oil (local)**
- **acupuncture**
- **…**

With no evidence of benefit

- folic acid
- ginger
- Gingko Biloba
- Pueraria root
- passionflower
- Ephedra
- Kava kava
- homeopathy
- …

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PREEMPT 1 & 2
Problems & questions

1. Is a 10% difference clinically relevant ?
2. What was the role of medication overuse ?
3. Was blinding effective ?
4. 40% of patients never had a preventive therapy
   despite chronic migraine since 20 years !
5. Are saline injections pharmaco-economically
   as efficient ?
6. Responders need to be identified ?
7. …to be used eventually in a specialized multidisciplinary setting

How to improve outcome ?

Novel more effective preventive drugs ? **NONE IN SIGHT**

1. Combine preventive drugs ?
2. Manage comorbidity!
3. Use botulinum toxin ?
4. Try non-drug treatments ?
5. Go for neurostimulation?
6. Consider multimodal therapy ?

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4. Non-drug therapies

- Cognitive & behavioural treatments
  - relaxation training,
  - thermal biofeedback comb.with relax. train.,
  - electromyographic biofeedback, and
  - cognitive-behavioral therapy

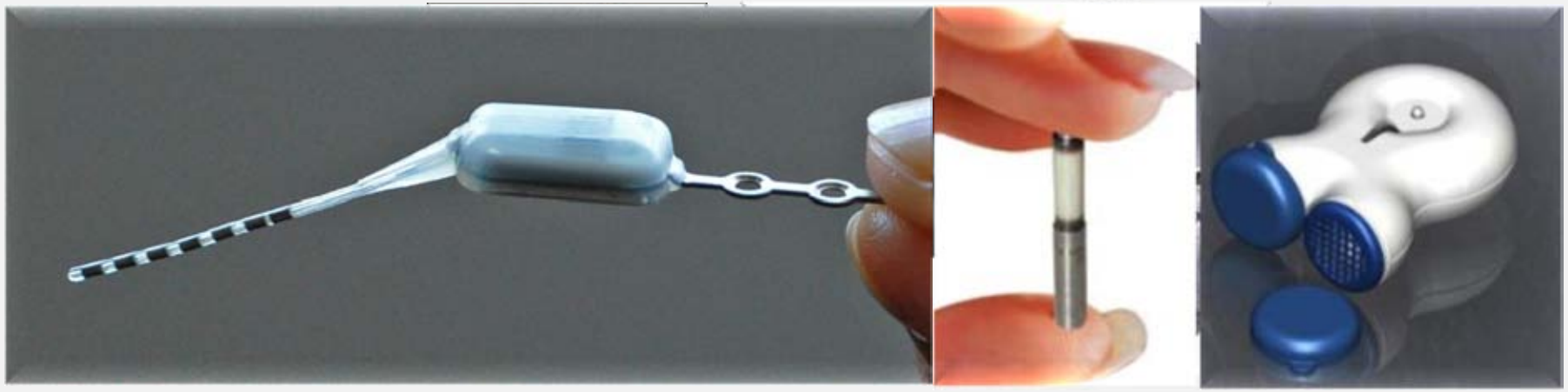
= ***evidence-based efficacy***

- Others with possible effect :
  - (auto)hypnosis
  - massages
  - manual therapy
  - acupuncture
  - oriental stress managing techniques
  - …..

5. MEDICAL DEVICE TREATMENTS FOR HEADACHE

Scribonius Largus, physician to Emperor Claudius, was a staunch advocate of the remedy. He wrote in the 1st century:

“ ***To immediately remove and permanently cure a headache, …. a live black torpedo is put on the place which is in pain, until the pain ceases and the part grows numb***.”



GIGA-NEUROSCIENCES
& NEUROLOGY DEPT
Headache Research Unit
Université de Liège

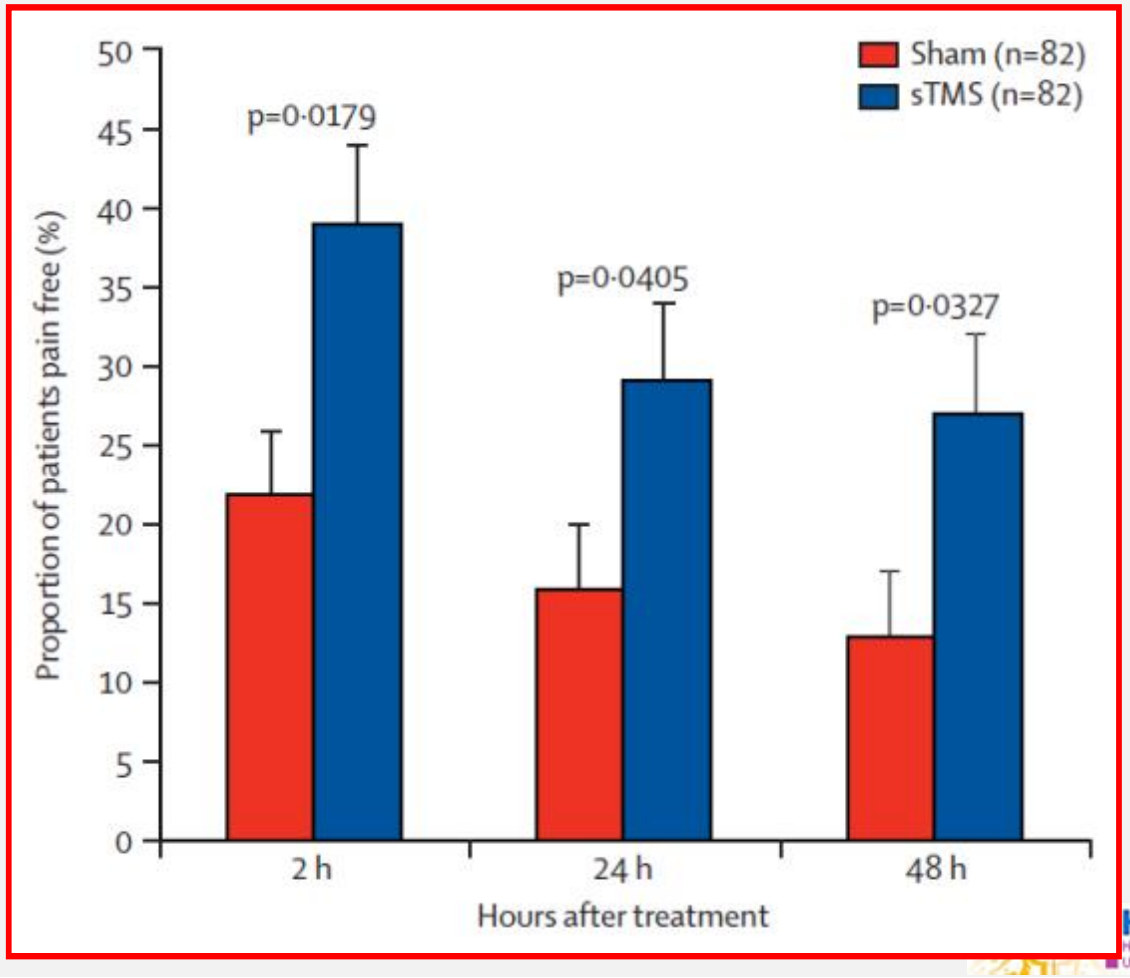
Can we do better….with neurostimulation methods ?

Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial

Richard B Lipton, David W Dodick, Stephen D Silberstein, Joel R Saper, Sheena K Aurora, Starr H Pearlman, Robert E Fischell, Patricia L Ruppel, Peter J Goadsby

Lancet Neurol 2010; 9: 373–80

N=164 (82 sham)
TMS 2 pulses over occiput
Within 1h after aura onset



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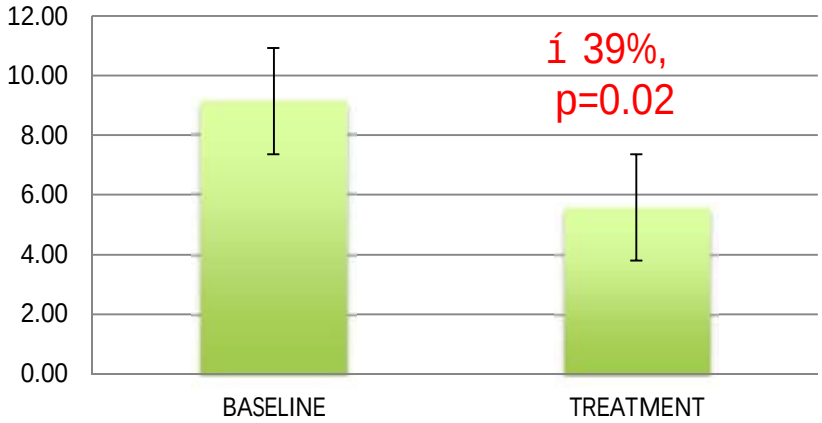
Pilot trial of *excitatory anodal tDCS* of visual cortex in episodic migraine

Transcranial Direct Current Stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine Viganò et al.

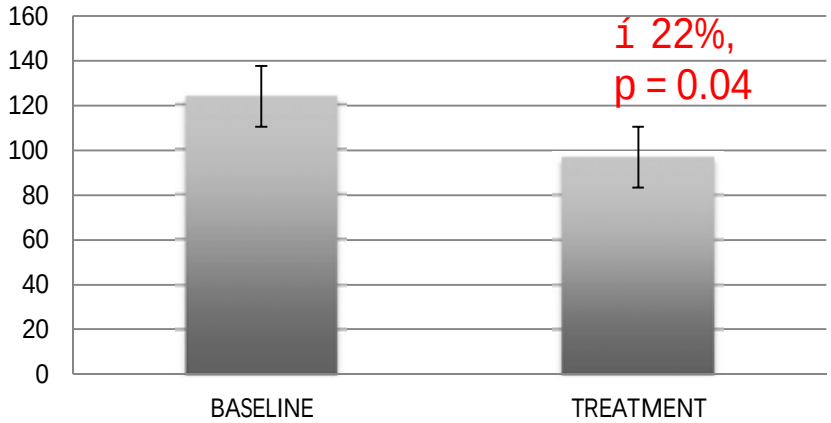
The Journal of Headache and Pain 2013, 14:23 doi:10.1186/1129-2377-14-23

N ° of patients =13 (tDCS 1mA per 15 mins) 2/wk 8wks; Baseline= 2 months; Treatment= 2 months

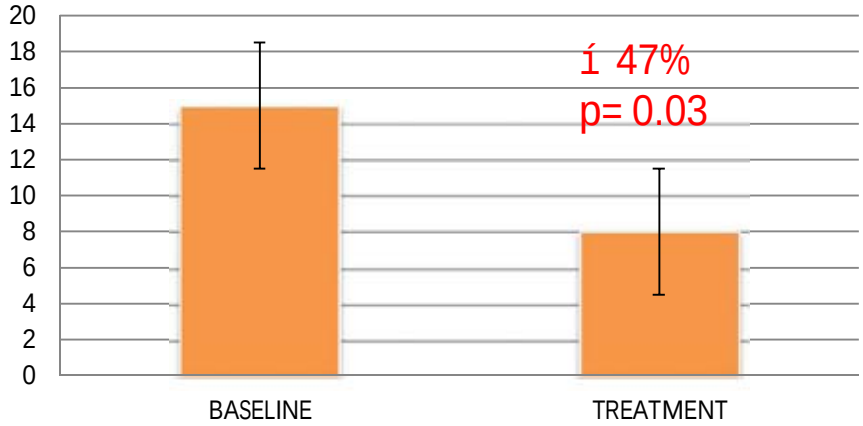
Migraine attacks



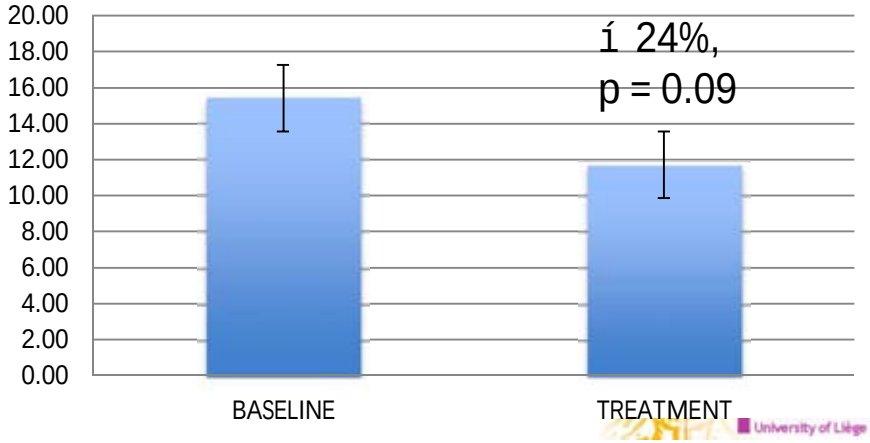
Attack duration - hours

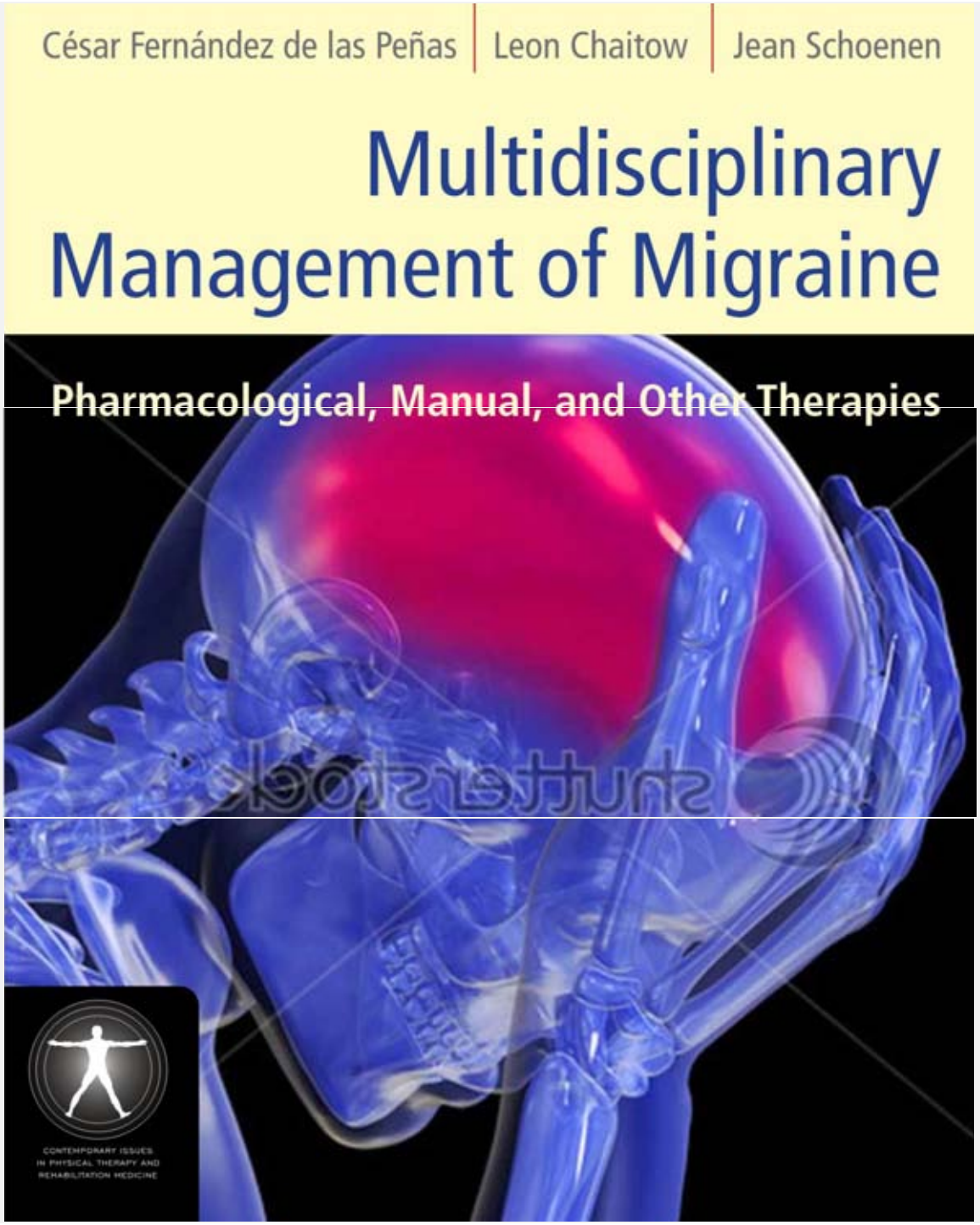


Migraine days



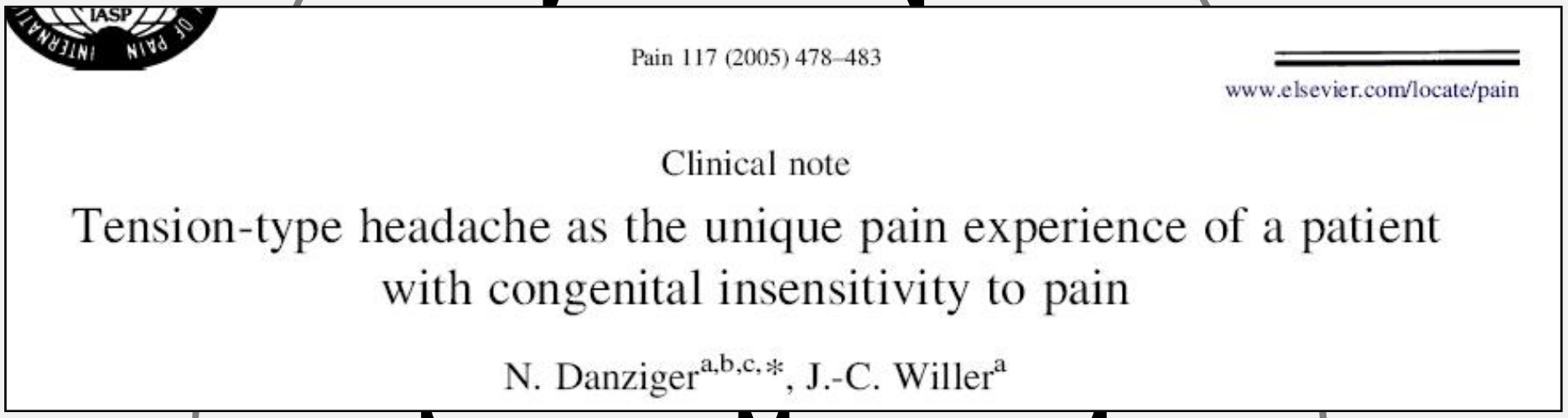
Drug intake




César Fernández de las Peñas
Leon Chaitow
Jean Schoenen
Multidisciplinary Management of Migraine
Pharmacological, Manual, and Other Therapies
CONTEMPORARY ISSUES IN PHYSICAL THERAPY AND REHABILITATION MEDICINE

The pathophysiological matrix of TTH

Dysfunctioning Limbic Control
(depression)



Pain 117 (2005) 478–483

www.elsevier.com/locate/pain

Clinical note

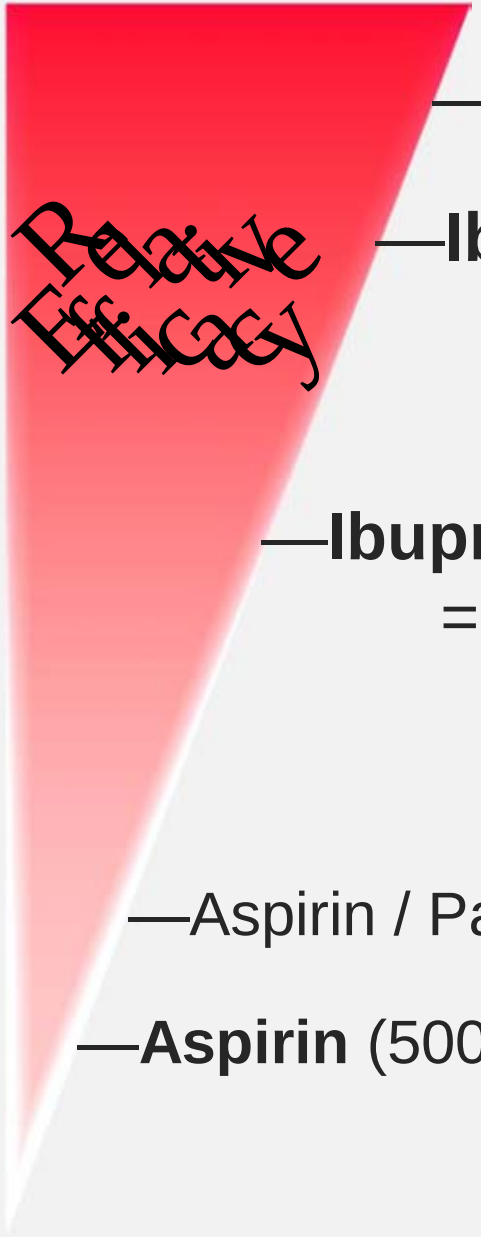
Tension-type headache as the unique pain experience of a patient with congenital insensitivity to pain

N. Danziger[a,b,c,*], J.-C. Willer[a]

Central Trigeminal Sensitisation

Peripheral Myofascial Strain

Tension-type Headache : acute pharmacotherapy



—Ibuprofen (400mg) + Caffeine (200mg)

—**Ibuprofen** (400mg)
= **Ketoprofen** (50mg)

—**Ibuprofen** (200mg)
= **Ketoprofen** (25mg)
= **Naproxen** (275mg)

—Aspirin / Paracetamol (500-1000mg) + Caffeine

—**Aspirin** (500-1000mg) = **Paracetamol** (500-1000mg)

(8 randomised, controlled trials 1995-1997)

TTH: preventive therapies

1. **Preventive pharmacotherapy: *tricyclics***

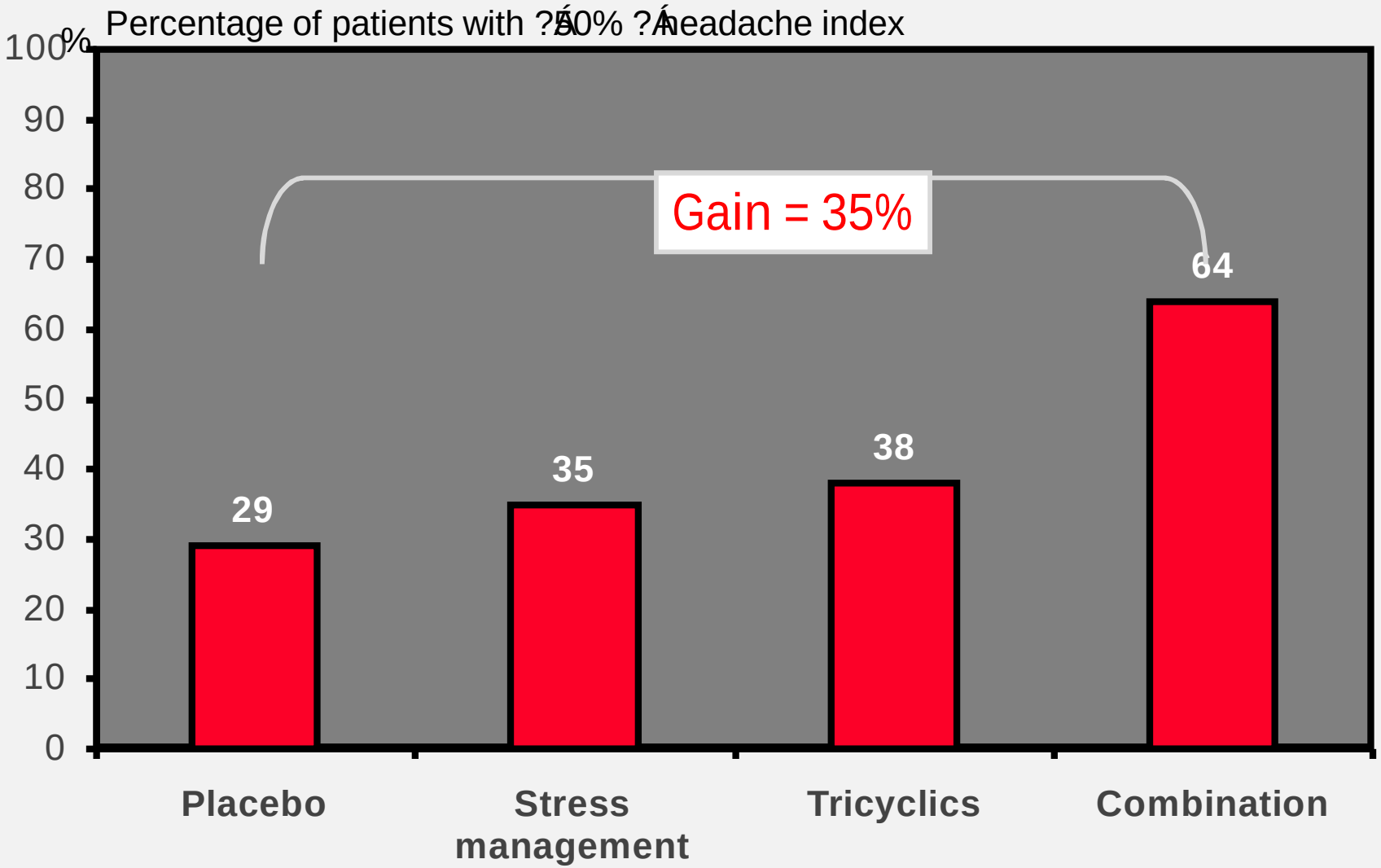
2. **Non-pharmacological treatments**

   2.1. Psycho-behavioral techniques (*relaxation, biofeedback, stress management)*

   2.2. Other non-pharmacological treatments

   - **physical therapy**
   - **oromandibular treatment (?)**
   - **acupuncture (?)**
   - **homeopathy:** not effective
   - **...**

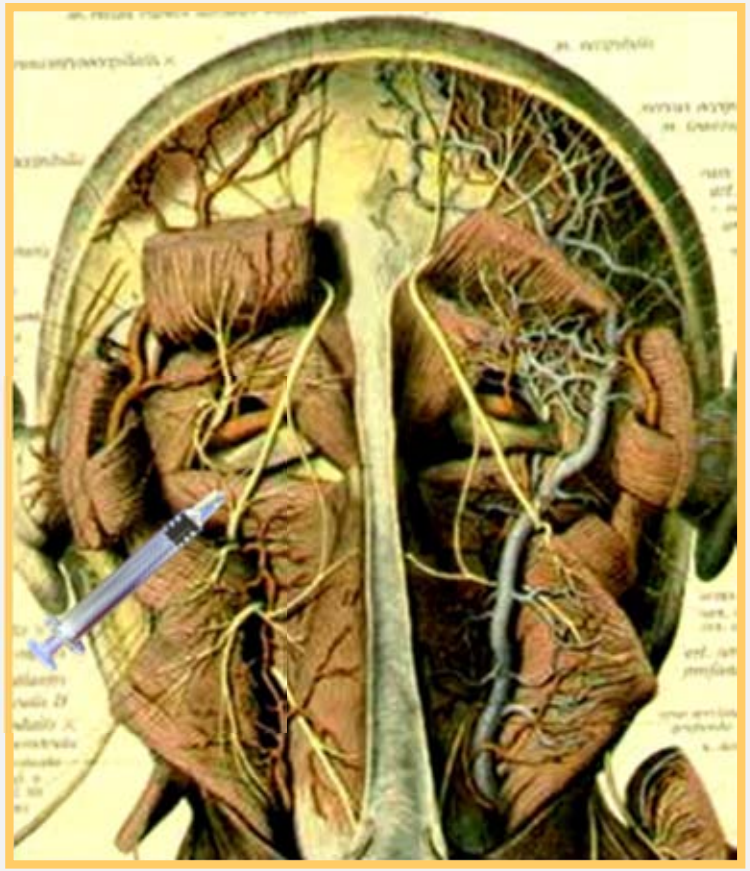
Combination of stress management therapy and amitriptyline/nortriptyline in CTTH



(Holroyd et al. JAMA 2001)

Greater occipital nerve « blocks » for CH attack prevention

- Long-acting steroid + Lidocaine (2%-0.3-1 ml)
- Responder rate: 60% (1,2)
- AEs: -local discomfort
  - alopecia (1%) (3) = avoidable by deep injections



1. Ambrosini et al Cephalalgia 2003
2. Afridi et al., Pain 2006;122:126
3. Shields et al., Neurology 2004;63:2193

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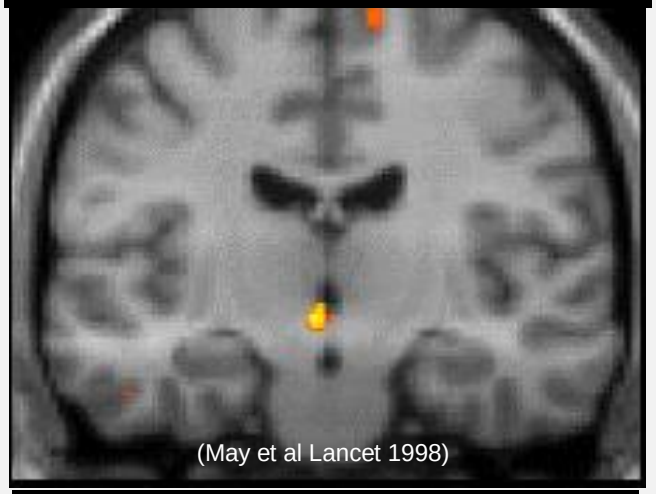
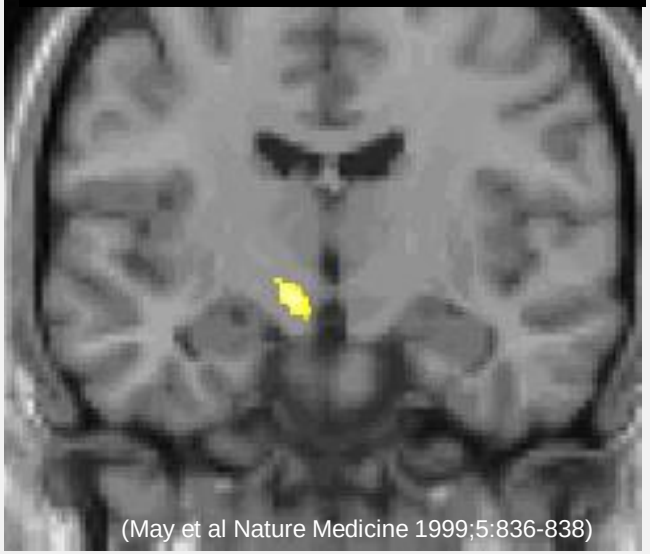
Hypothalamus & cluster headache

Functional change
(PET-activity)



(May et al Lancet 1998)

Structural change
(MRI voxel-based morphometry)

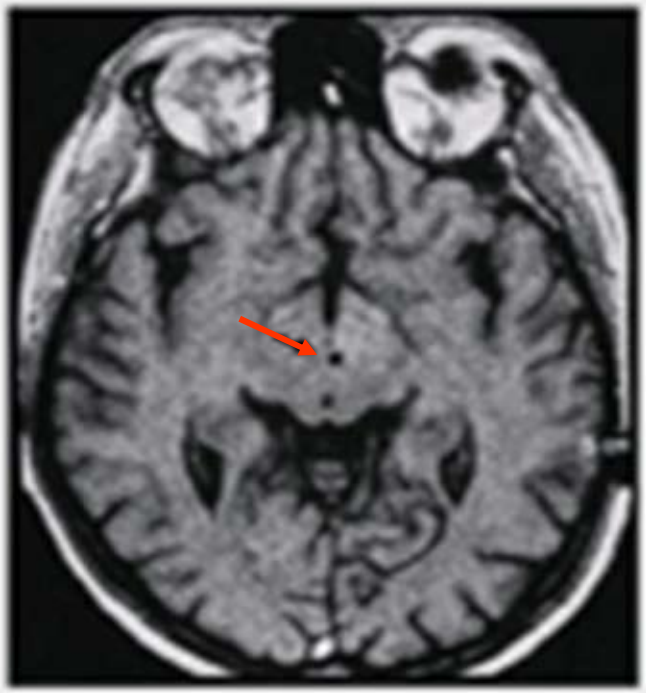


(May et al Nature Medicine 1999;5:836-838)

- **6 mm posterior to AC-PC midpoint**
- **2 mm left of midline**
- **8 mm below commissural plane**

The New England Journal of Medicine

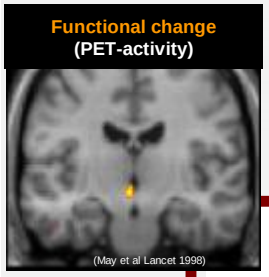
Volume 345:1428-1429 November 8, 2001 Number 19



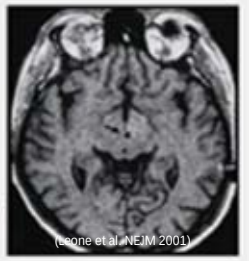
Stereotactic Stimulation of Posterior Hypothalamic Gray Matter in a Patient with Intractable Cluster Headache

Massimo Leone, M.D.
Angelo Franzini, M.D.
Gennaro Bussone, M.D.
Carlo Besta Neurological Institute
20133 Milan, Italy

HeadRUN Headache Research Unit University of Liège



Hypothalamic DBS in CCH: synopsis of results



Auteur	Nb patients	Nb rémission	Nb amélioration >50%	Durée de suivi (ans)
Schoenen	6	2	1	4
D'Andrea	3	2	0	2.5
Leone	16	10	0	4
Benabid (A)	1	1	0	1
Starr	4	0	2	1
Owen	1	1	0	0.7
Nikkhah	2	0	0	2
Mateos (A)	2	1	1	1
Black (A)	2	0	2	2.6
Bartsch	6	2	1	1.4
Fontaine	11	3	3	1
Piacentino (A)	4	3	1	>0.4
Total	58	25 (43%)	11 (19%)	1.8

= 62% améliorés

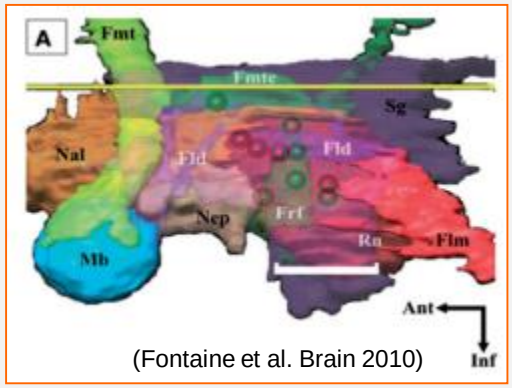
Lessons learnt from Hypothalamic DBS

1. before starting the procedure, 12 patients were recruited: while on the waiting list for 4 months, **10 went into remission** !

   ?á ***« refractory » chronic cluster may not be irreversibly refractory !!***

2. The relevant target & mode of action are not known

   ?á ***fiber tract stimulation ?***
   ?á ***neuromodulatory effect***



(Fontaine et al. Brain 2010)

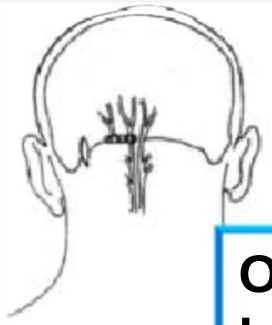
3. hypothalamic DBS is an effective treatment for intractable chronic cluster headache,

   ?á ***no controlled RCTs, but recurrence with stimulator OFF***
   ?á ***but it is not a benign, riskless procedure***

4. Are there less invasive procedure ?

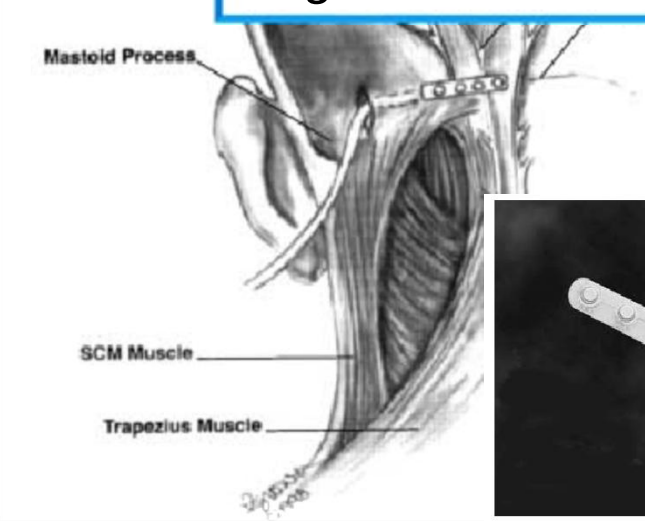
Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study

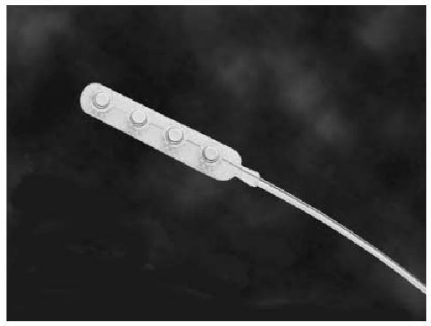
Delphine Magis, Marta Allena, Monica Bolla, Victor De Pasqua, Jean-Michel Remacle, Jean Schoenen
Lancet Neurology 2007



Oh MY, Ortega J, Bellotte JB, Whiting DM, Aló K. Peripheral nerve stimulation for the treatment of occipital neuralgia and transformed migraine using C1-2-3 subcutaneous paddle style electrode : a [illegible] 103-112.

Occipital nerve stimulation for chronic cluster headache Trentman TL, Dodick DW, Zimmerman RS
Mayo Clinic Scottsdale, Scottsdale, AZ USA
Reg Anesth Pain Med 2003;28:A44





[illegible]rode (Medtronic 3587A *Resume II* °) was implanted on the CCH side subcutaneously via a retromastoid C2–3 approach.

• The stimulator (Medtronic 7425 *Itrel 3* °) was switched on as soon as a typical attack occurred.

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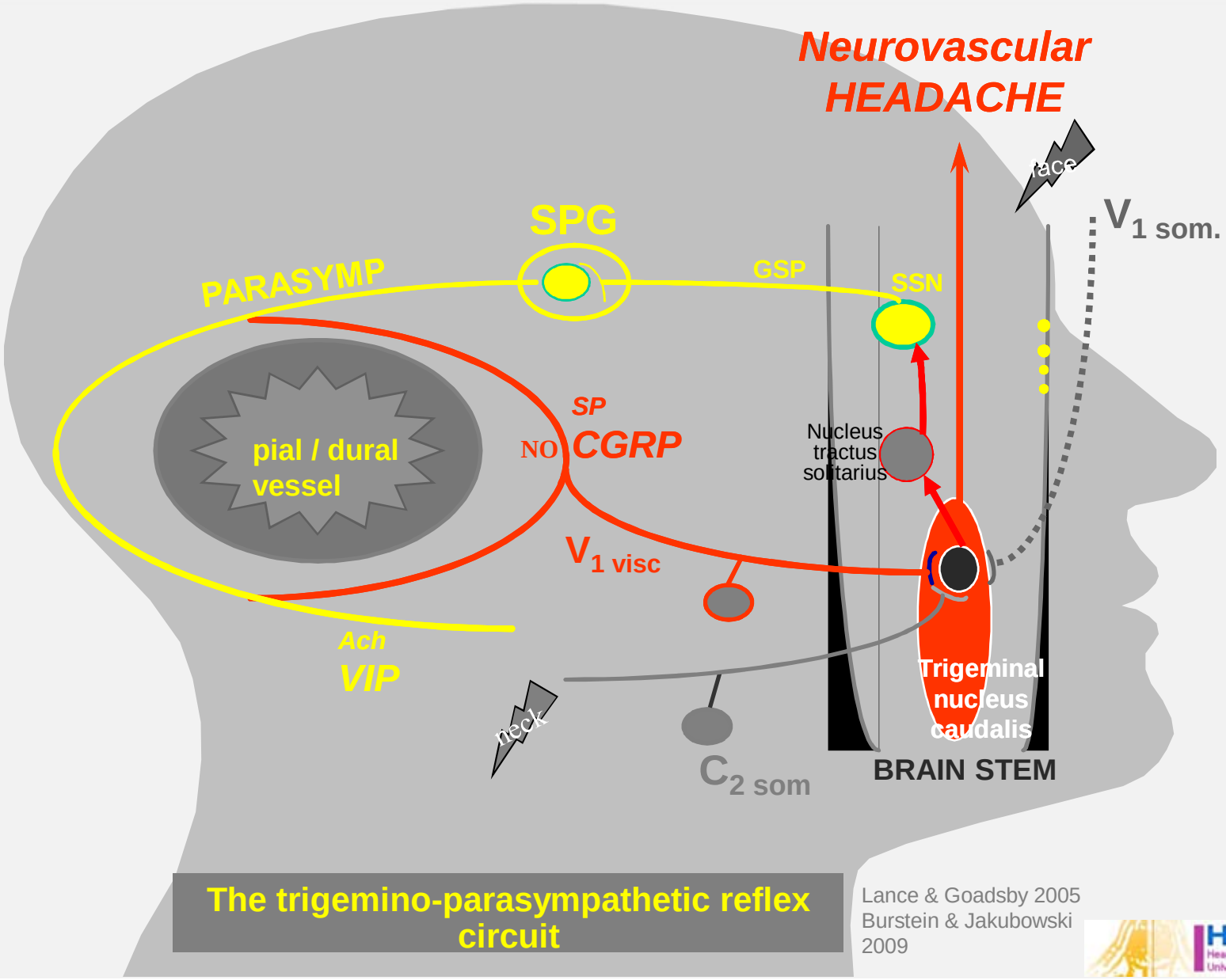
Cluster Headache and the Sphenopalatine ganglion (SPG)



The trigemino-parasympathetic reflex circuit

Lance & Goadsby 2005
Burstein & Jakubowski 2009

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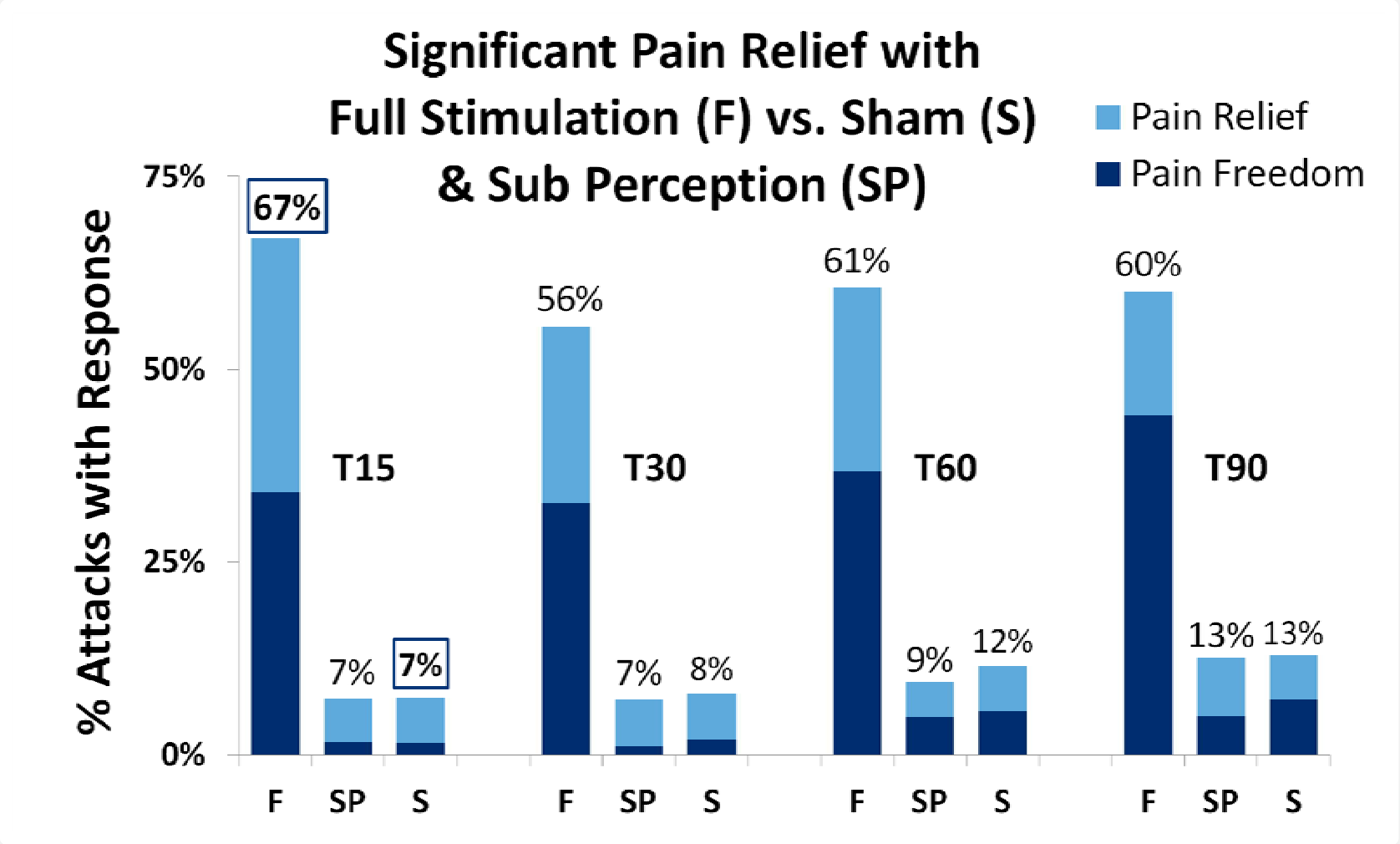
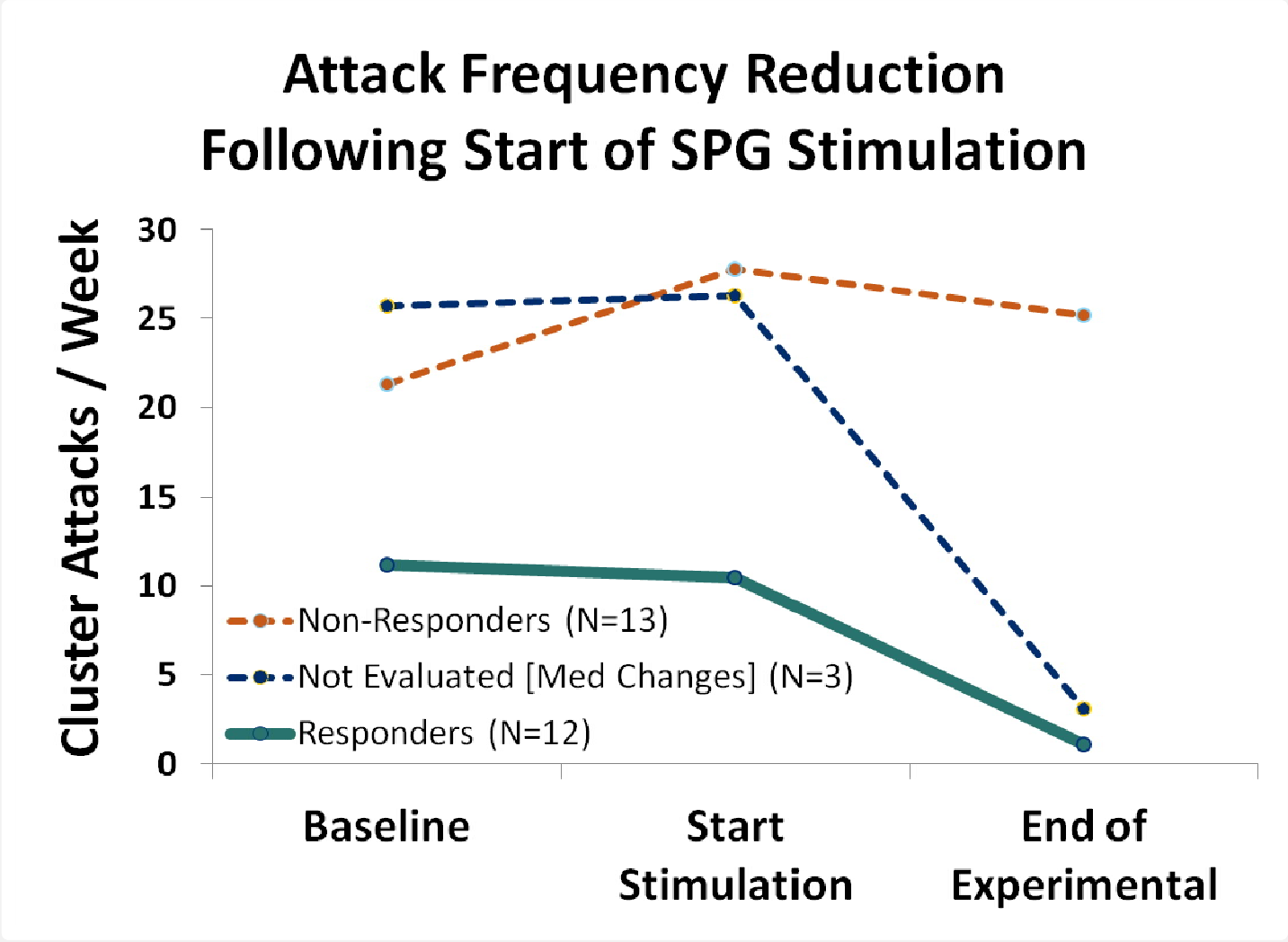
Pathway CH-I: **ACUTE RESPONSE**



Pathway CH-I:
POSSIBLE PREVENTIVE RESPONSE (?)



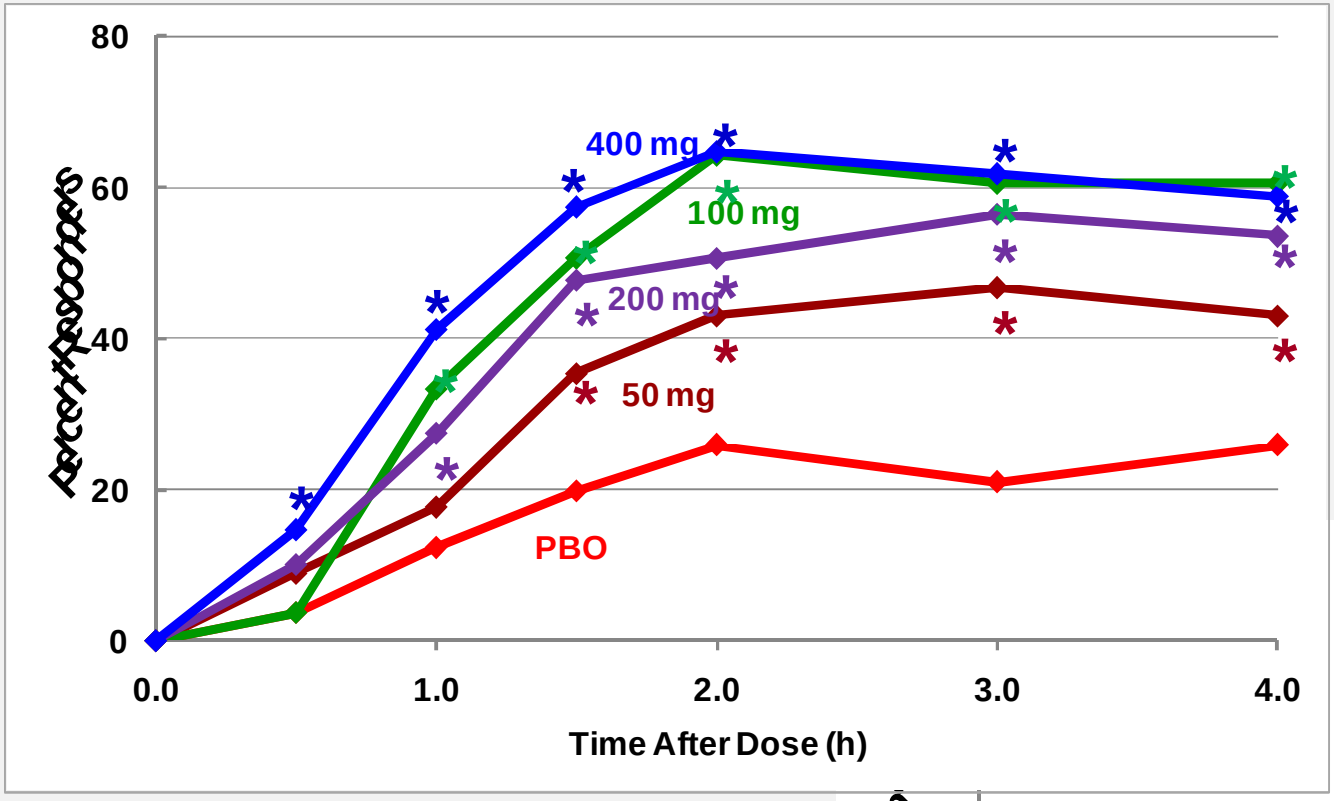
ADVERSE EVENTS

SAFETY

- Sensory disturbances in maxillary division of the trigeminal nerve (81% of patients)
  - *Cranial nerve exams to proactively identify sensory disturbances*
  - *Most ranked mild/moderate and resolved within 3 months*
  - *Surgical adverse events similar in number, severity and duration to other trans-oral, gingival buccal surgical procedures*
- 2 infections, resolved with antibiotics, none required explant
- 2 incidences of mild paresis at nasolabial fold
  - *3 lead revisions*
  - *2 leads originally placed within PPF but not proximate to SPG*
  - *1 lead tip placed within maxillary sinus*
- 2 explants
  - *1 lead migration within the PPF within hours of implant*
  - *1 implant completed with Neurostimulator that was too long for the anatomy; lead migrated out of the PPF within weeks of implant*

5-HT1F receptor agonist Lasmiditan?Ø

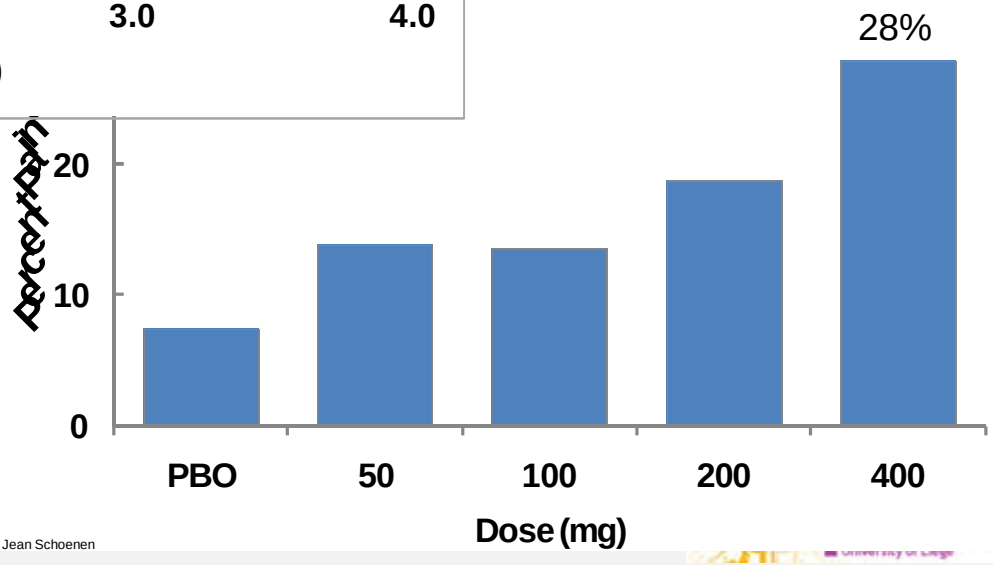
LASMIDITAN (COL-144 MIG-202): Response Time Course (4h)



I.V.: proof of concept
(Ferrari et al. 2010)

Oral: phase II
(Färkkila et al. 2010)

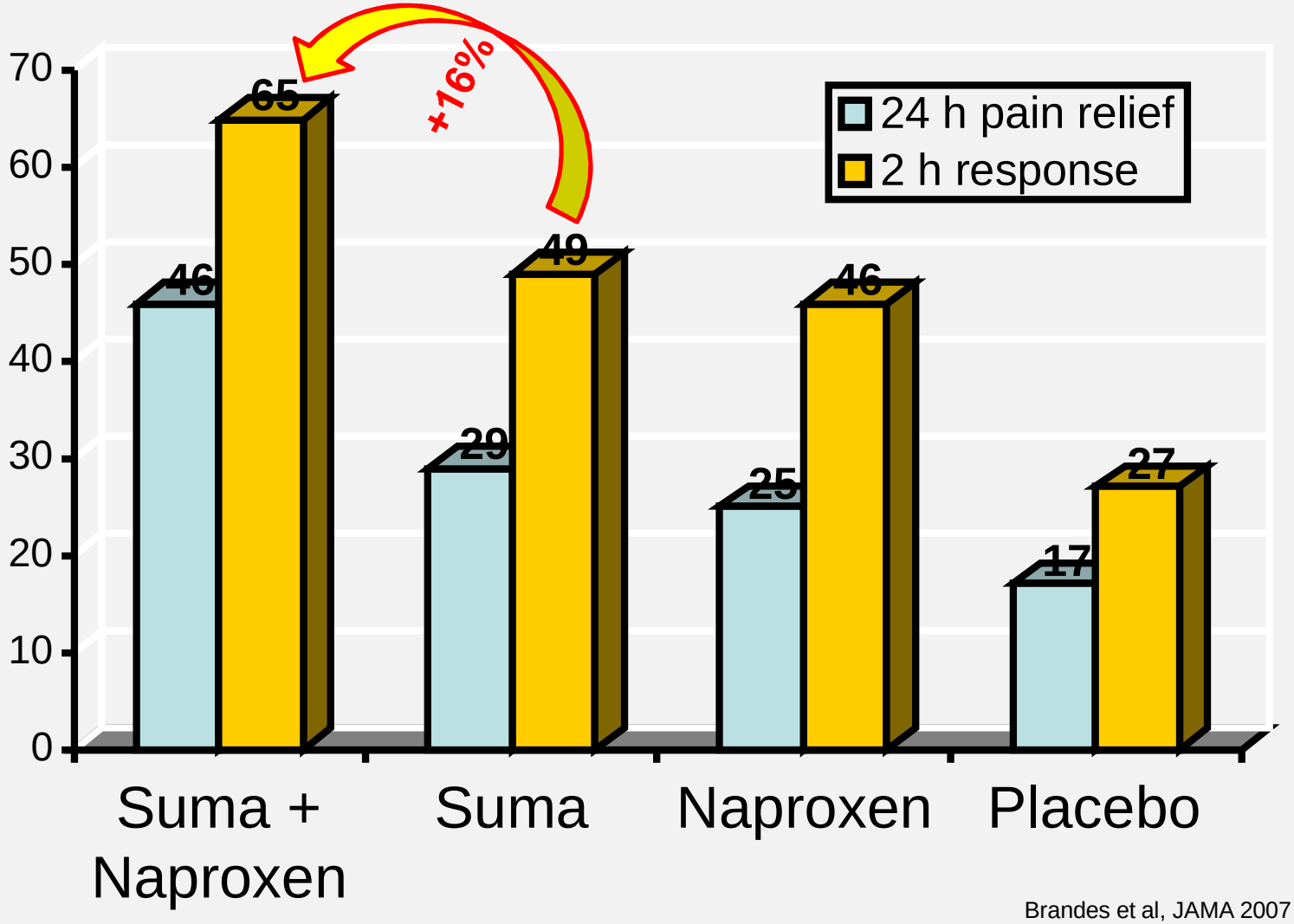
Pain Free, 2h



Complicated migraine attacks

Combination of sumatriptan and naproxen

(Treximet °)



Brandes et al, JAMA 2007

HORMONES

Oral contraceptives and increased headache prevalence.
The Head-HUNT Study (K. Aegidius et al Neurology 2006)

Migraine risk in 13,944 premenopausal women	
Oral contraceptive use	**Odds ratio for migraine**
Never	1 (ref)
Previous	**1.2**
Present – E2 30-50µg	**1.4**
Present – triphasic	**1.5**

- New onset migraine usually occurs in early cycles of OC use
- Stopping OC may not bring immediate relief (may take 4-12 months)
- Switching to an estrogen-free OCP (desogestrel-Cerazette™) improves migraine with aura (Nappi et al. 2011)

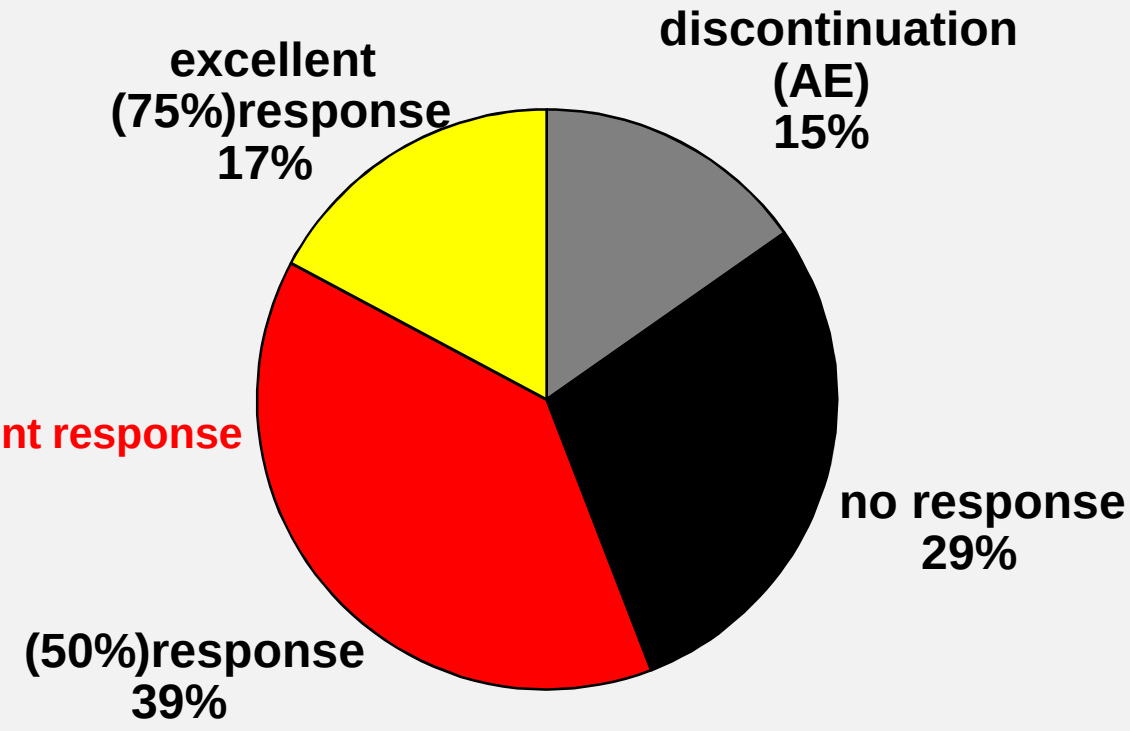
1. Combination therapy ?

Pascual J, Leira R & Láinez JM. Cephalalgia 2003; 23:961

- combination of propranolol/ nadolol & sodium valproate

- 52 patients

56% good/excellent response



BUT..you also combine side effects !

Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine

S.D. Silberstein, MD
D.W. Dodick, MD
A.S. Lindblad, PhD
K. Holroyd, PhD
M. Harrington, MS
N.T. Mathew, MD
D. Hirtz, MD

Correspondence & reprint requests to Dr. Lindblad: alindblad@emmes.com

ABSTRACT

Objective: To assess the efficacy and safety of adding propranolol to topiramate in chronic migraine subjects inadequately controlled with topiramate alone.

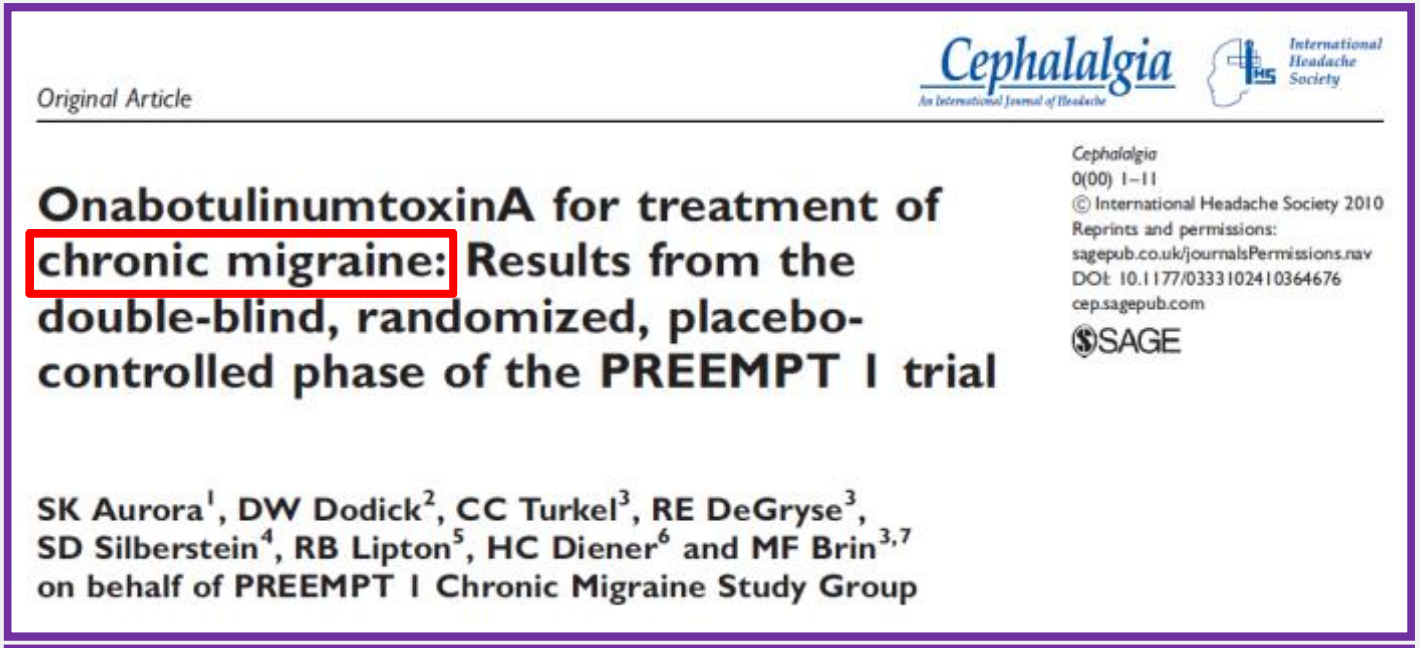
Methods: This was a double-blind, placebo-controlled, randomized clinical trial conducted through the National Institute of Neurological Disorders and Stroke Clinical Research Collaboration, expected to randomize 250 chronic migraine subjects inadequately controlled (≥10 headaches/month) with topiramate (50–100 mg/day) to either propranolol LA (long acting) (240 mg/day) or placebo. Primary outcome was 28-day moderate to severe headache rate reduction at 6 months (weeks 16 to 24) compared with baseline (weeks −4 to 0).

Results: A planned interim analysis was performed after 48 sites randomized 171 subjects. The data and safety monitoring board recommended ending the trial after determining that it would be highly unlikely for the combination to result in a significant reduction in 28-day headache rate compared with topiramate alone if all 250 subjects were randomized. No safety concerns were identified. At study closure, 191 subjects were randomized. The 6-month reduction in moderate to severe 28-day headache rate and total 28-day headache rate for combination therapy vs topiramate alone was not significantly different: 4.0 vs 4.5 days (moderate to severe 28-day headache rate; $p = 0.57$) and 6.2 vs 6.1 days (total 28-day headache rate; $p = 0.91$).

Conclusions: This study does not provide evidence that the addition of propranolol LA to topiramate adds benefit when chronic migraine is inadequately controlled with topiramate alone.

Classification of evidence: This study provides Class II evidence that propranolol LA, added to topiramate, is ineffective in chronic migraine patients who fail topiramate monotherapy. *Neurology*® 2012; 78:976-984

3. Botulinum toxin



Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

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DOI: 10.1177/0333102410364676
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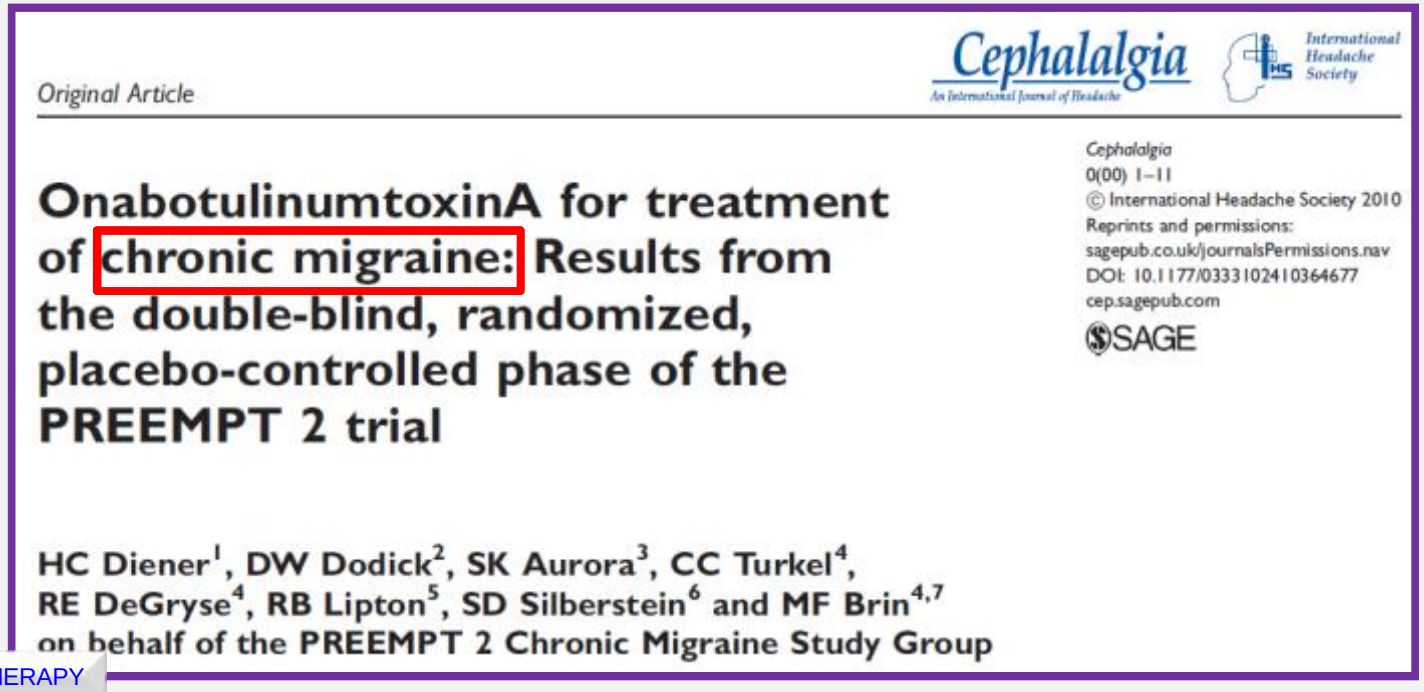
OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial

SK Aurora[1], DW Dodick[2], CC Turkel[3], RE DeGryse[3], SD Silberstein[4], RB Lipton[5], HC Diener[6] and MF Brin[3,7] on behalf of PREEMPT 1 Chronic Migraine Study Group



Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
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DOI: 10.1177/0333102410364677
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OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial

HC Diener[1], DW Dodick[2], SK Aurora[3], CC Turkel[4], RE DeGryse[4], RB Lipton[5], SD Silberstein[6] and MF Brin[4,7] on behalf of the PREEMPT 2 Chronic Migraine Study Group

Exercise as migraine prophylaxis: A randomized study using relaxation and topiramate as controls

Cephalalgia
0(0) 1–11

DOI: 10.1177/0333102411419681
cep.sagepub.com
SAGE

Emma Varkey[1], Åsa Cider[1,2], Jane Carlsson[1] and Mattias Linde[1,3,4]

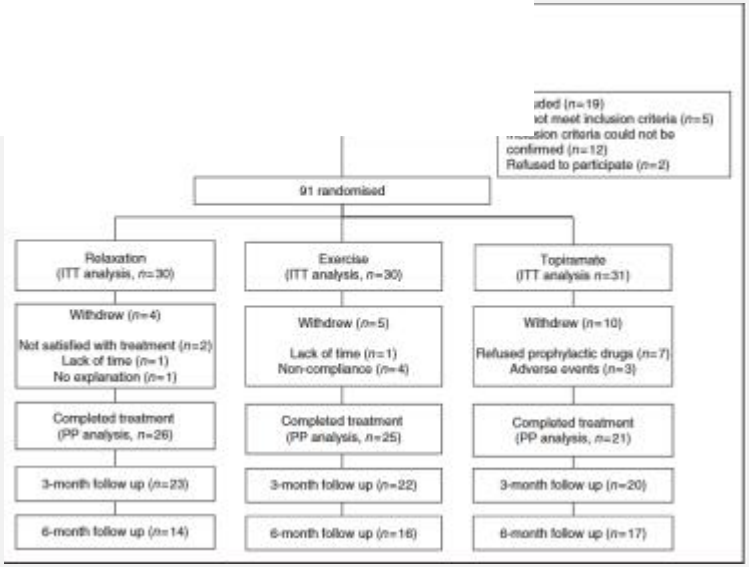


Table 3. Participants who responded to the different treatments

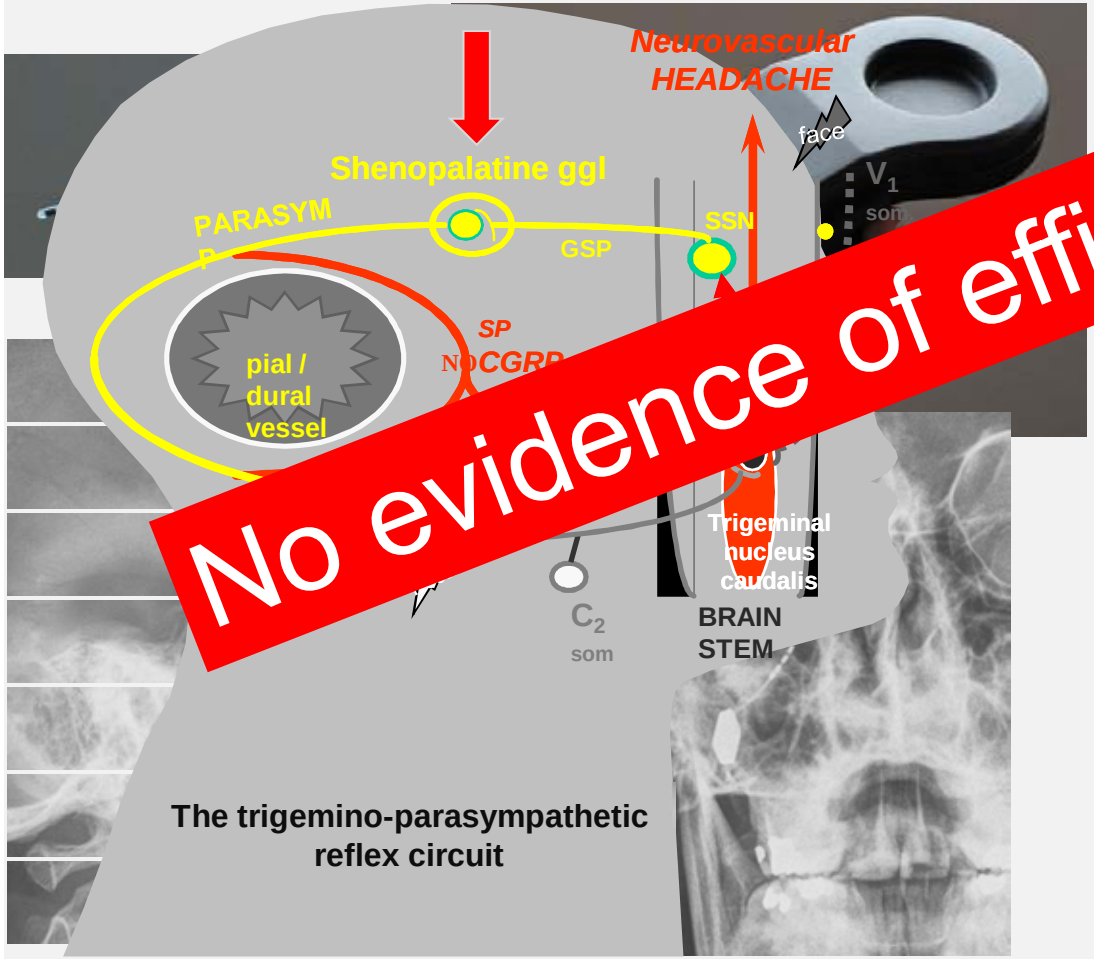
	ITT		
Response	Relaxation ($n=30$)	Exercise ($n=30$)	Topiramate ($n=31$)
Responders (≥50% improvement)	7 (23)	9 (30)	8 (26)
Somewhat improved (25–49% improvement)	5 (17)	5 (17)	3 (10)
Not clinically improved (≤25% improvement)	18 (60)	16 (53)	20 (65)

Values are *n* (%). ITT: $p=0.86$; PP: $p=0.93$.

Can we do better….with neurostimulation methods ?

Implantable Shenopalatine ganglion Stimulator

(Pathway Migraine-1 Trial ongoing)



The trigemino-parasympathetic reflex circuit

Transcutaneous Vagus Nerve Stimulators

No evidence of efficacy….yet !!

Jean Schoenen

GIGA-NEUROSCIENCES & NEUROLOGY DEPT Headache Research Unit
Université de Liège

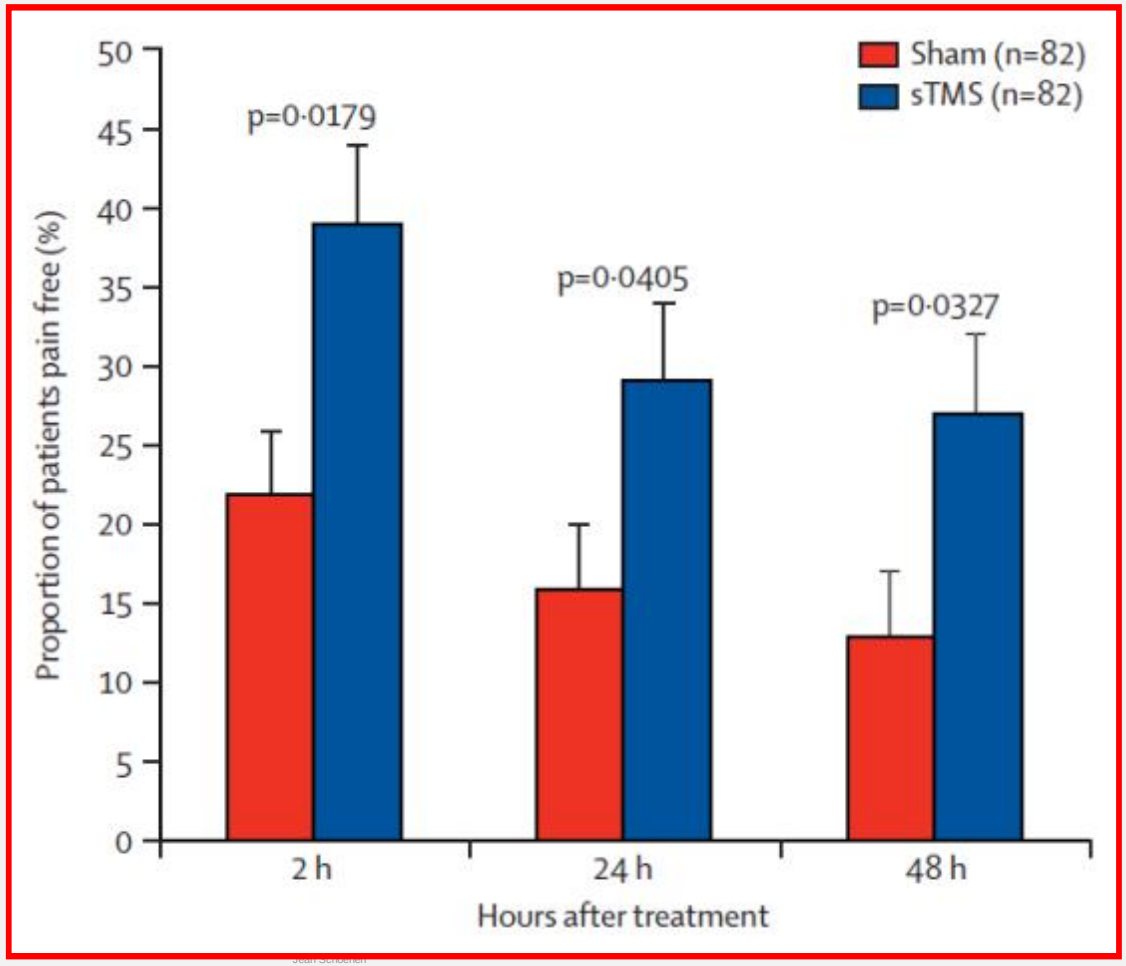
Can we do better….with neurostimulation methods ?

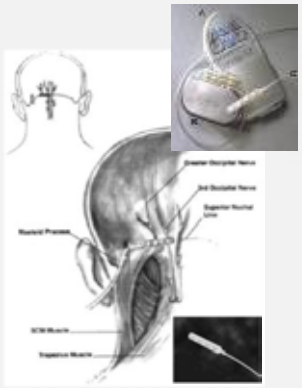
Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial

Richard B Lipton, David W Dodick, Stephen D Silberstein, Joel R Saper, Sheena K Aurora, Starr H Pearlman, Robert E Fischell, Patricia L Ruppel, Peter J Goadsby

Lancet Neurol 2010; 9: 373–80

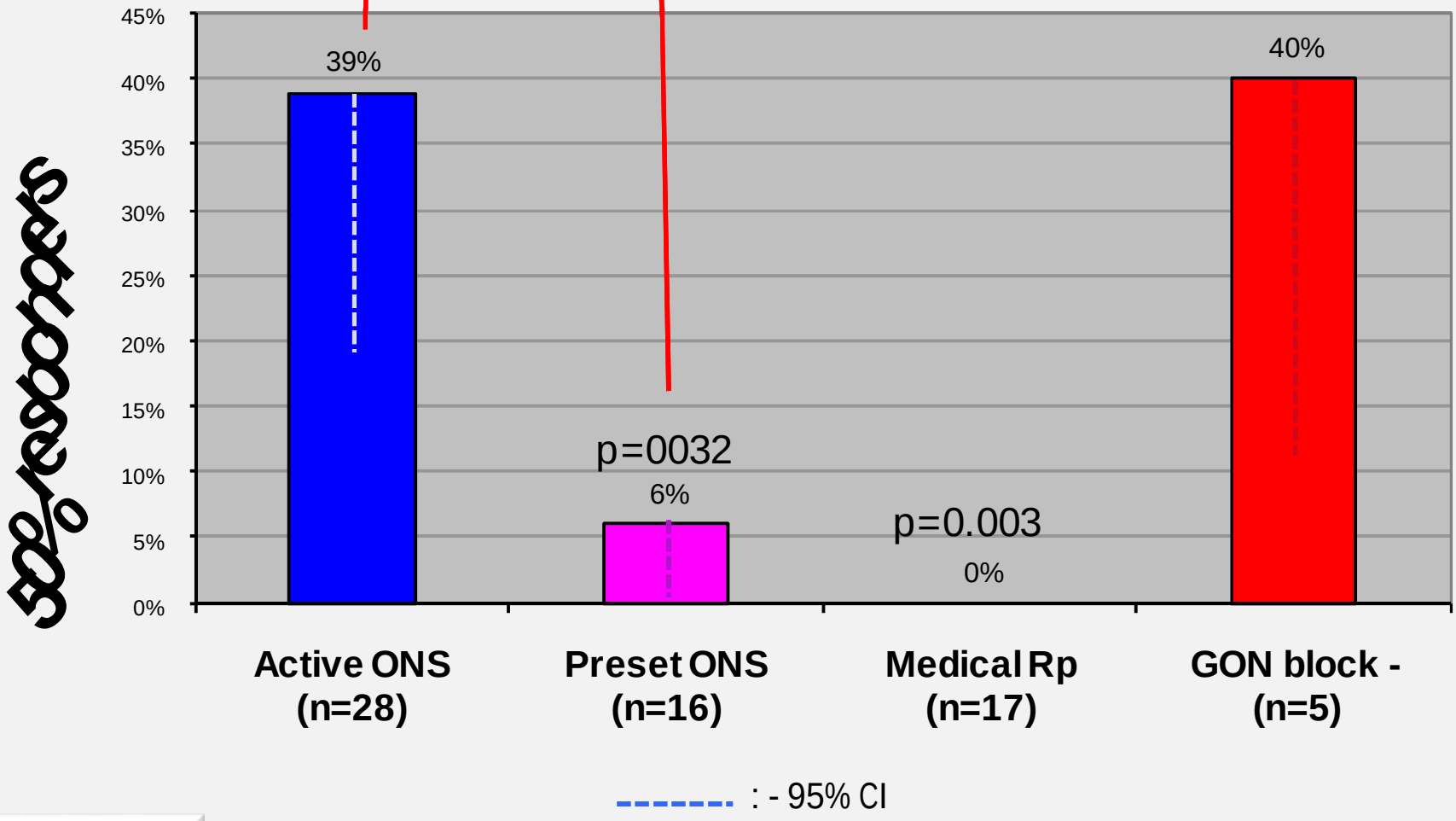
N=164 (82 sham)
TMS 2 pulses over occiput
Within 1h after aura onset



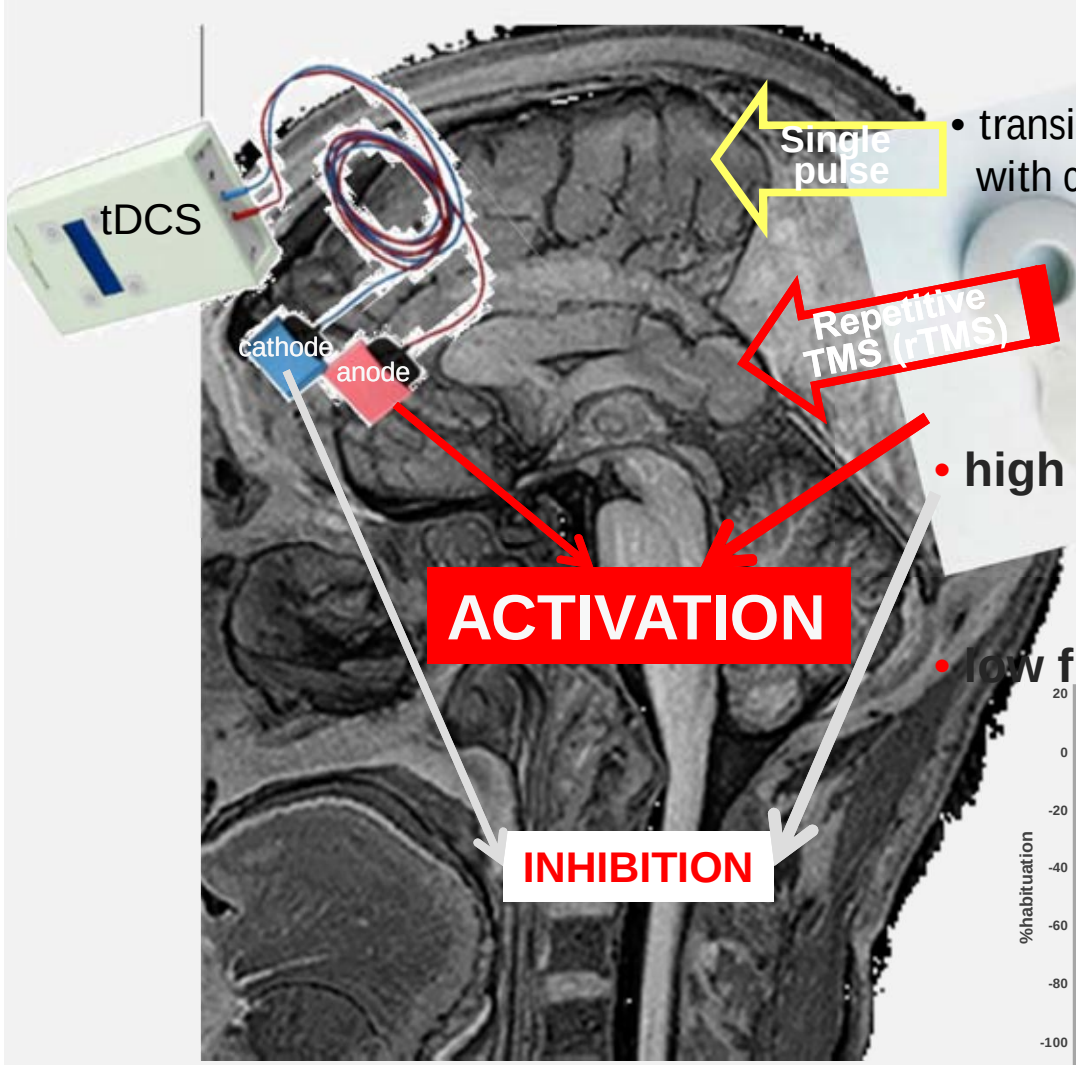


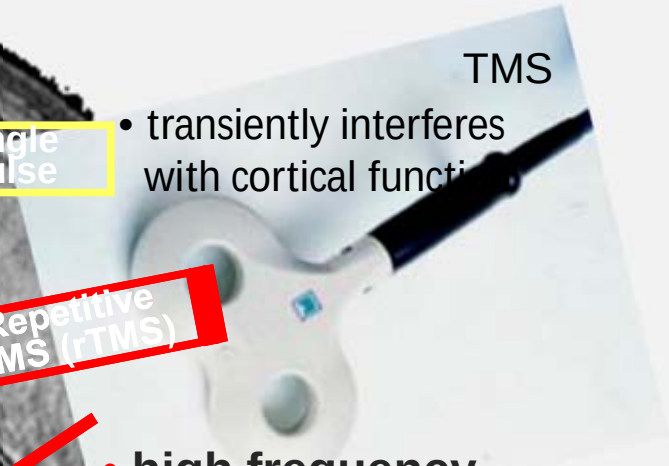
« ONSTIM » in Chronic Migraine

(Saper et al. Cephalalgia 2010 – n=66 RCT – Medtronic °)



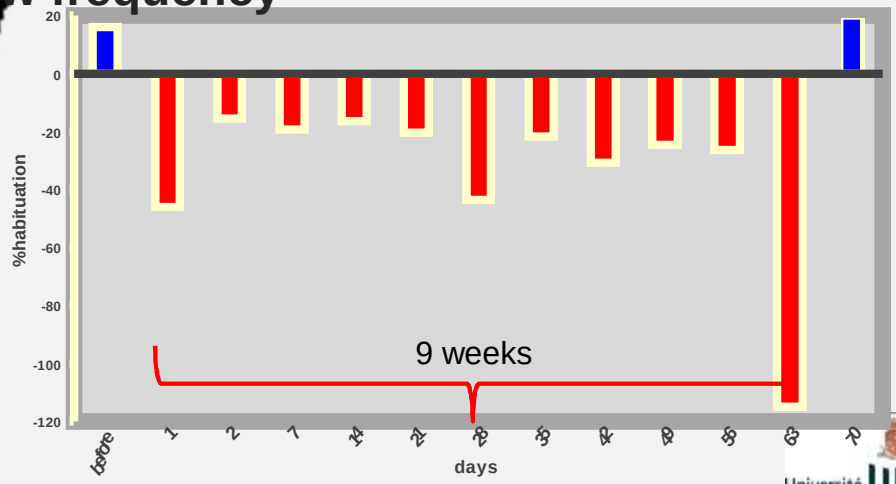
Transcranial magnetic stimulation (TMS) & transcranial direct current stimulation (tDCS)





- transiently interferes with cortical functi
- **high frequency**
- **low frequency**

Effect of **1 Hz rTMS** (5daily sessions) on **VEP habituation**
In a healthy subject



(Fumal et al 2007)

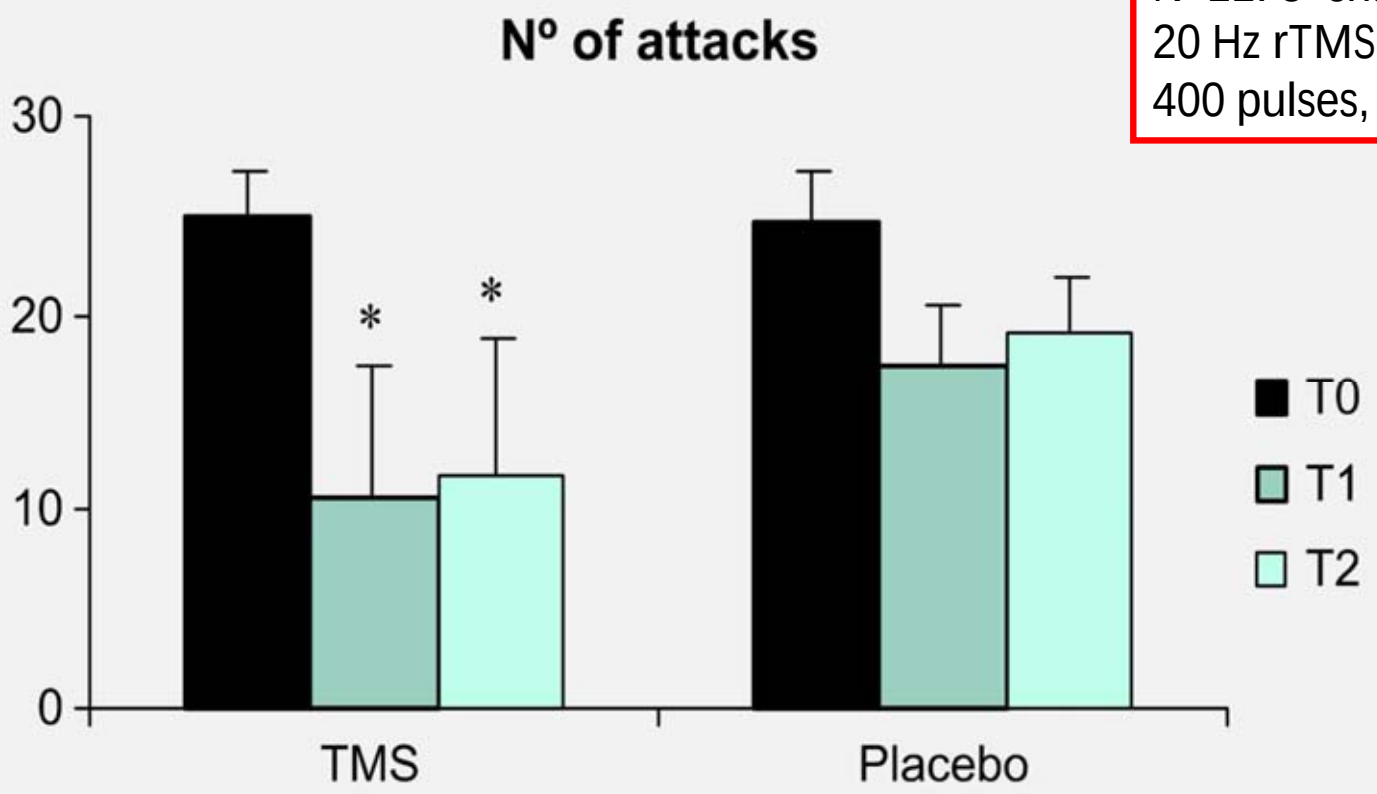
Journal of the Neurological Sciences 227 (2004) 67–71

www.elsevier.com/locate/jns

rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study

Filippo Brighina, Aurelio Piazza, Gaetano Vitello, Antonina Aloisio, Antonio Palermo, Ornella Daniele, Brigida Fierro*

N=11: 5=sham (placebo) parallel
20 Hz rTMS left DLPFC
400 pulses, 12 sessions/2nd day



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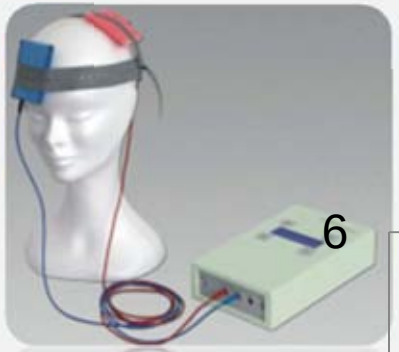
Université de Liège

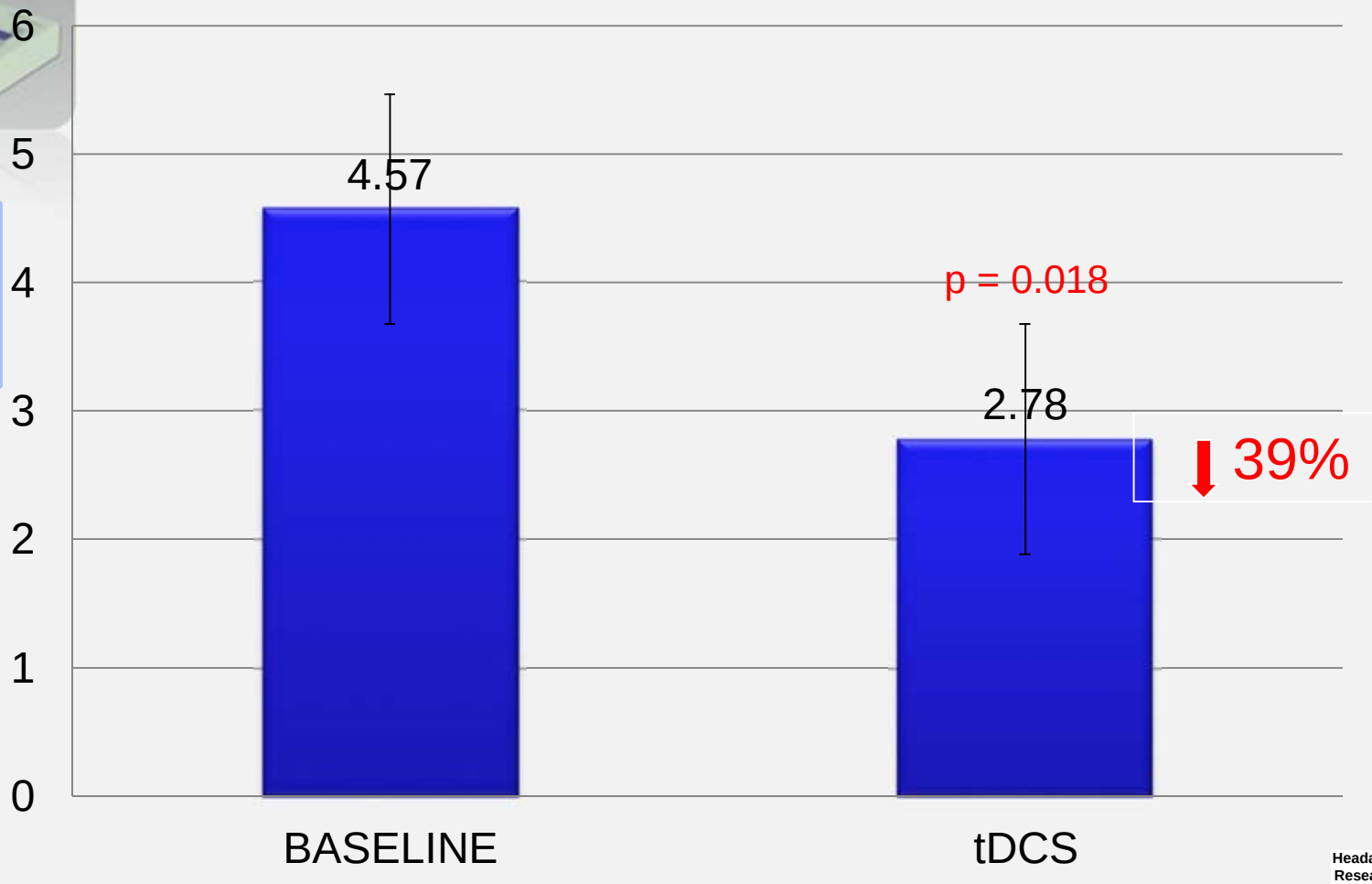
Transcranial direct stimulation in the prevention of episodic migraine

(anode over visual cortex)



- Episodic MO
- Anodal tDCS
- Visual cortex
- 2 sessions/week
- 8 weeks

MIGRAINE ATTACK FREQUENCY/mth (n=7)



(Vigàno et al. 2012 abstract)

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How to improve outcome ?

1. Combine preventive drugs ?
2. Manage comorbidity!
3. Use botulinum toxin ?
4. Try non-drug treatments ?
5. Go for neurostimulation?
6. Consider multimodal therapy ?

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WEST GERMAN HEADACHE CENTER

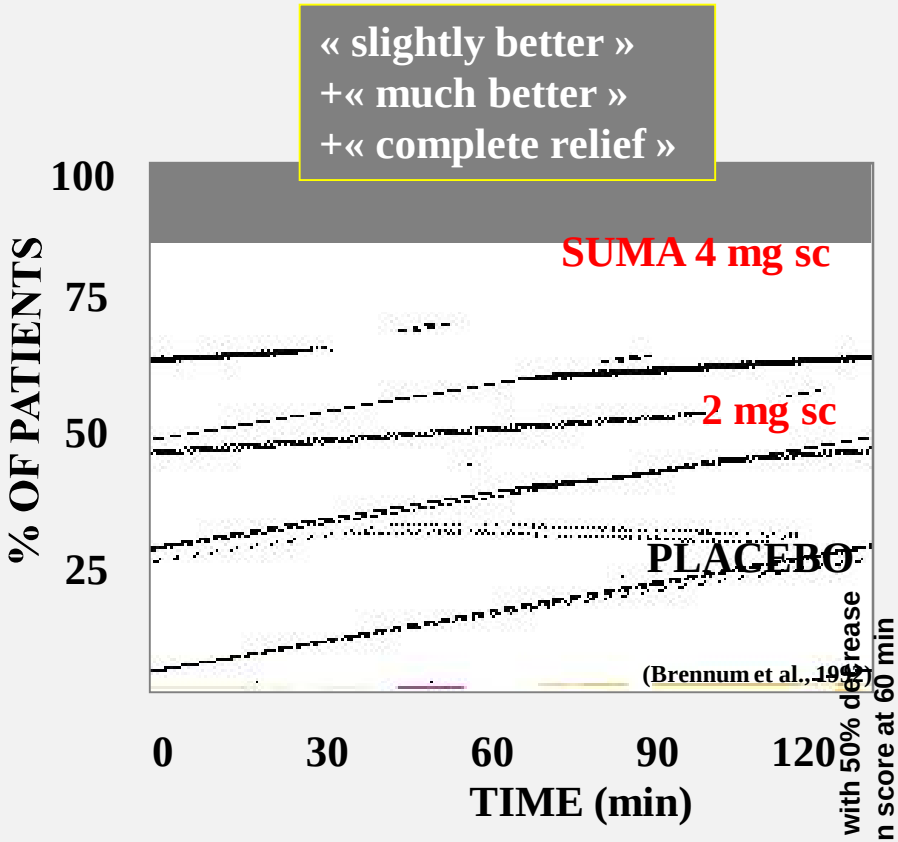
(Essen - Prof HC Diener, Dr C Gaul..)

Table 1 Class schedule day hospital

Time	*Monday*	*Tuesday*	*Wednesday*	*Thursday*	*Friday*	*Responsible*
9-10am	Medical education on headache	Medical education on headache	Clinical round Prof. Dr. Diener	Medical education on headache	Medical education on headache	Neurologist
10-11:30 am	Psychology group discussion	Psychology group discussion	Psychology group discussion	Psychology group discussion	Psychology group discussion	Psychologist
11:30-12:30am	Endurance sport	Endurance sport	Endurance sport	Endurance sport	Endurance sport	Physical therapist
12:30-2pm	Lunch break					
2-3pm	Physical therapy	Physical therapy	Physical therapy	Physical therapy	Physical therapy	Physical therapist
3-4pm	Relaxation training	Relaxation training	Relaxation training	Relaxation training	Relaxation training	Psychologist

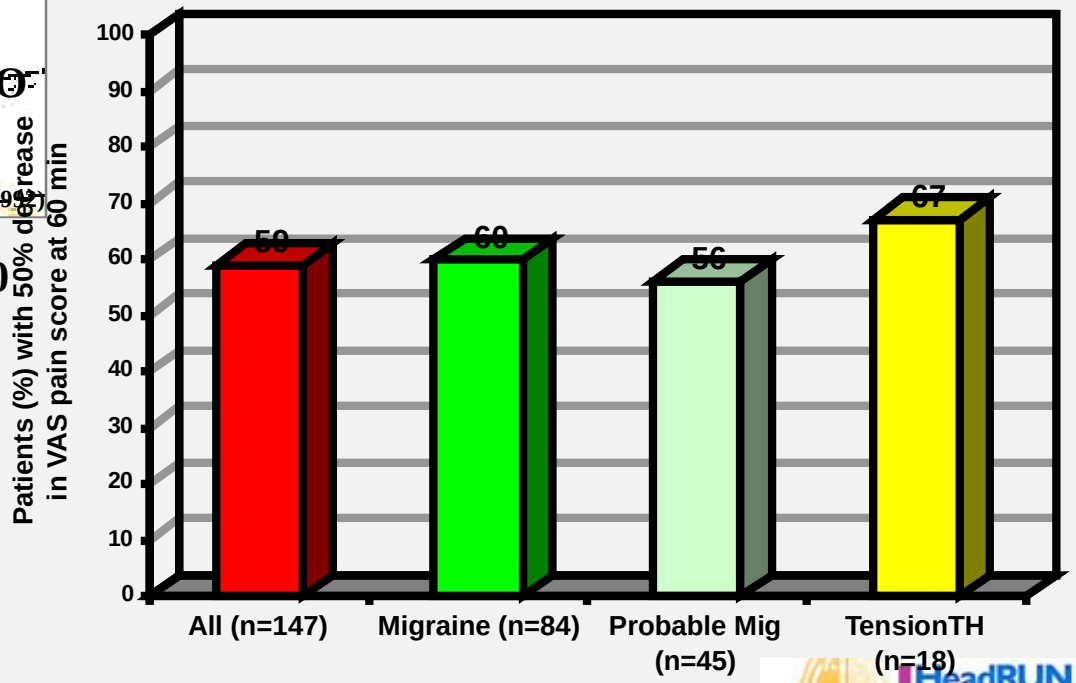
Some TTH patients respond to acute anti-migraine drugs

Effect of sumatriptan in tension-type headache (?)



Sumatriptan s.c. for headache in the emergency ward

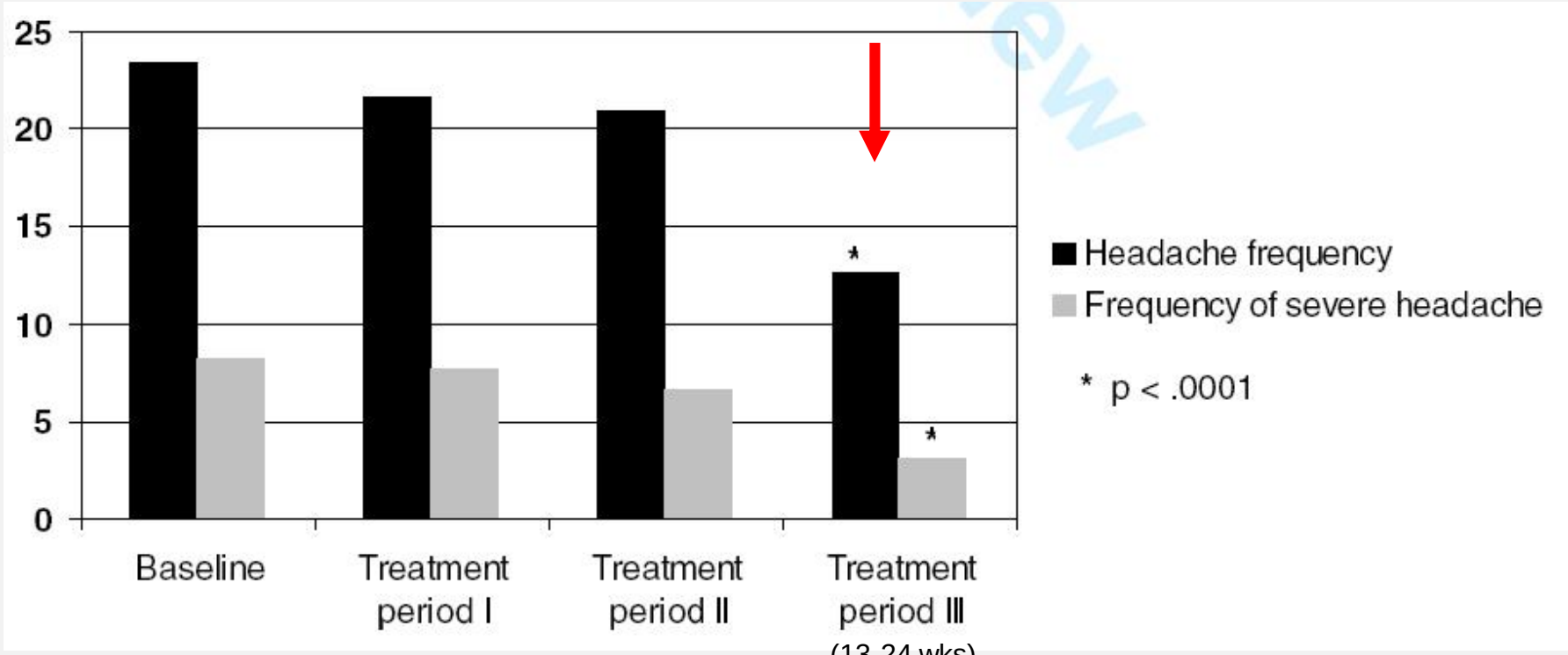
(Miner et al. Am J Emerg Med 2007)



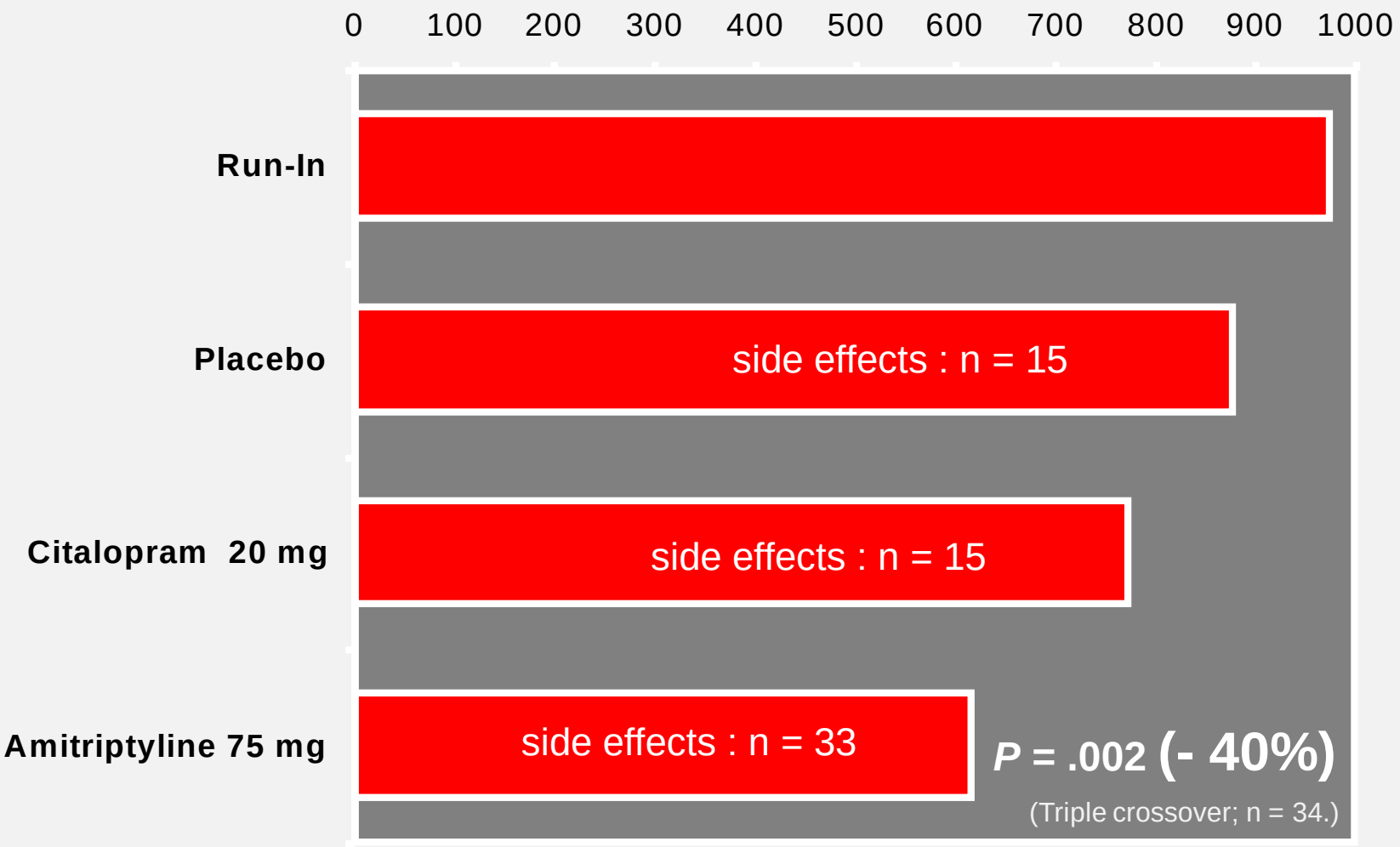
Some TTH patients respond to preventive anti-migraine drugs!

Topiramate was found effective in the prophylaxis of CTTH

(open label study. Lampl et al Cephalalgia 2007)



Pharmacothérapie prophylactique des CT: tricyclic vs SSRI

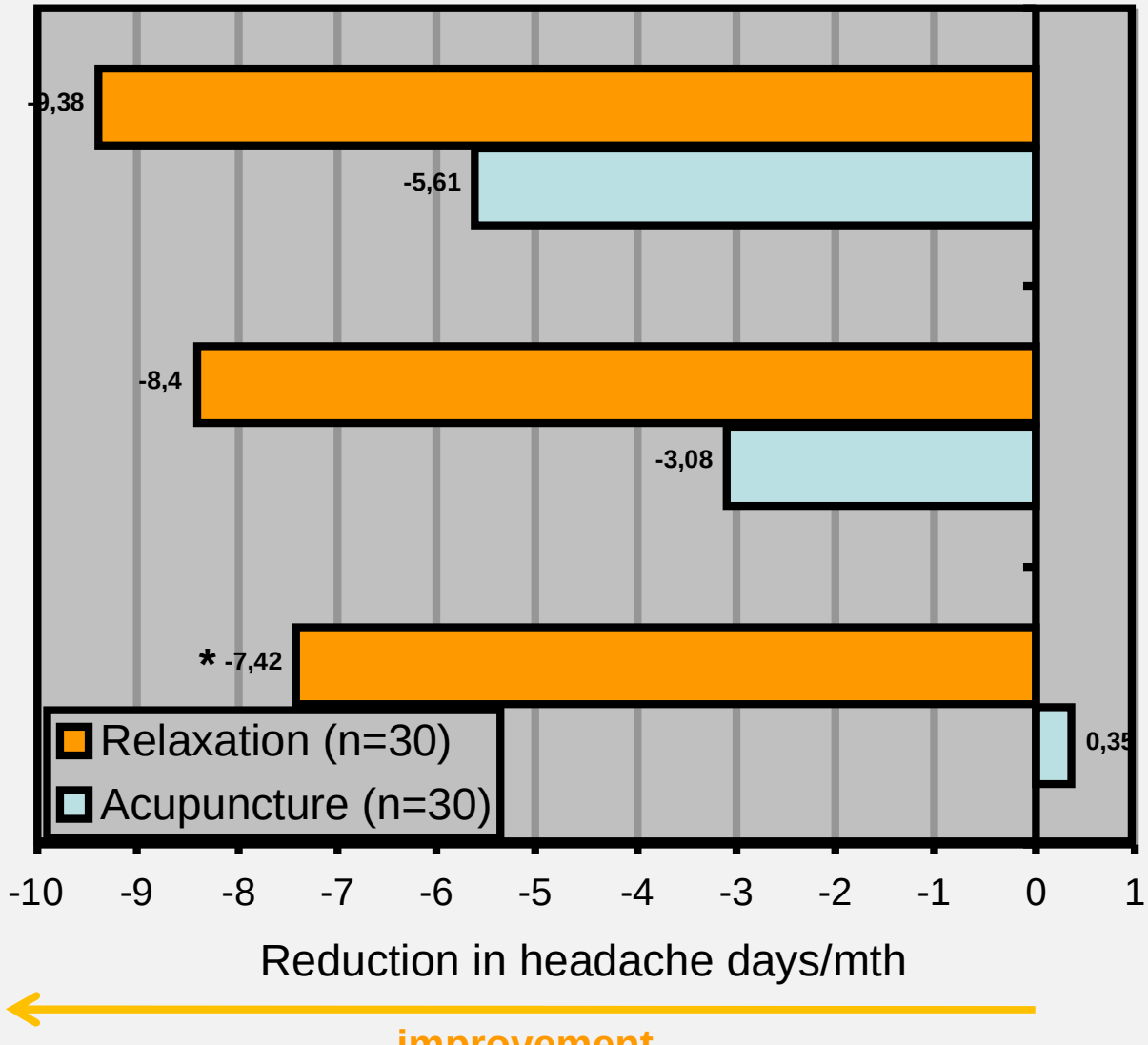


Area Under the Curve (Duration x Intensity) per 4 Weeks

(Bendtsen et al. *J Neurol Neurosurg Psychiatry.* 1996;61:285-290.)

Acupuncture and relaxation therapy in CTTH: headache days

(Söderberg et al. Cephalalgia 2006)



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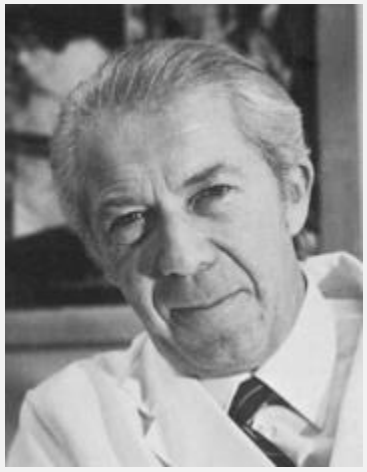
« What my mind elaborates has no value until nature which I study
has told me whether I’m right or wrong. »

(Christian de Duve, Nobel prize winner 1974, + May 4, 2013)



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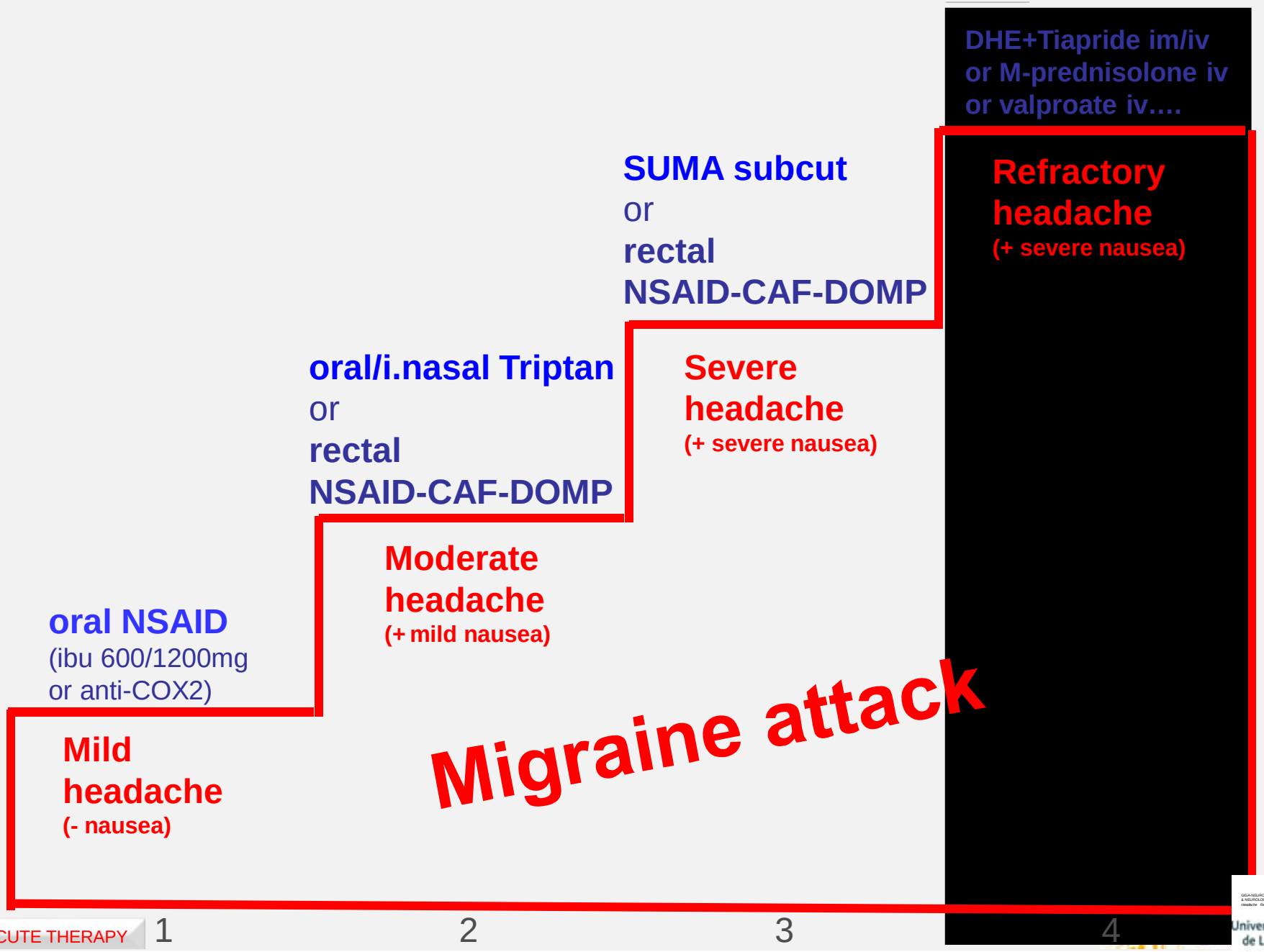
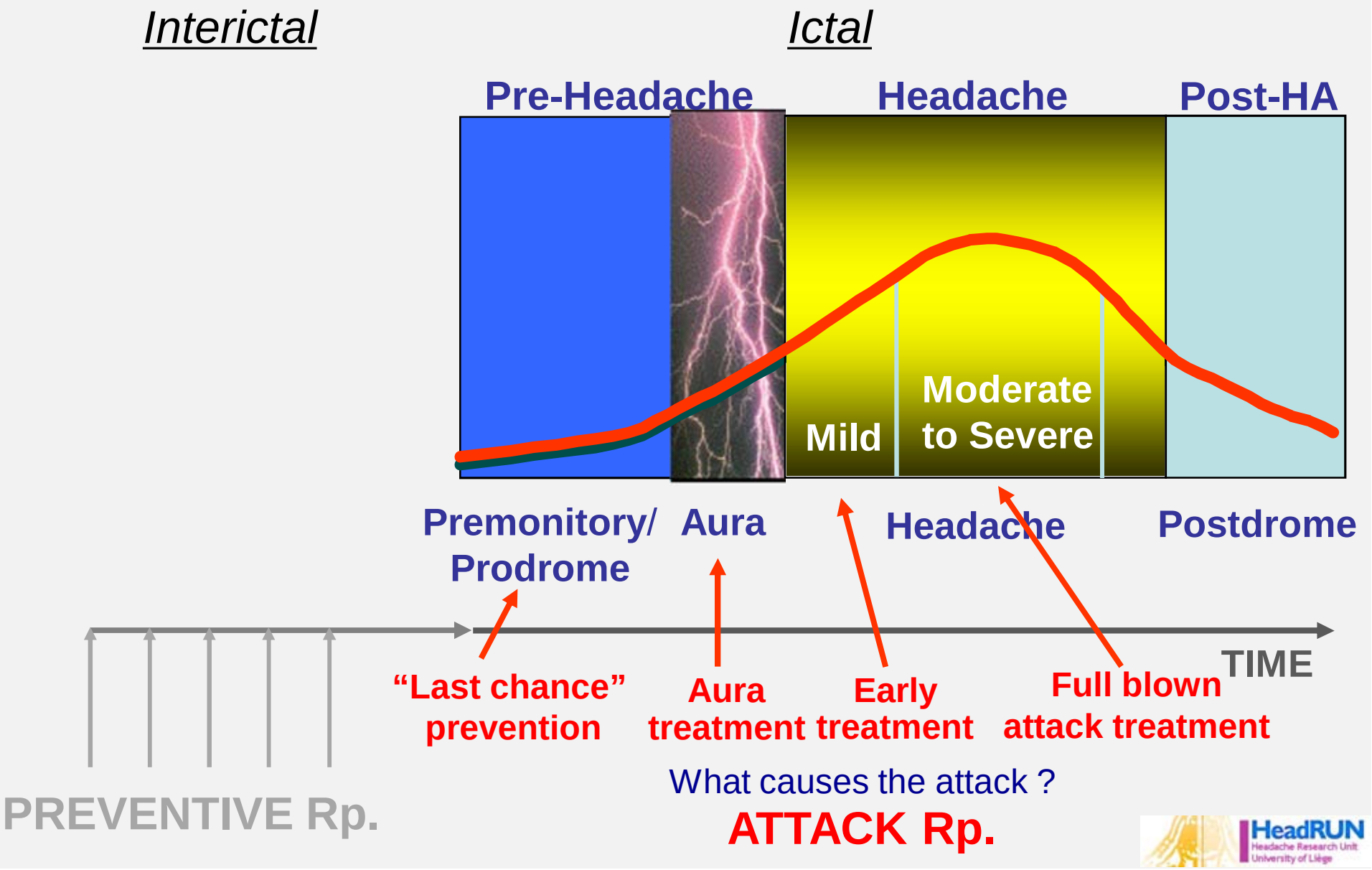
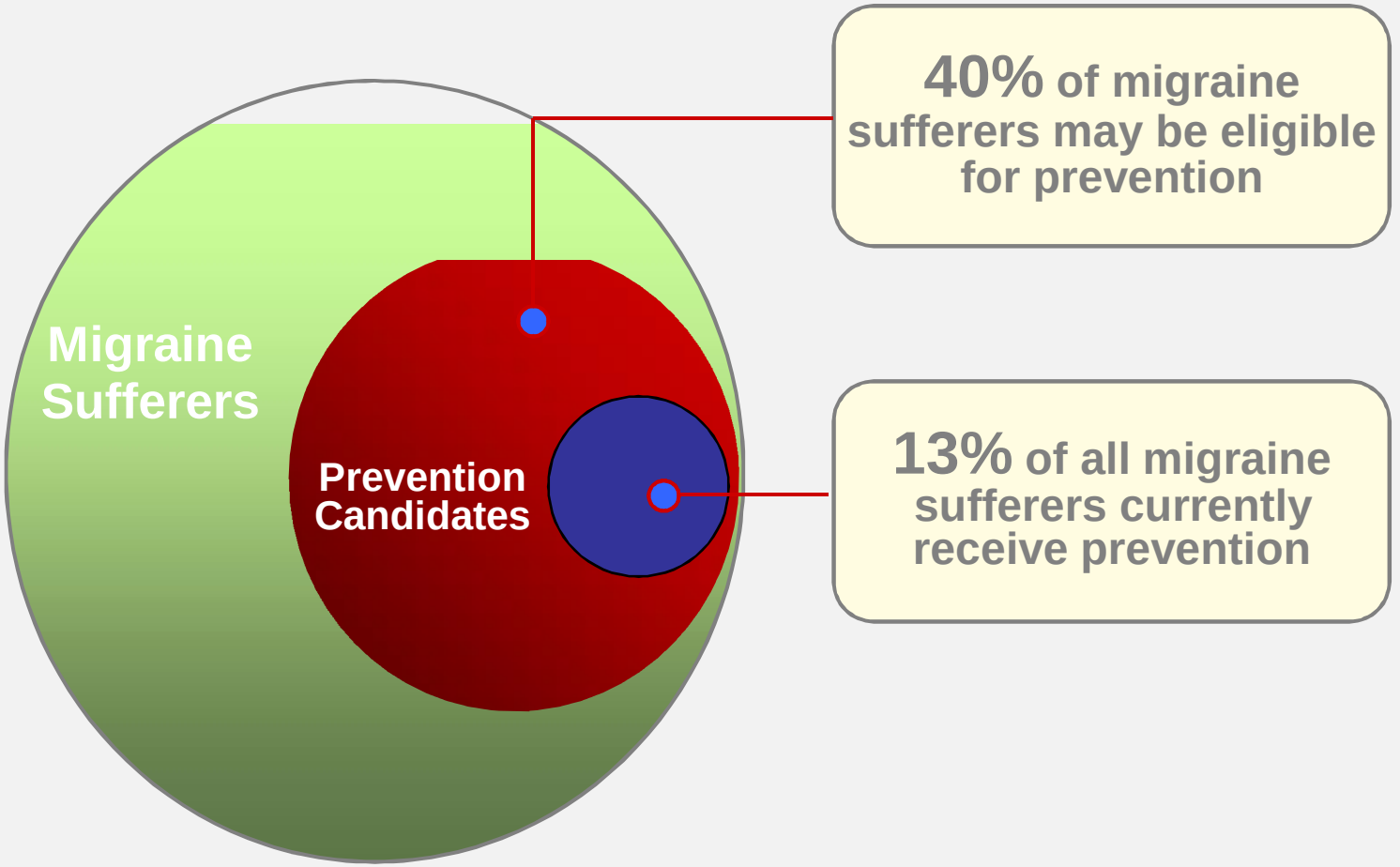
Step-wise strategy within attacks



Migraine Attacks are multi-stage sequential processes

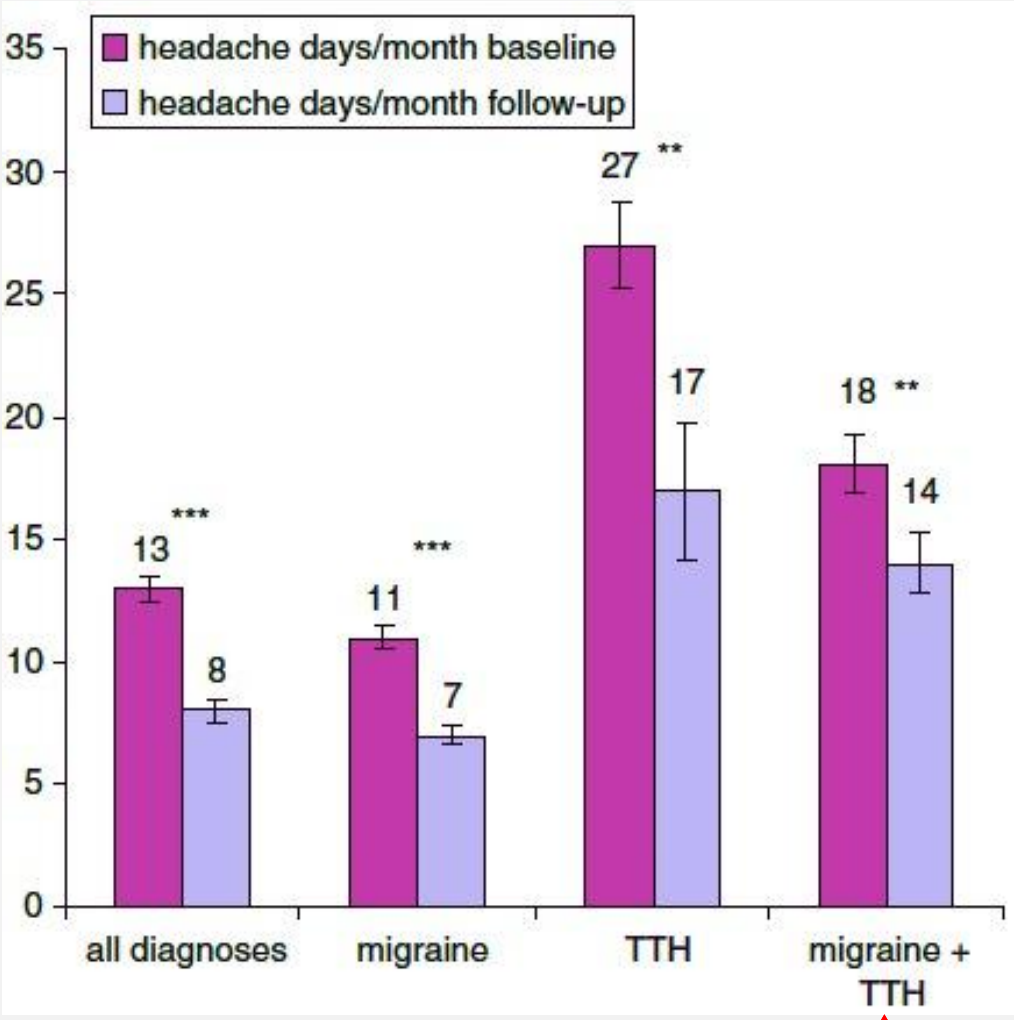


Migraine Prevention Underutilized (AMPP)



Lipton et al Neurology, 2007

Reduction in headache days



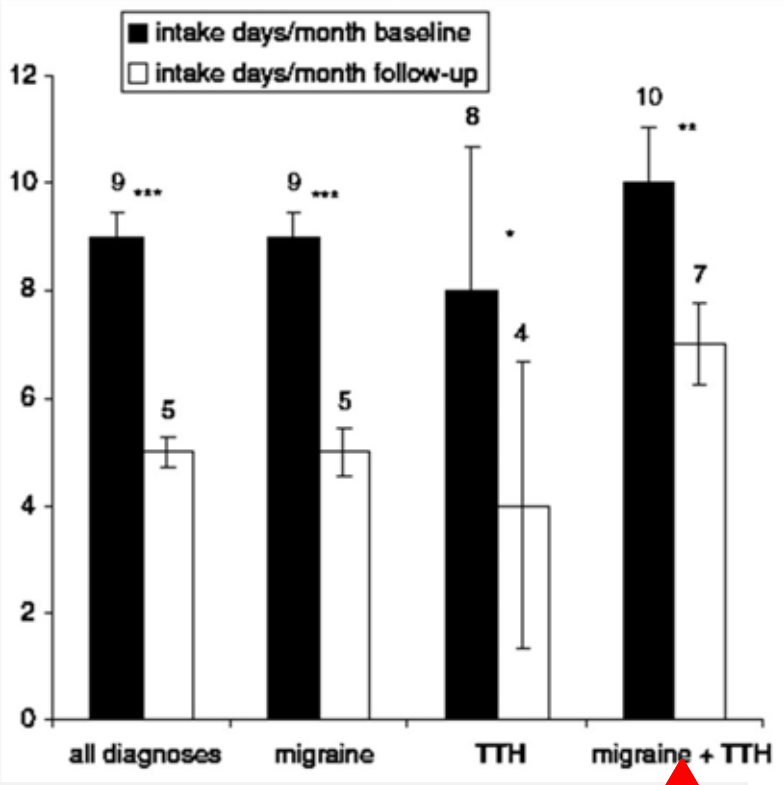
J Headache Pain
DOI 10.1007/s10194-011-0348-y

ORIGINAL

Clinical outcome of a headache-specific multidisciplinary treatment program and adherence to treatment recommendations in a tertiary headache center: an observational study

Charly Gaul · Christina van Doorn · Nadine Webering · Martha Dlugaj · Zaza Katsarava · Hans-Christoph Diener · Günther Fritsche

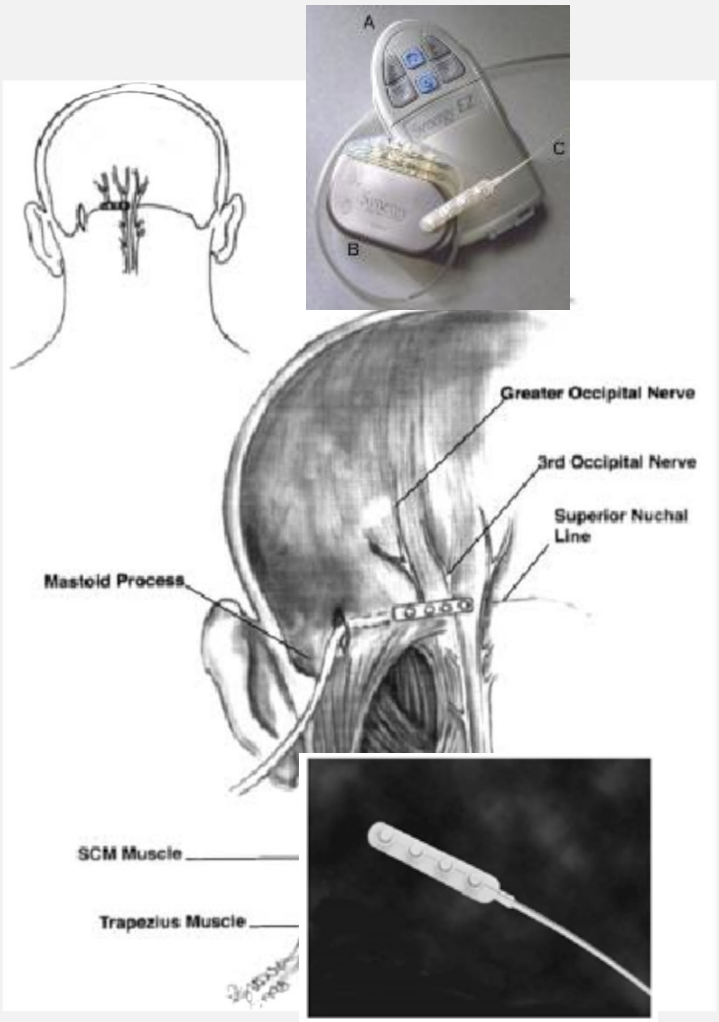
Reduction in days with acute medication intake

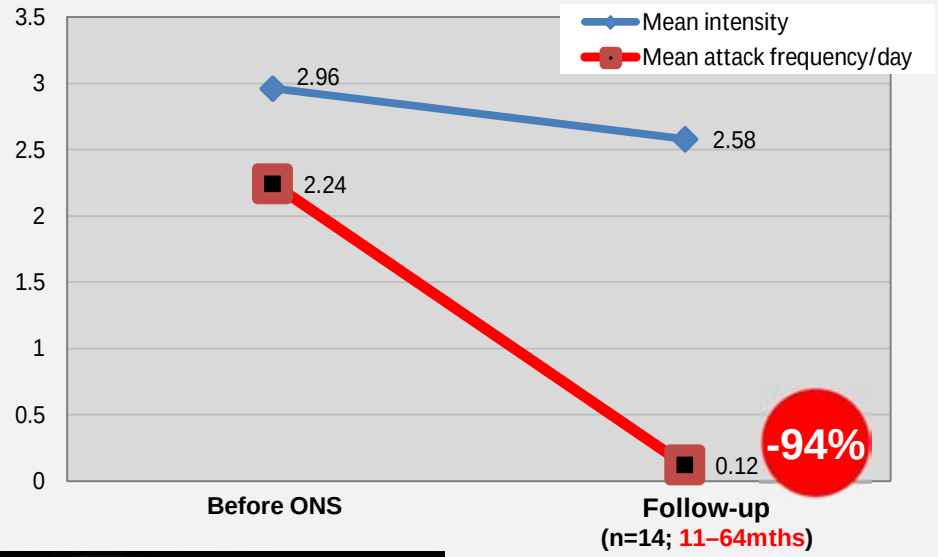


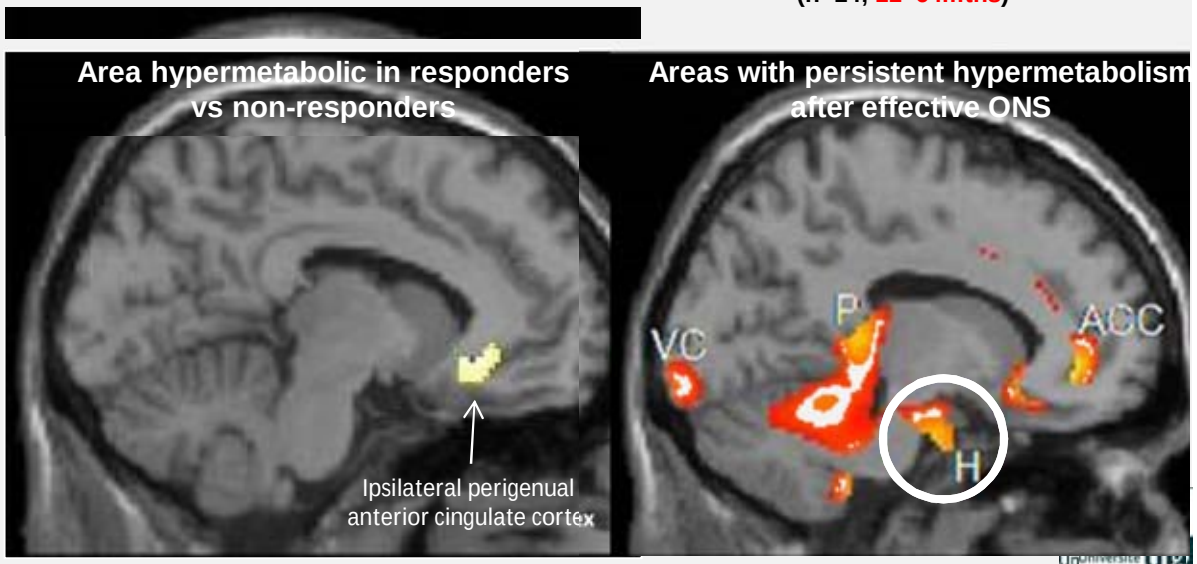
Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study

Delphine Magis, Marta Allena, Monica Bolla, Victor De Pasqua, Jean-Michel Remacle, Jean Schoenen

Lancet Neurology 2007 & Headache 2011-long term follow-up







(Magis et al. BMC Neurology 2011)

NSAIDs in migraine

- **First choice**: NSAIDs (including paracetamol, aspirin...)
- **Evidence of efficacy** for
  - ASA (**!**)
  - paracetamol
  - ibuprofen (**!**)
  - diclofenac (**!**)
  - naproxen
  - metamizol
  - tolfenamic acid (**!**)
  - phenazone
  - combination (ASA, paracetamol, caffeine)
- **No superiority** of a specific NSAID (except combination with caffeine)

! = not inferior to a triptan in controlled trials

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University of Liège

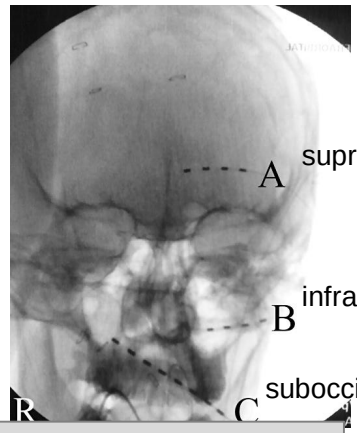
ONS for refractory headache: the future

1. Other ONS studies:
    - Implantable BION generator – *Goadsby et al. 2009*

2. Further controlled studies are needed, especially in migraine

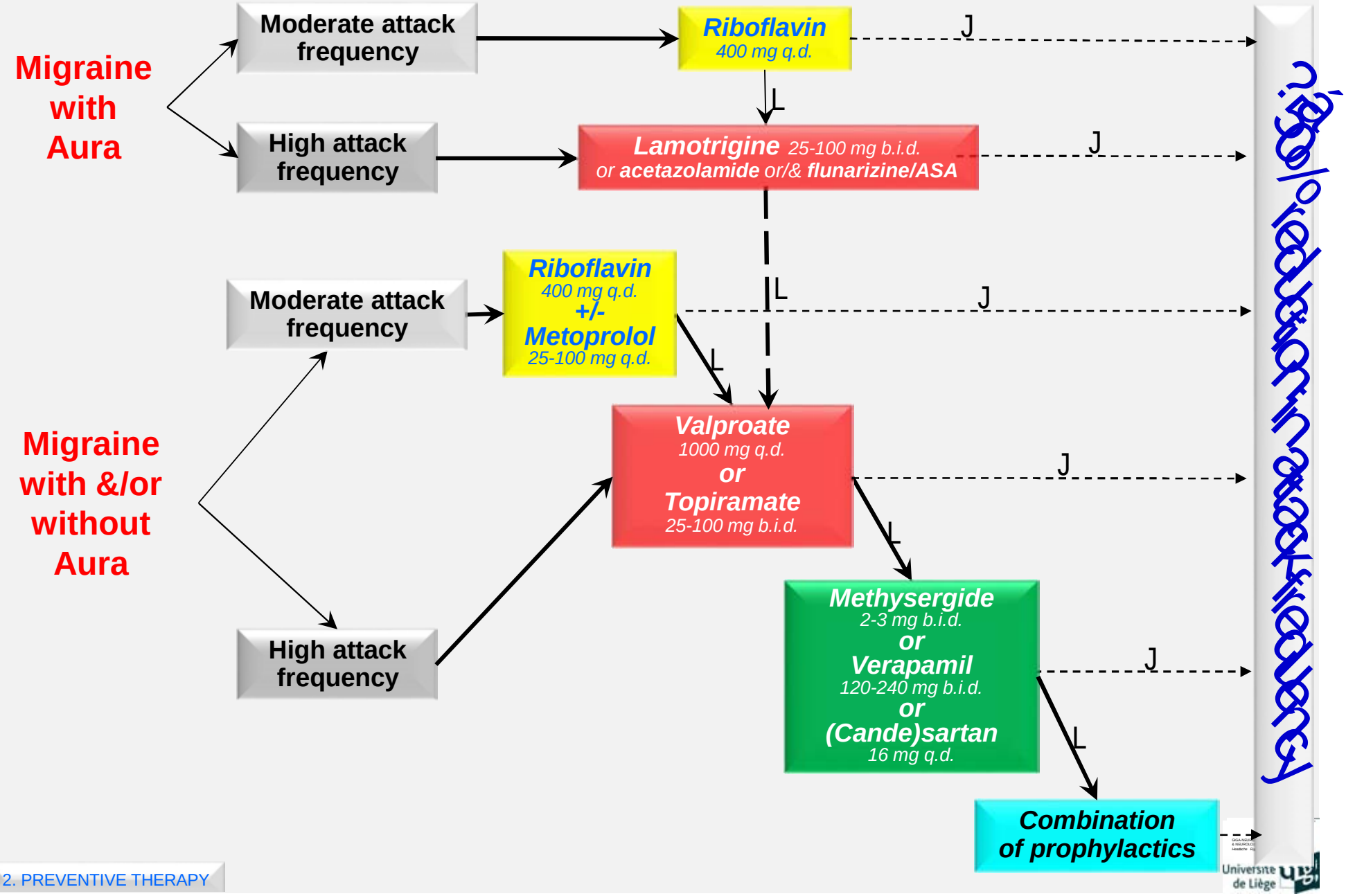
3. Multi-site neurostimulation may be more effective, but it is also « multi-invasive »

4. There may be a place for non-invasive transcutaneous ONS

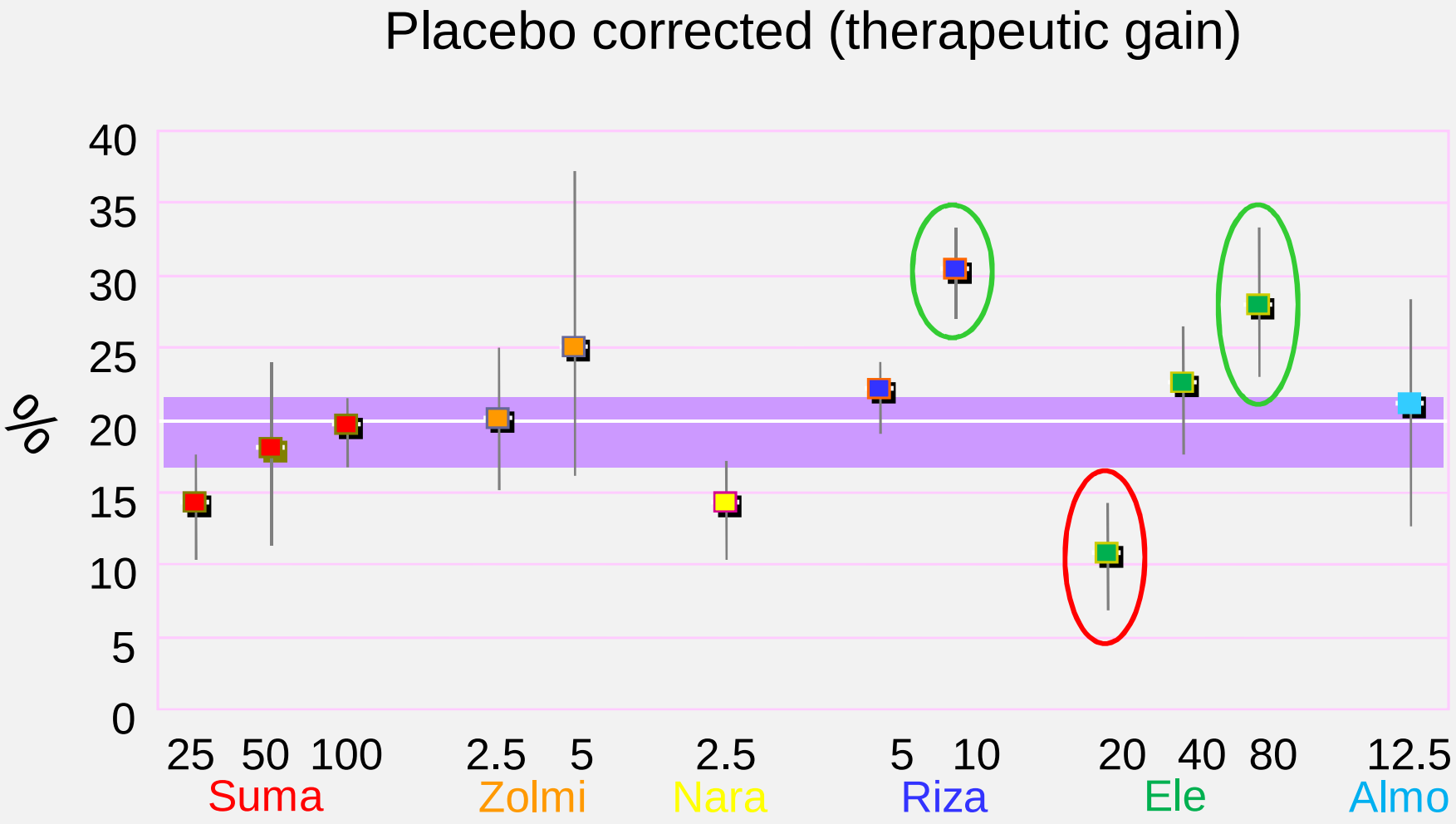


Triple neurostimulation in drCCH (Neuromodulation 2011)

An algorithm for « stratified » & « step-wise » preventive anti-migraine treatment



Triptans: pain free after 2 h



Ferrari M et al. Lancet 2001; 358: 1668-1675

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„I take an analgesic as soon as the pain begins.“

(yes in %)

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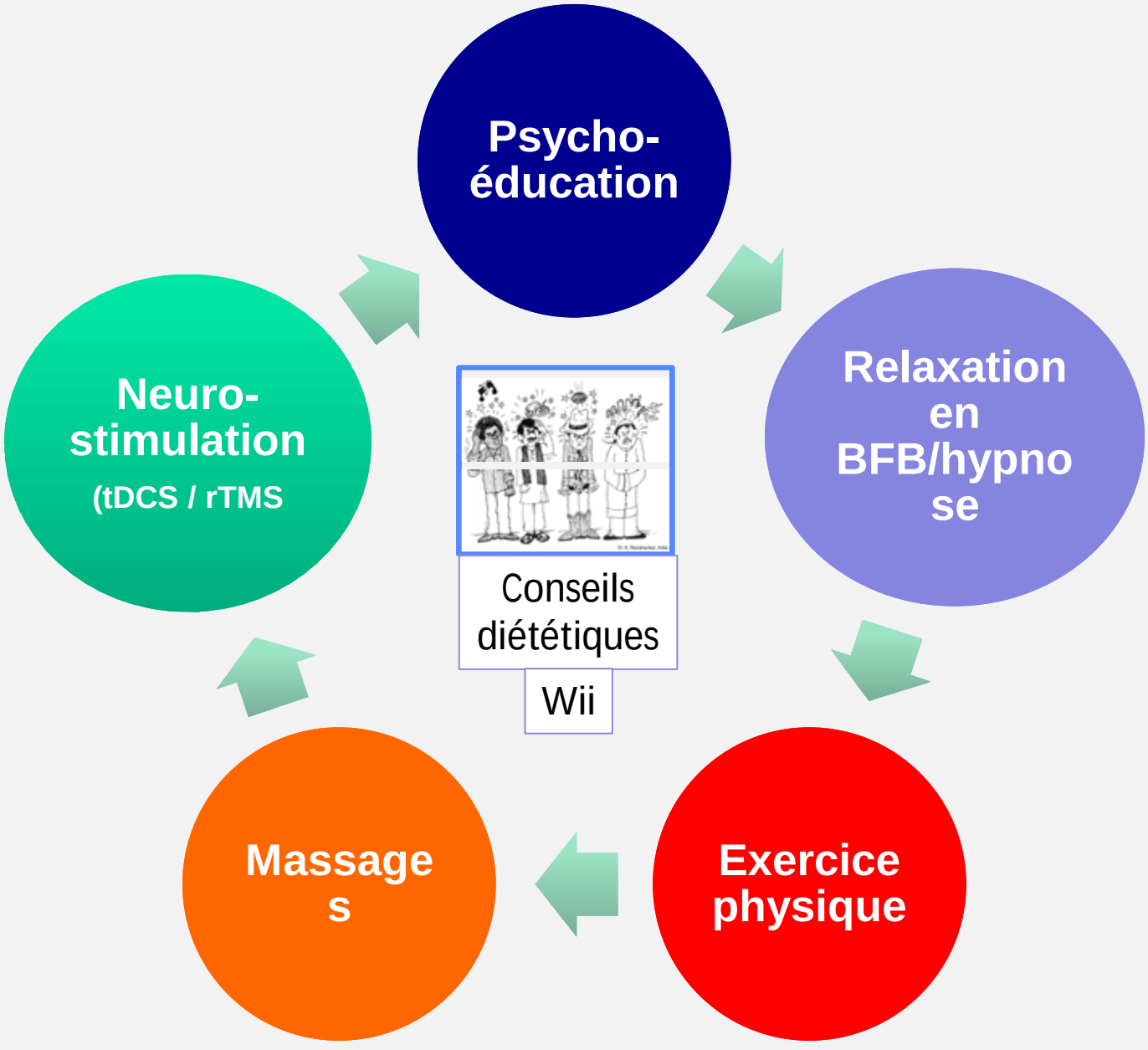
Traitement Multimodal des Céphalées Chroniques



Background

Guide to Pain Management in a Low Resource Setting

Editors

Nilesh B. Patel
Department of Medical Physiology
University of Nairobi
Nairobi, Kenya

Andreas Kopf
Director Pain Management
Department of Anaesthesiology
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Visiting Professor University of Nairobi

CHARITÉ

Chapter 24
Headaches

Arnaud Fumal and Jean Schoenen

European Journal of Neurolog
CME ARTICLE
EFNS guideli
of an EFNS t
S. Evers[a], J. Áfra[b],
[a]Department of Neurology,
of Manual Medicine, Müns
[e]UCL, Institute of Neurolog
[g]Department of Neurology,
11/j.1468-1331.2009.02748.x
evised report
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apest, Hungary; [c]Academy
, San Francisco CA, USA;
n, Gothenburg, Sweden;
rich, Switzerland

Akuttherapie und Pr
Leitlinie der Deutschen Migräne
und der Deutschen Gesellschaft
S. Evers[1], A. May[2], G. Fritsche[3], P. Kropp
A. Straube[9], H.-C. Diener[3]
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Brüder, Linz, Österreich; [6]Neurologische Klinik, Kliniken der Stadt Köl
[7]Neurologische Praxis, Reutlingen; [8]Neurologische Klinik und Poliklini
[9]Neurologische Klinik der Universität München, Klinikum Großhadern
Nervenheilkunde 2008; 27: 933–949

ROLOGY
ised guidelines for migraine headache (an
the Quality Standards Subcommittee of the
cademy of Neurology
n D. Silberstein
y 2000;55:754-762
This information is current as of November 9, 2009
ersion of this article, along with updated information and services, is located on
the World Wide Web at:
http://www.neurology.org/cgi/content/full/55/6/754

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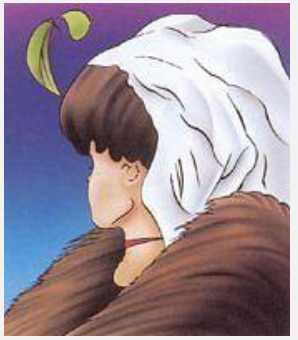
MIGRAINE THERAPY : 2 faces of a coin



1. Act on the causes of the migraine attack
   → Acute therapy

↓

Novel **drug** treatments

Emerging neurostimulation methods

2. **Modify the causes of attack repetition**
   → **Preventive therapy**

↓

Emerging drug treatments

Novel **neurostimulation** methods

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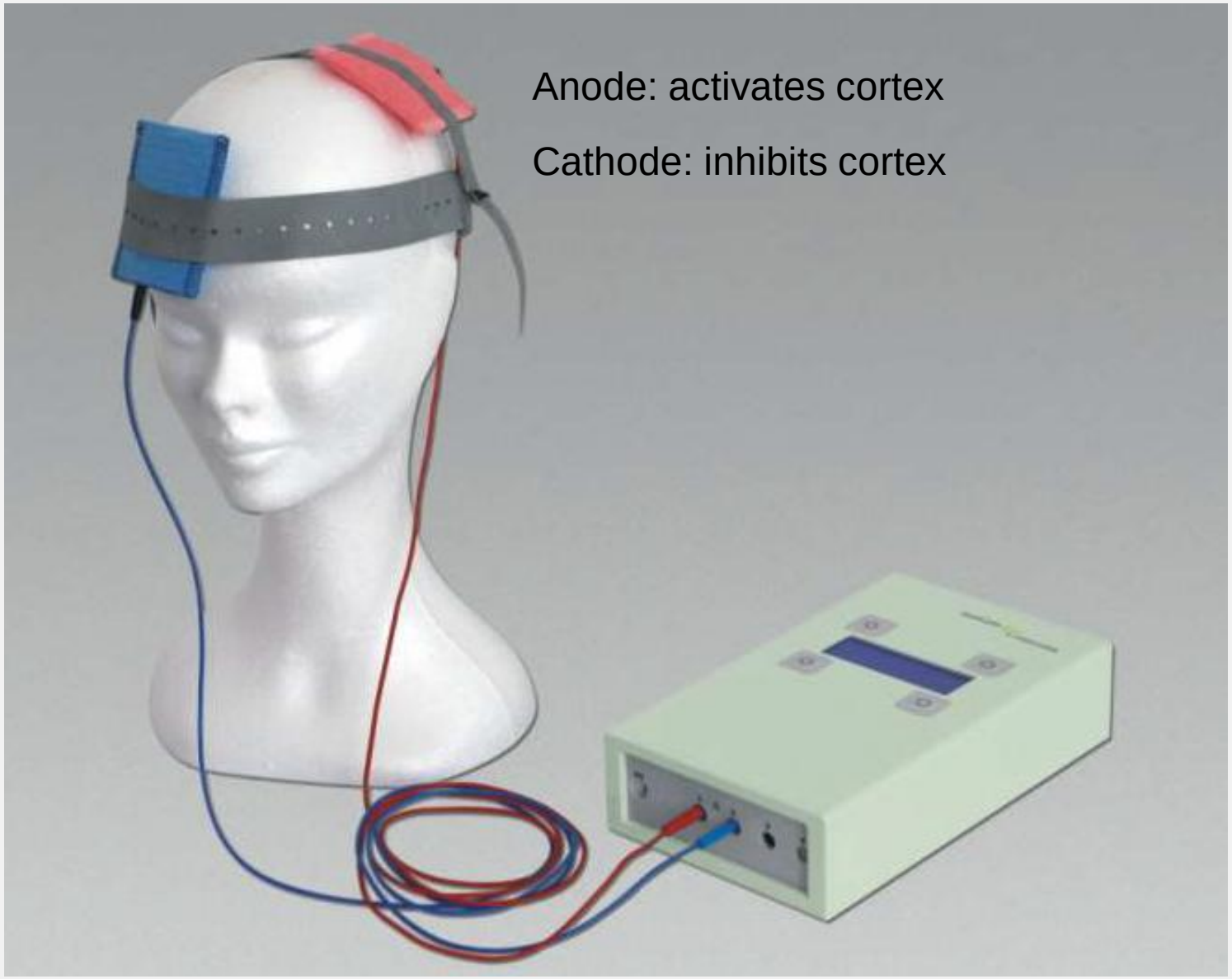
NEUROSTIMULATION FOR HEADACHES

- occipital nerve stimulation (ONS)
- sphenopalatine ganglion stimulation
- vagus nerve stimulation (VNS)
- transcutaneous stimulation (TENS)
- transcranial magnetic stimulation (TMS) & direct current transcranial stim. (dTCS)

Transcranial direct current stimulation (tDCS)



Central neurostimulation methods

Cathodal TDC stimulation

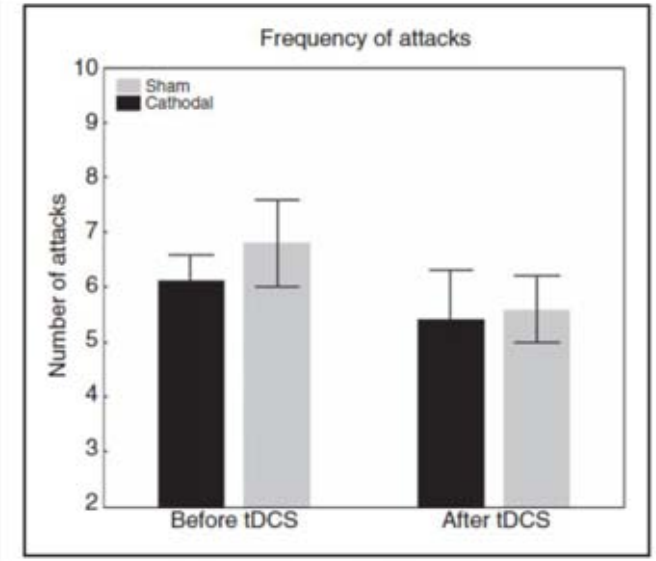
Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine

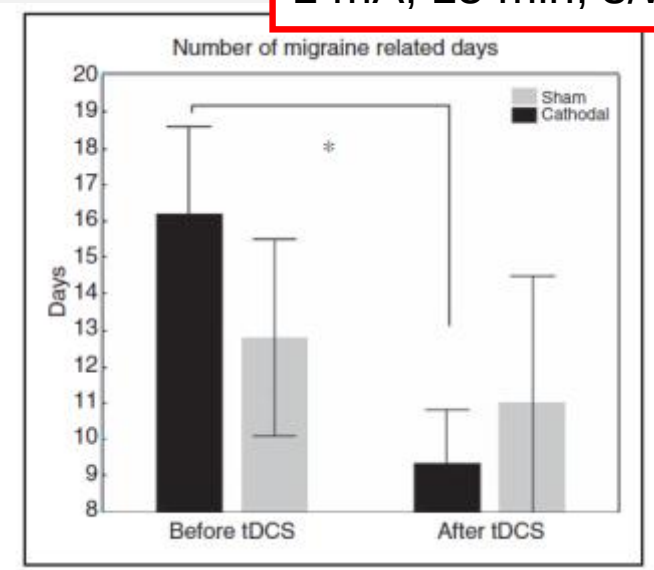
Cephalalgia
31(7) 820–828

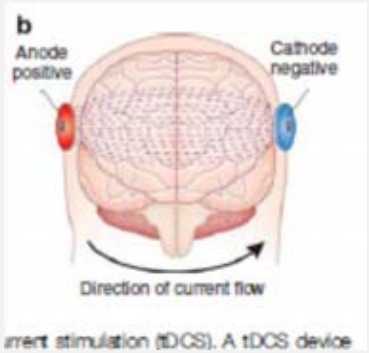
DOI: 10.1177/0333102411399349
cep.sagepub.com
SAGE

Andrea Antal[1], Naomi Kriener[1], Nicolas Lang[2], Klara Boros[1] and Walter Paulus[1]

N=26, 13 sham (placebo)
Oz=cathode, Cz=anode
1 mA, 15 min, 3/w, 6 weeks







rrent stimulation (tDCS). A tDCS device

No difference between verum and sham except for migraine intensity

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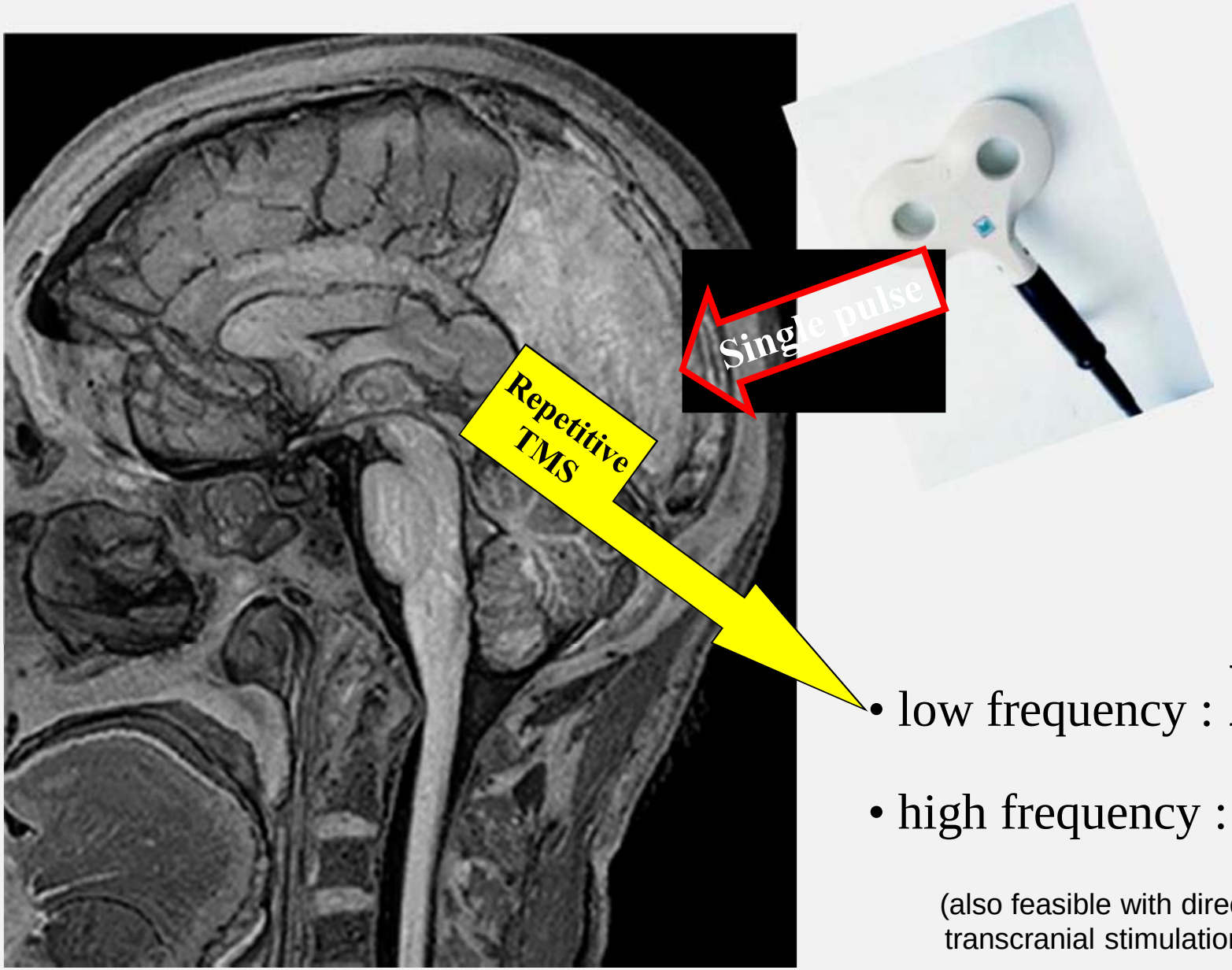
Transcranial magnetic stimulation



- low frequency : INHIBITS
- high frequency : EXCITES

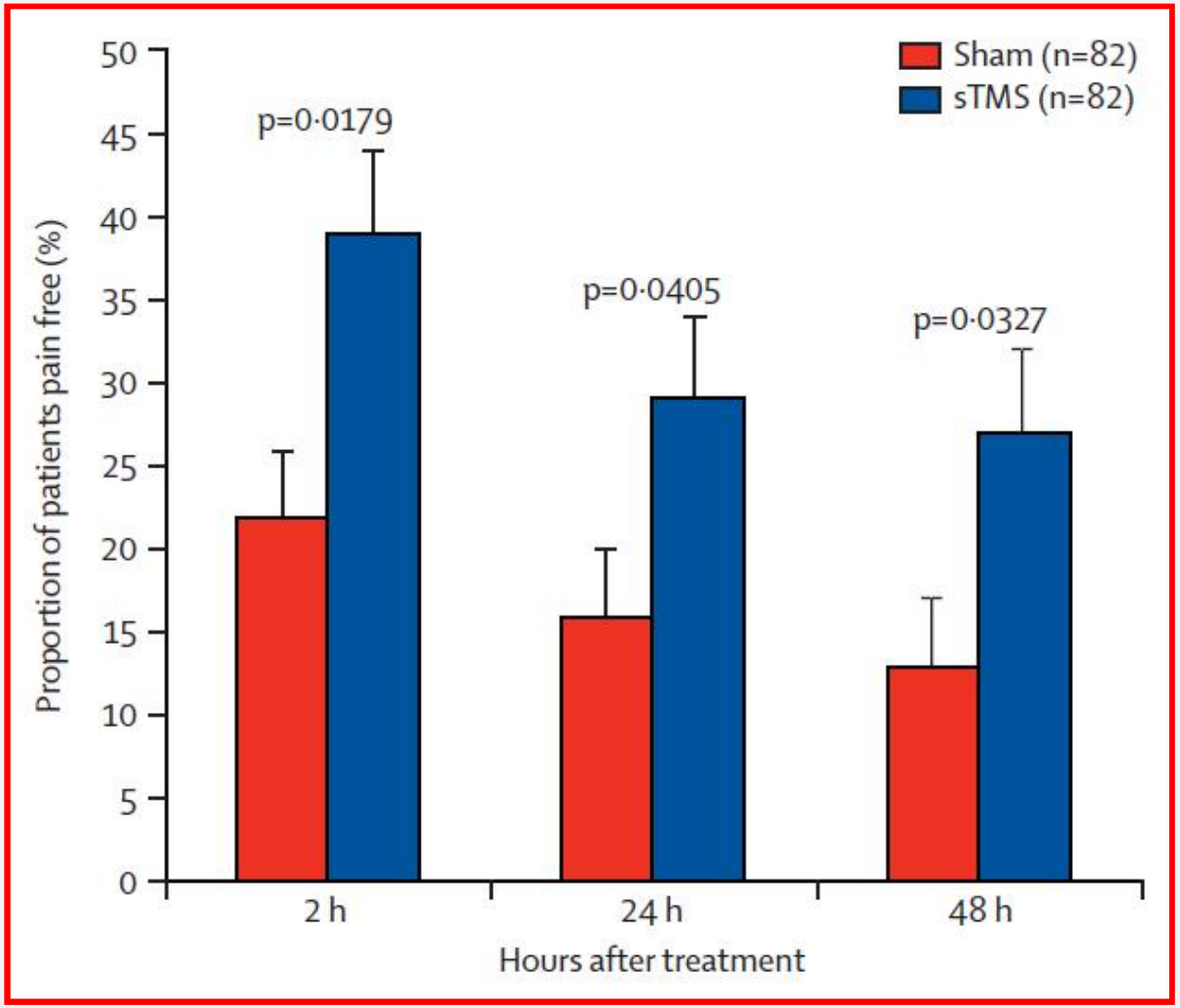
(also feasible with direct current transcranial stimulation – dcTS)

Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial

Richard B Lipton, David W Dodick, Stephen D Silberstein, Joel R Saper, Sheena K Aurora, Starr H Pearlman, Robert E Fischell, Patricia L Ruppel, Peter J Goadsby

Lancet Neurol 2010; 9: 373–80

N=164 (82 sham)
TMS 2 pulses over occiput
Within 1h after aura onset



Cephalalgia
An International Journal of Headache
International Headache Society

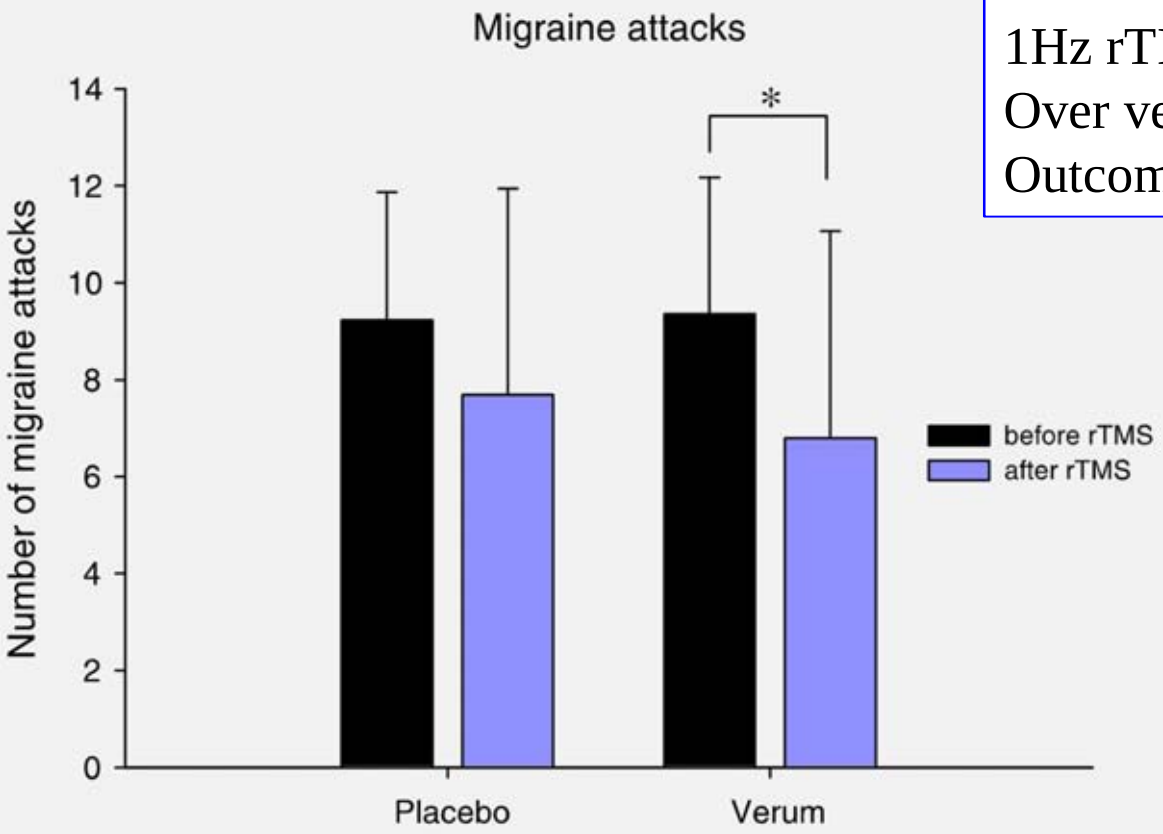
Low-frequency rTMS of the vertex in the prophylactic treatment of migraine

Cephalalgia
30(2) 137–144

DOI: 10.1111/j.1468-2982.2009.01911.x
cep.sagepub.com

M Teepker[1], J Hötzel[1], N Timmesfeld[2], J Reis[1], V Mylius[1], A Haag[1], W H Oertel[1], F Rosenow[1] and K Schepelmann[1,3]

N=27
1Hz rTMS -2x500 pulses – 5 days
Over vertex
Outcome 8 weeks

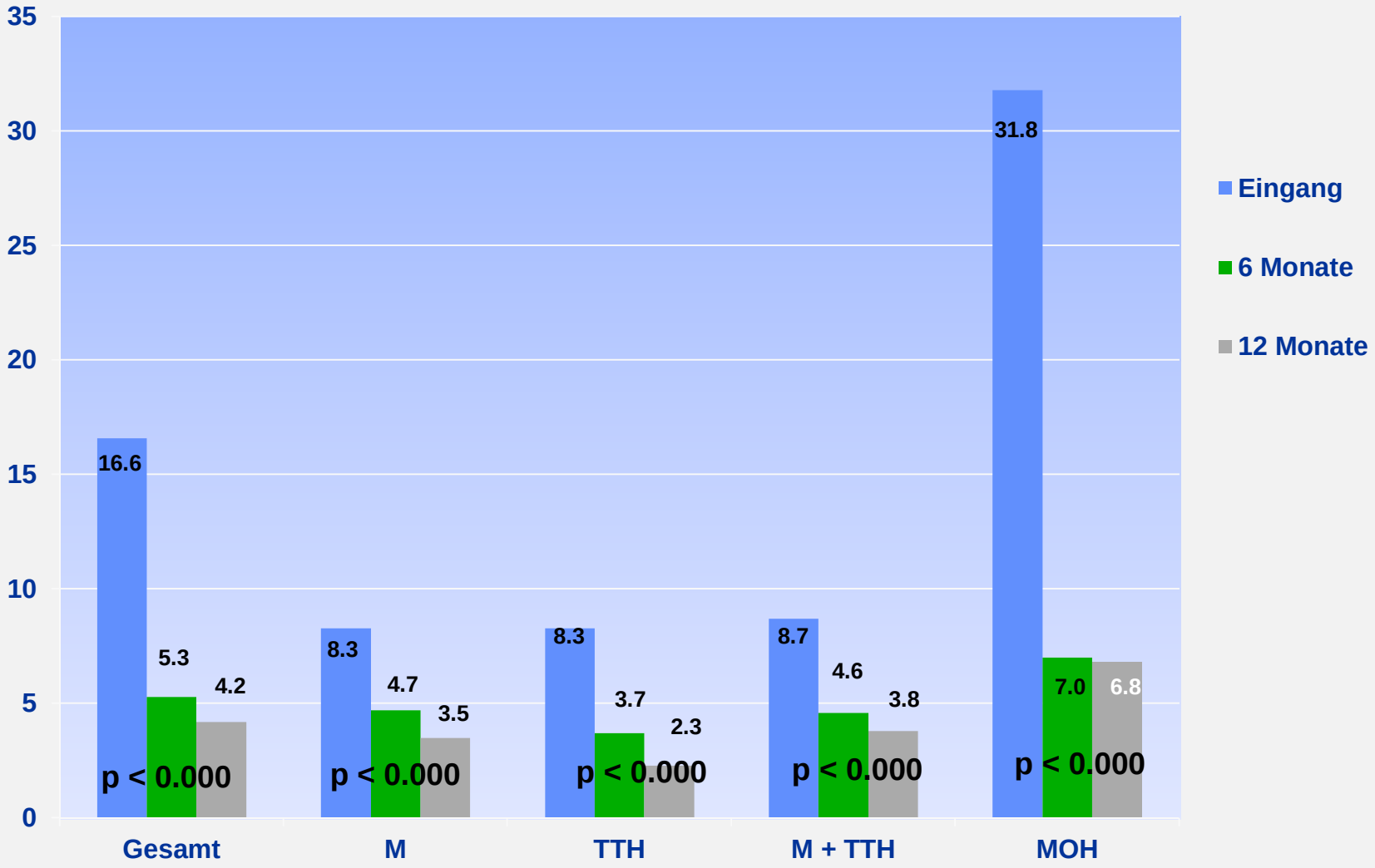


Non/minimally invasive NEUROMODULATION techniques for headache (..and other pains)

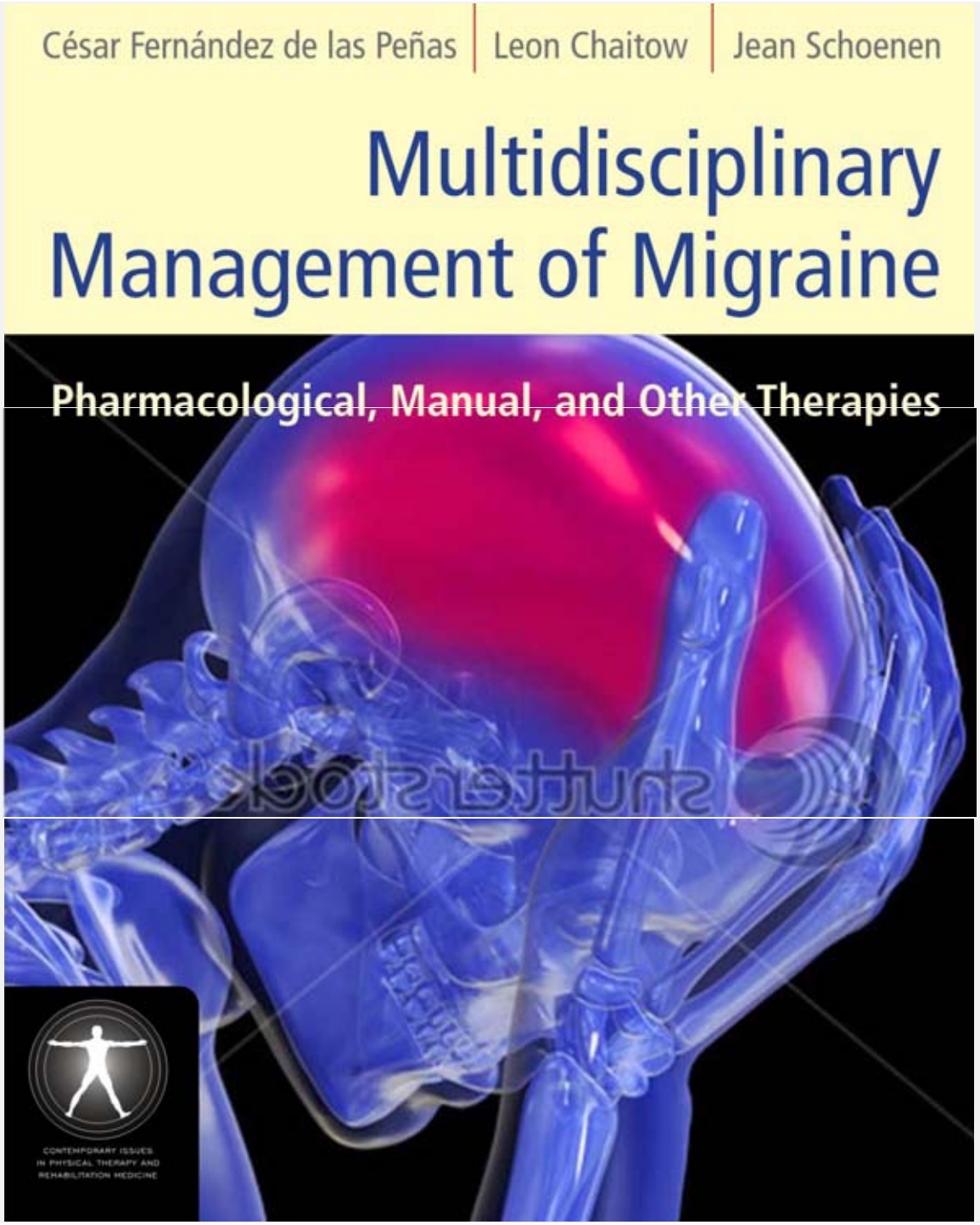
Promising if: 1. their efficacy can be proven in *RCTs*
2. their *mode of action* can be understood

GIGA-NEUROSCIENCES & NEUROLOGY DEPT
Headache Research Unit
Université de Liège

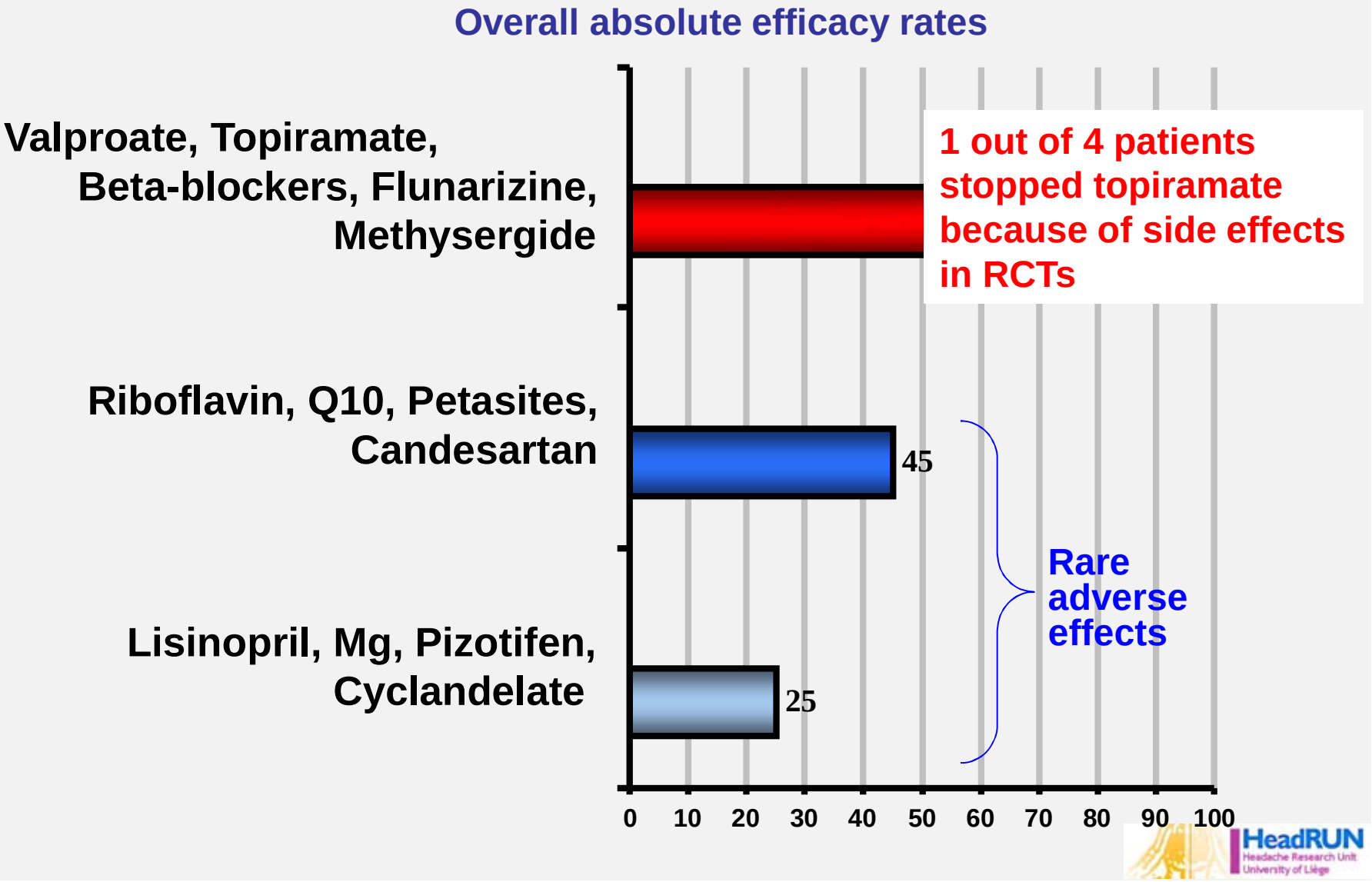
Acute medication intake (N ° / month)



(Wallasch T. Kopfschmerzklinik Berlin-St Gallen)


César Fernández de las Peñas
Leon Chaitow
Jean Schoenen
Multidisciplinary Management of Migraine
Pharmacological, Manual, and Other Therapies
CONTEMPORARY ISSUES IN PHYSICAL THERAPY AND REHABILITATION MEDICINE

Preventive Anti-Migraine Drugs



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AAN preventive guidelines

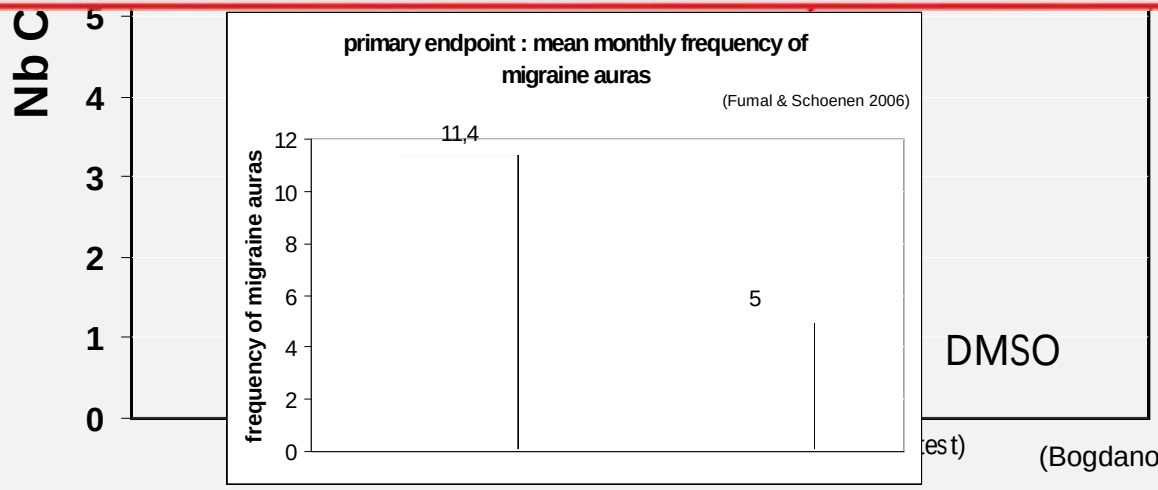
Level A Established efficacy	Level B: Probably effective	Level C: Possibly effective	Level U: Inadequate or conflicting	Possibly, or probably ineffective
AEDs Divalproex Valproate Topiramate **B-blockers** Metoprolol Propranolol Timolol*	**SNRI/TCA** Amitriptyline Venlafaxine **B-blockers** Atenolol* Nadolol*	**ARBs** Candesartan Lisinopril **?ł agonists** Clonidine* Guanfacine* **AEDs** Carbamazepine* **B-blockers** Nebivolol Pindolol* **Ca++ Blockers** Nimodipine Verapamil **Leukotriene Antag** Cyproheptadine	**CA inhibitor** Acetazolamide **Anticoagulants** Coumadin Picotamide **SSRI /SSNR1** Fluvoxamine* **AEDs** Gabapentin **TCAs** Protriptyline* **B-blockers** Bisoprolol* **Ca++ Blockers** Cyclandelate Nicardipine* Nifedipine*	**NOT effective** Lamotrigine **Probably NOT effective** Clomipramine* **Possibly NOT effective** Acebutolol* Clonazepam* Nabumetone* Oxcarbazepine Telmisartan

Preventive treatment of migraine with aura

Table 2 Treatment response to lamotrigine

Parameter	n/N	%
Responder (aura)*	44/59	75
Non-responder (aura)	15/59	25
Total	59	100

(Lampl et al. 2005)



(Bogdanov et al 2009)

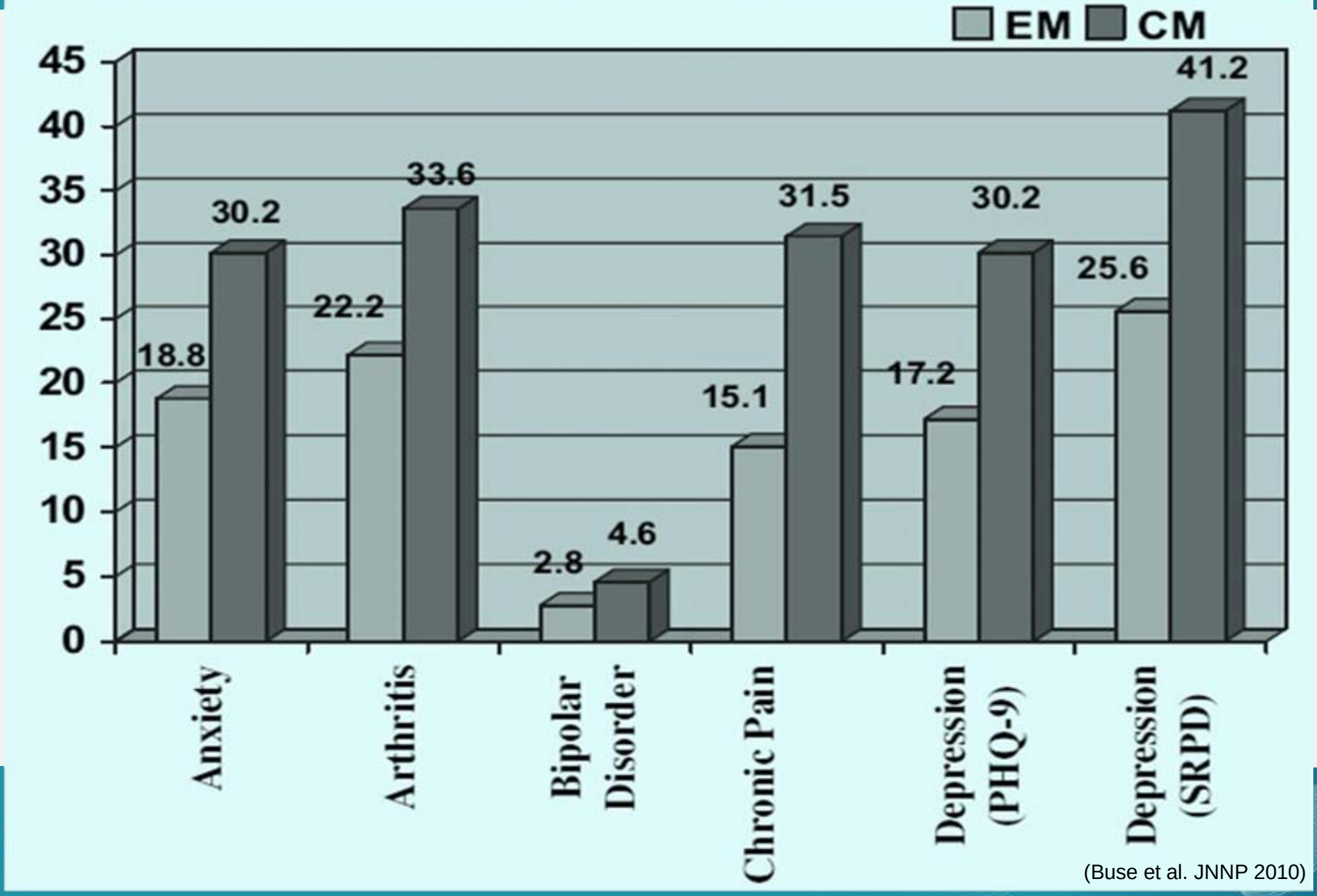
What about BOTOX™ ?

- ineffective in episodic migraine, tension-type headache
- may be effective in **chronic migraine**
  (Preempt 1 & 2 trials)

PREEMPT 1 & 2: Problems & questions

1. Is the 10% difference between Botox & saline clinically relevant ?
2. What was the role of medication overuse ?
3. Was blinding effective ?
4. 40% of patients never had a preventive therapy
   despite chronic migraine since 20 years !
5. Are saline injections pharmaco-economically as efficient ?
6. Responders need to be identified ?
7. …to be used eventually in a specialized multidisciplinary setting

Manage comorbidity



(Buse et al. JNNP 2010)

Perspective: NEUROMODULATION techniques

Promising if: 1. we can prove their efficacy in RCTs
2. we manage to understand how they work

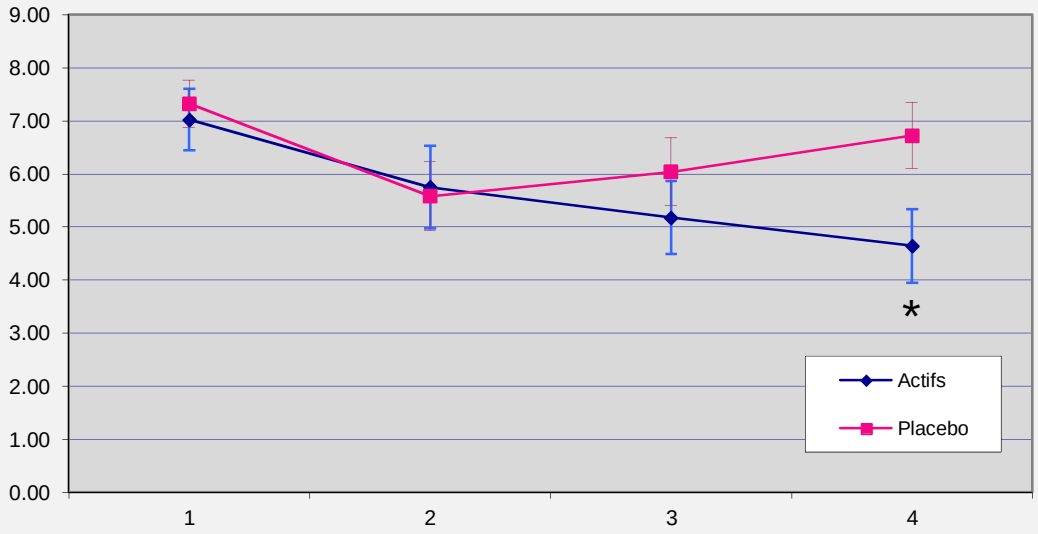
Prevention of Migraine by supraorbital transcutaneous neurostimulation using the Cefaly® device (PREMICE):

a multi-centre, randomised, sham-controlled trial.

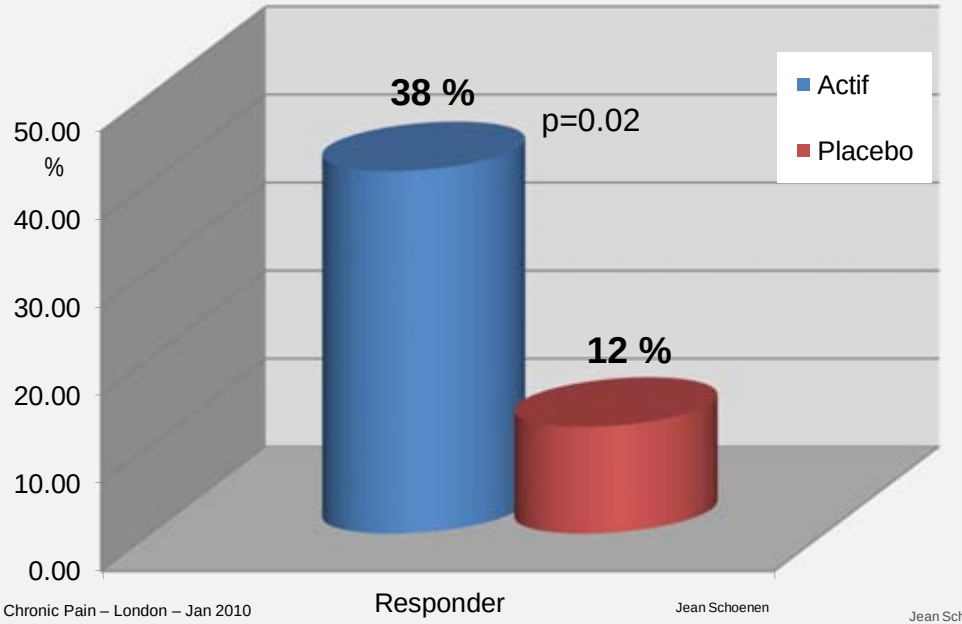
(square pulse, 60Hz, 300?sec, max 14.99 mA, 20 min)

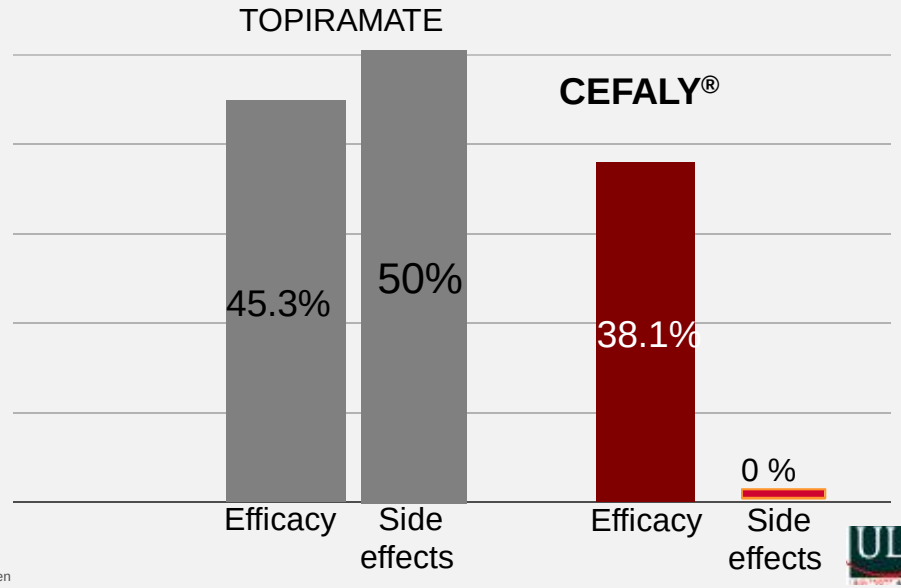
- Migraine without aura: 2-8 attacks/mth
- N= 5 centres (Belgian Headache Society)
- N= 34 active stimulation
- N= 33 sham stimulation
- Duration: 1 month baseline
  +3 months Cefaly®
- Sponsored by STX-Med

Mean number of migraine days



Percentage of 50% responders





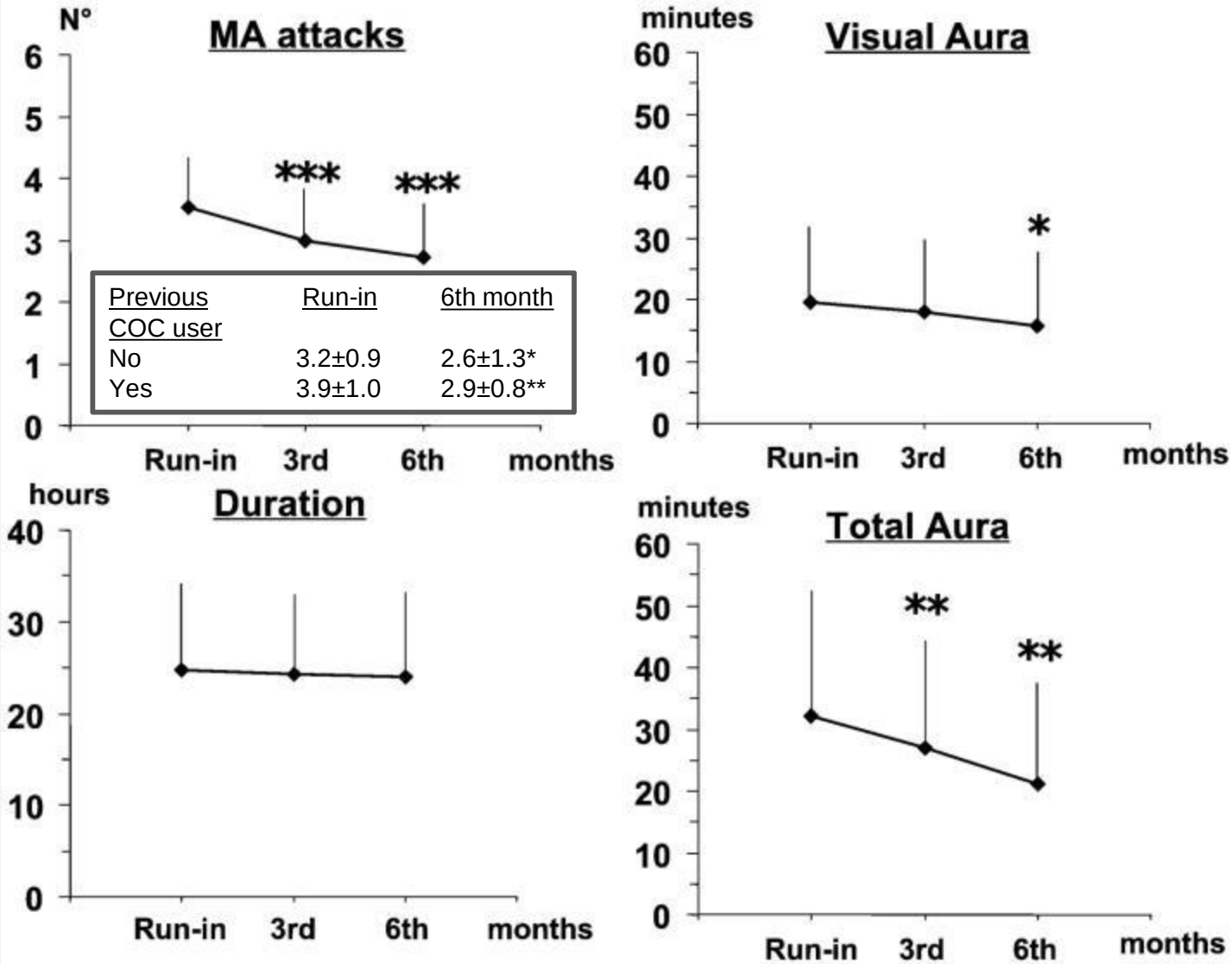
Jean Schoenen

Jean Schoenen

HORMONES

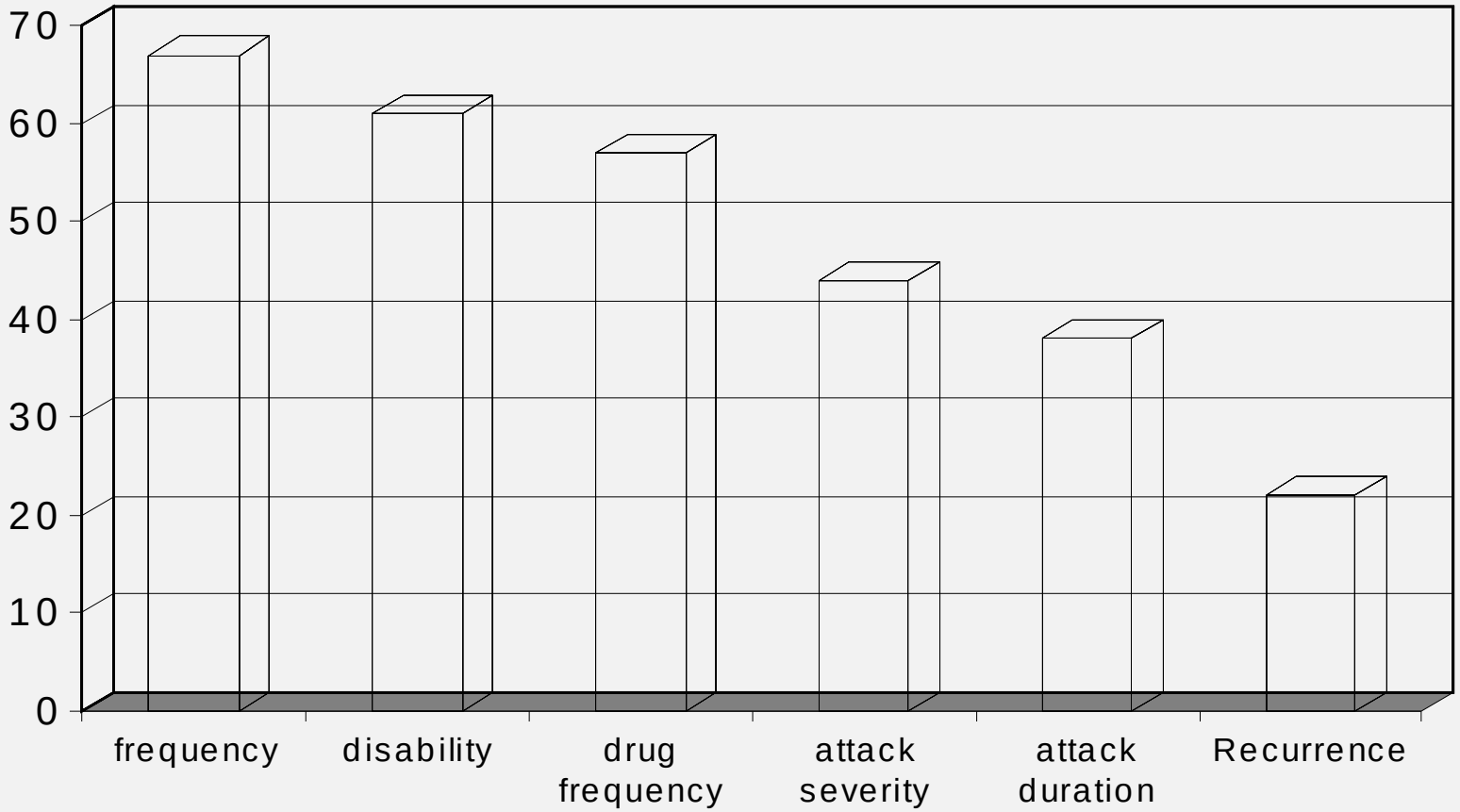
Effect on **migraine with aura** of an estrogen-free oral contraceptive

(desogestrel – Cerazette °) (Nappi et al. 2011)



Previous COC user	Run-in	6th month
No	3.2±0.9	2.6±1.3*
Yes	3.9±1.0	2.9±0.8**

Migraine prophylaxis: indication



Guidelines for migraine prophylaxis

Drugs of first choice:	EFNS	US
– Betablockers:		
propranolol up to 240 mg	+	+
metoprolol up to 200 mg	+	-
– Flunarizine 5 to 10 mg	+	na
– Valproate up to 1,800 mg	+	-
– Topiramate up to 100 mg	+	+
– Amitriptyline up to 75 mg	-	+

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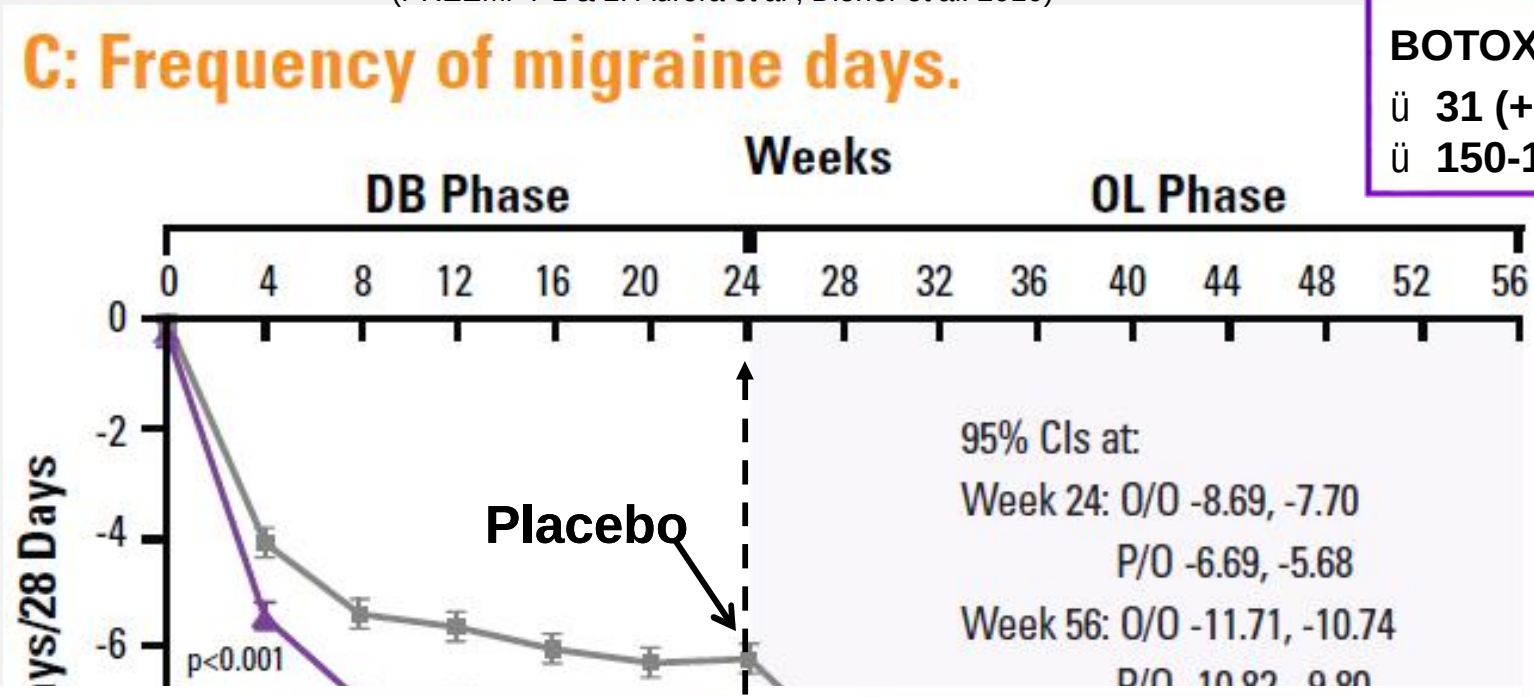
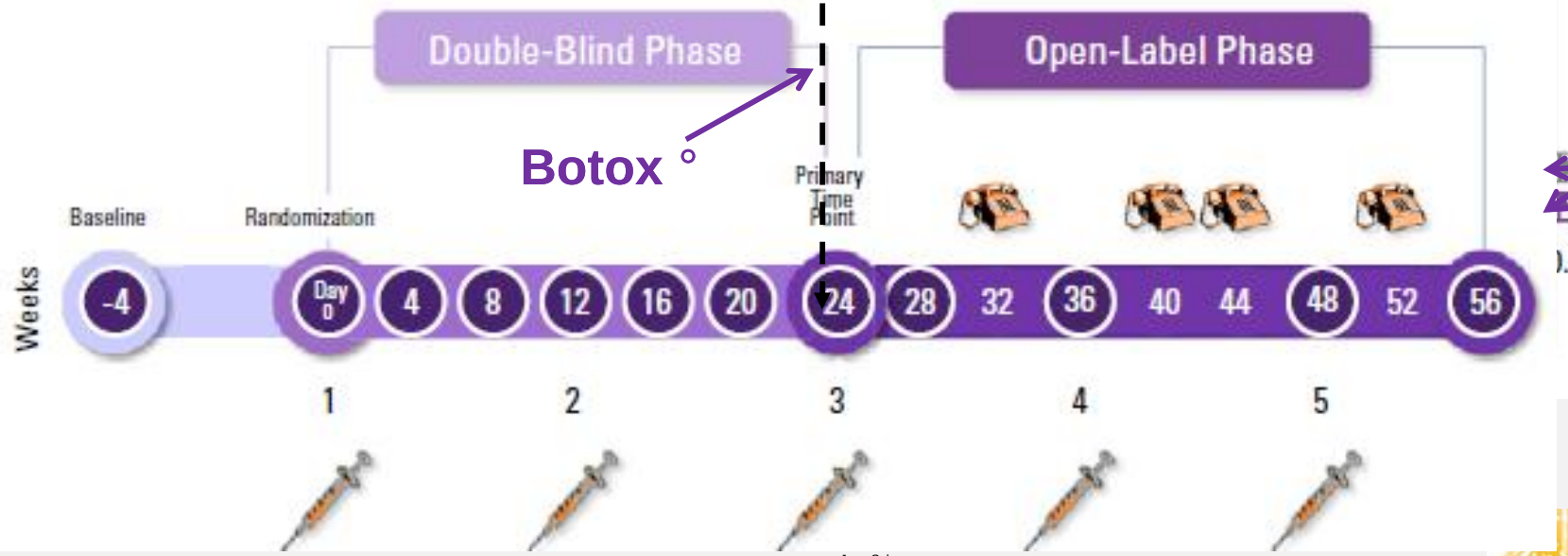
Effect of onabotulinumtoxinA (Botox °) in CHRONIC Migraine

(PREEMPT 1 & 2. Aurora et al , Diener et al. 2010)

BOTOX °

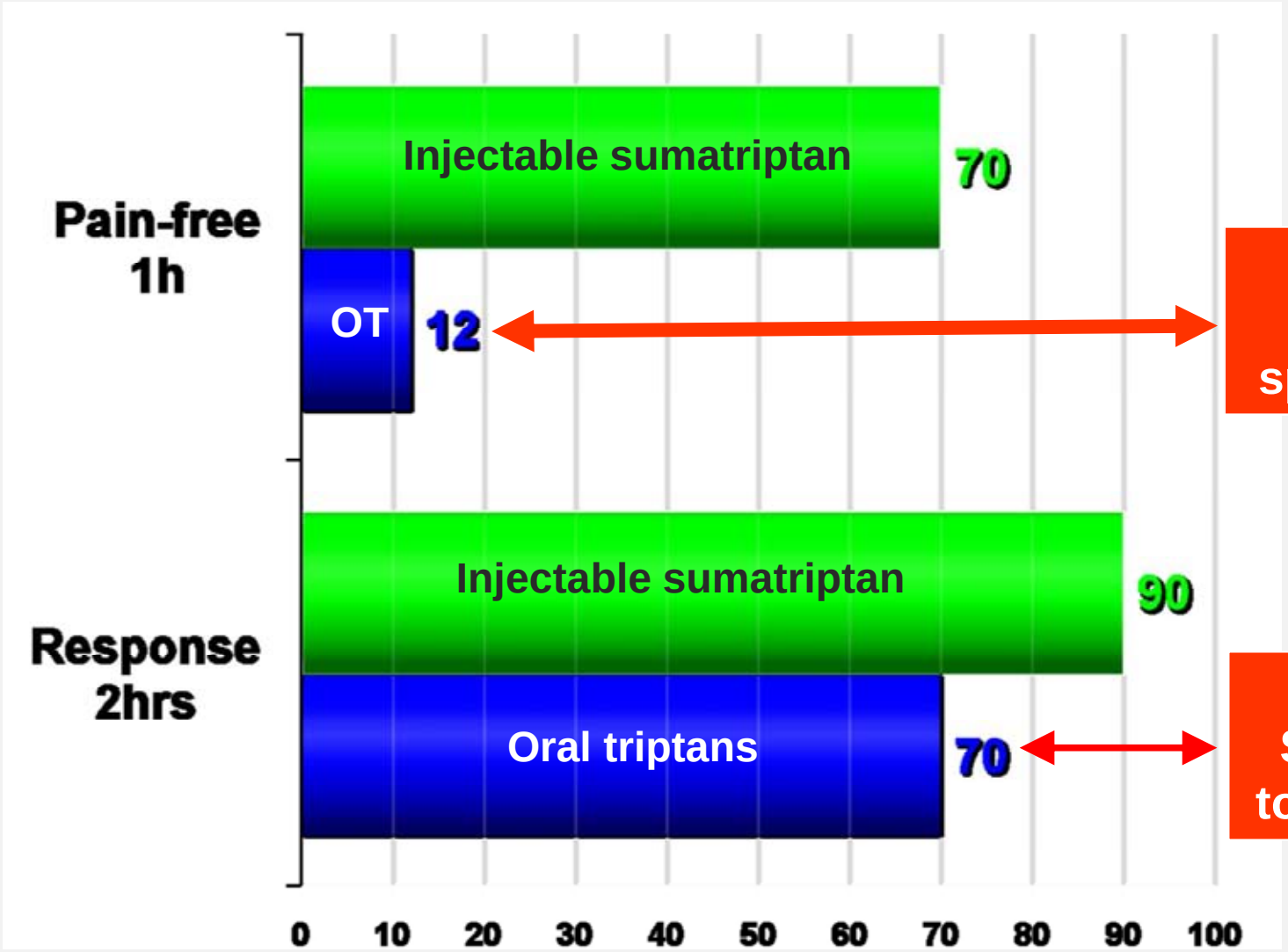
- ü **31 (+8) inj sites**
- ü **150-195 U**





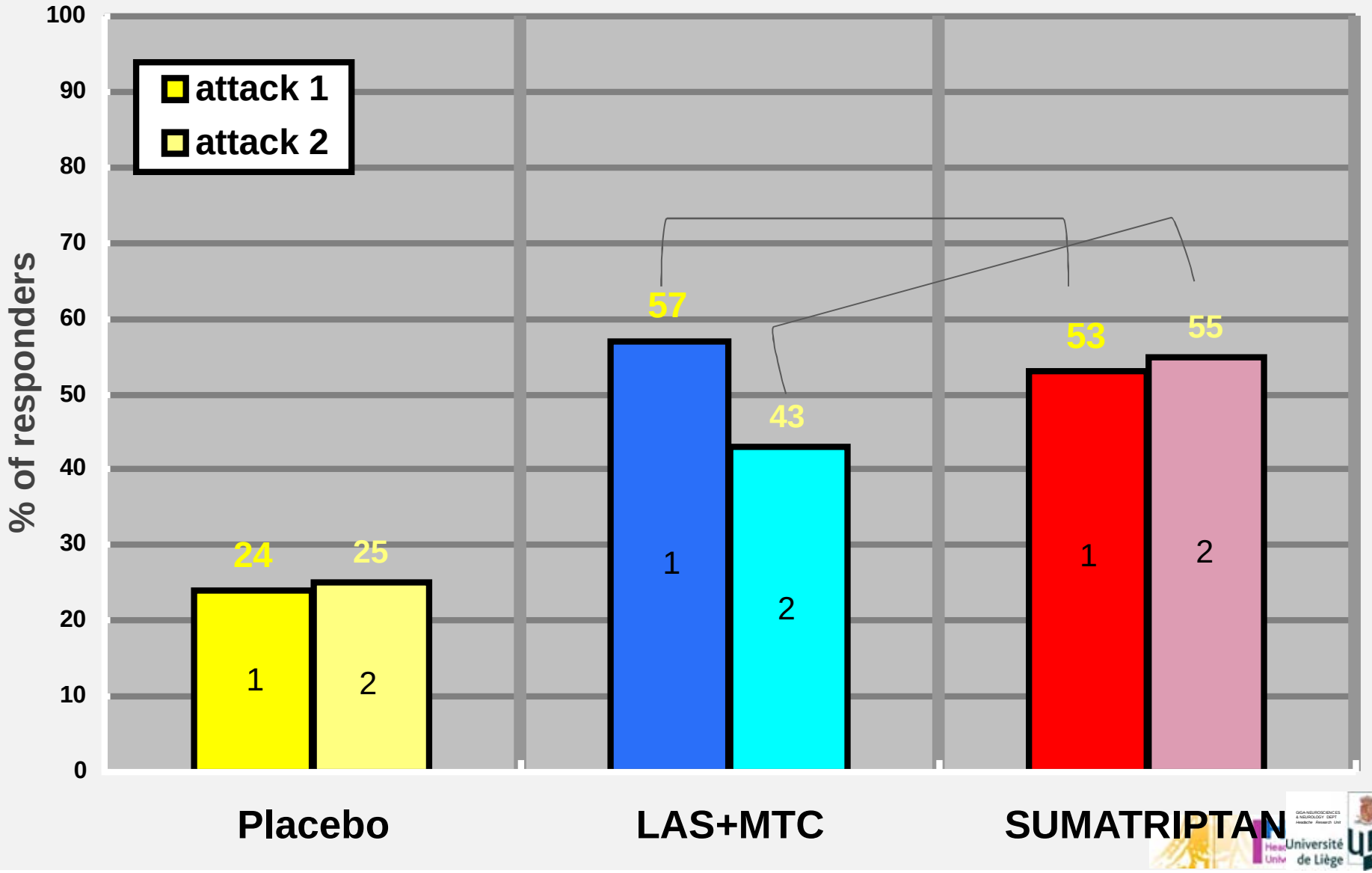
Acute Migraine Therapy

Overall absolute efficacy rates of triptans (%)



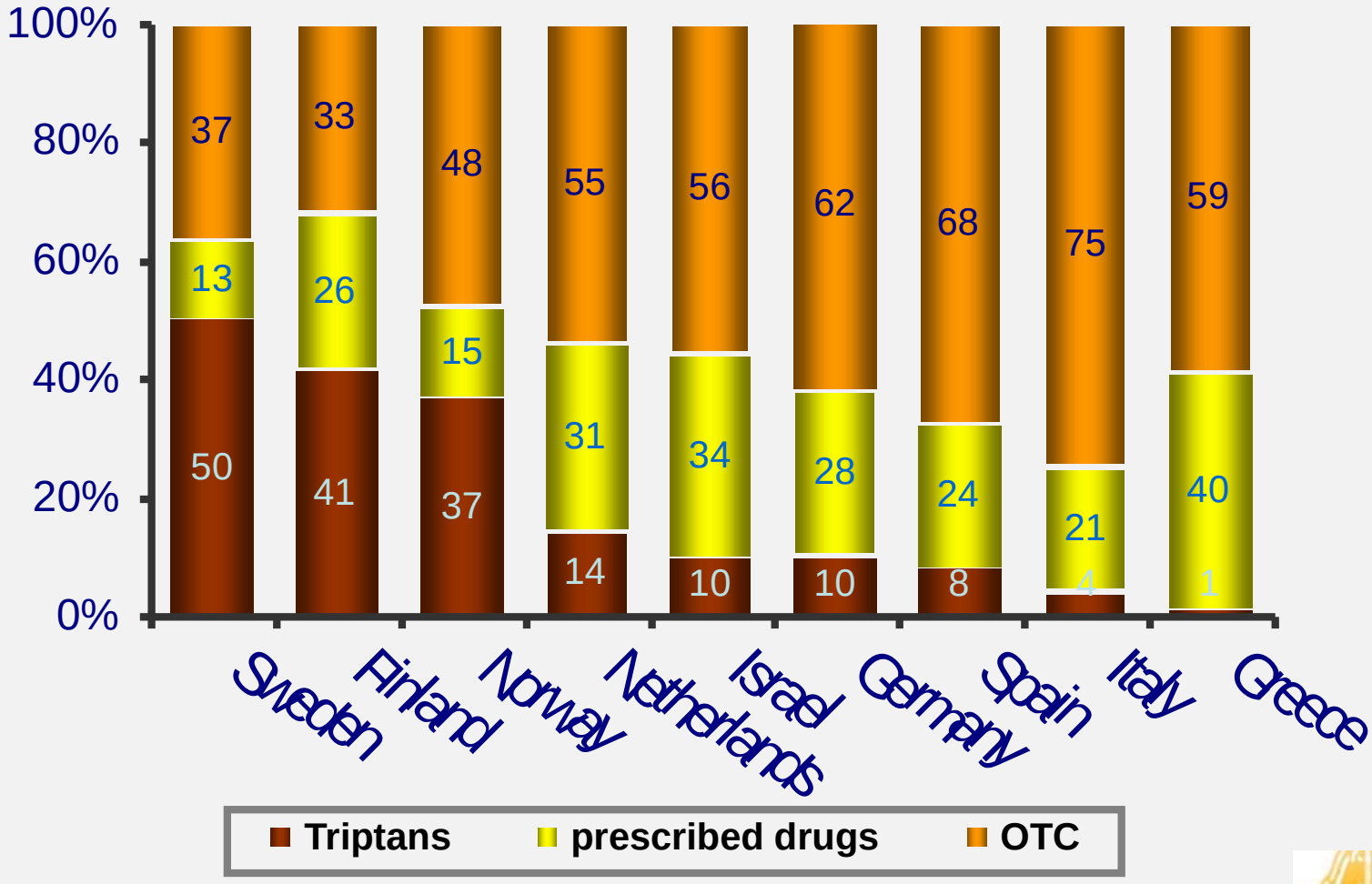
The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine.

(The Lancet 1995; 346: 923-926)



Triptans are the most effective drugs for the severe migraine attack, ….but only 1 out of 5 migraineurs at best is using them

Acute treatment of migraine in different European countries



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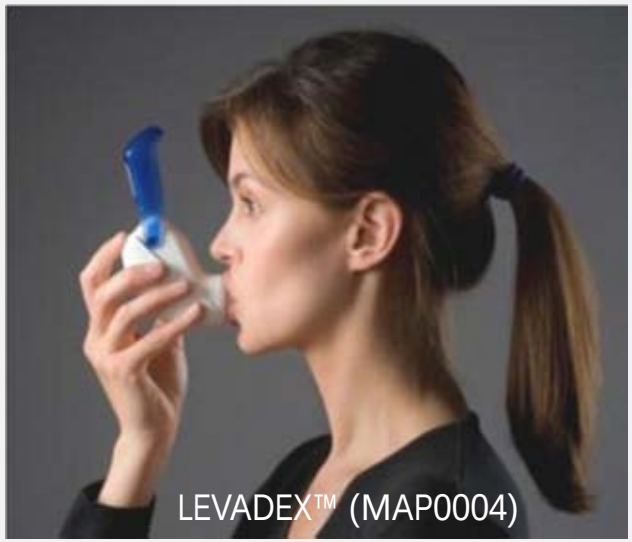
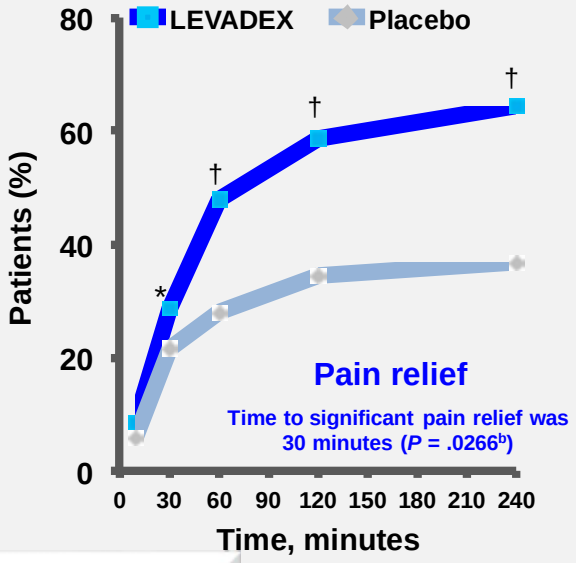
Fooling nausea and « needlephobia »

New devices for administration of old drug (phase III)

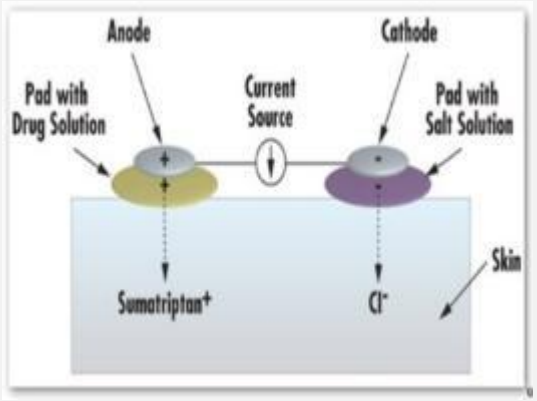


DHE Tempo ° inhaler



Needle-less injection by pressured air

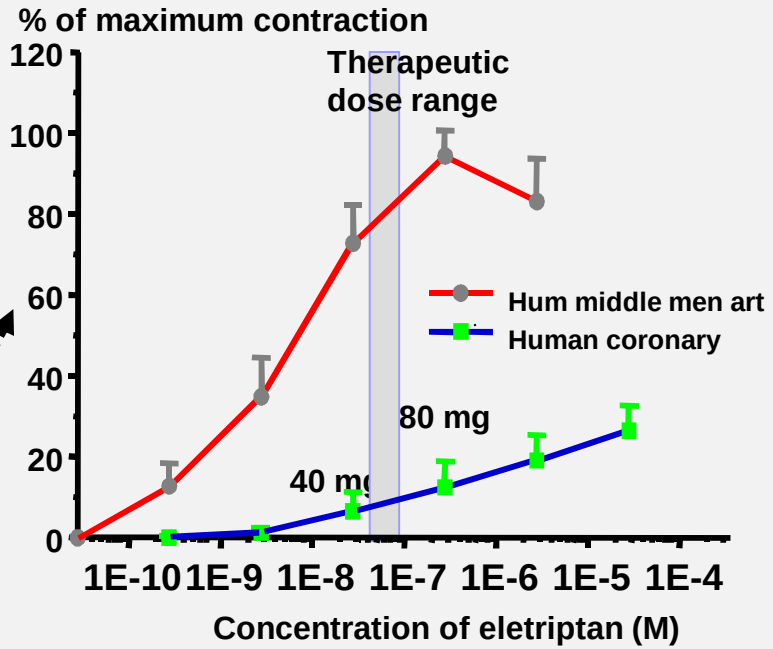
(Zogenix)



(NuPathe Inc)

Shortcomings of triptans

- Incomplete efficacy
- High recurrence rate
- Triptan-specific side effects
- Propensity to induce MOH
- Cardiovascular safety



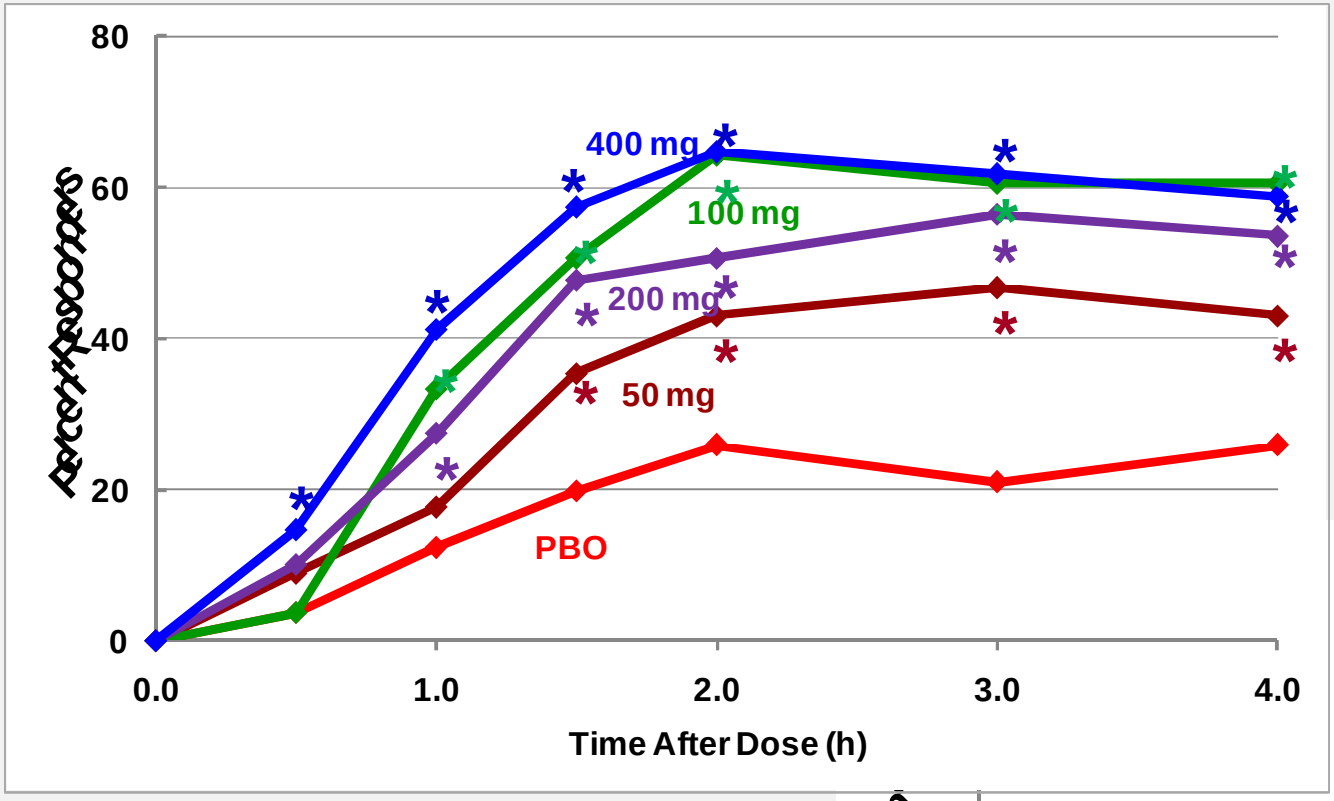
- no association between triptan prescription and stroke (HR 1.13; 95% CI 0.78, 1.65) or myocardial infarction (HR 0.93; 95% CI 0.60, 1.43)

"patients with vascular risk factors were less likely to receive a triptan!"

(GC Hall et al, Neurology 2004;62:563–568)

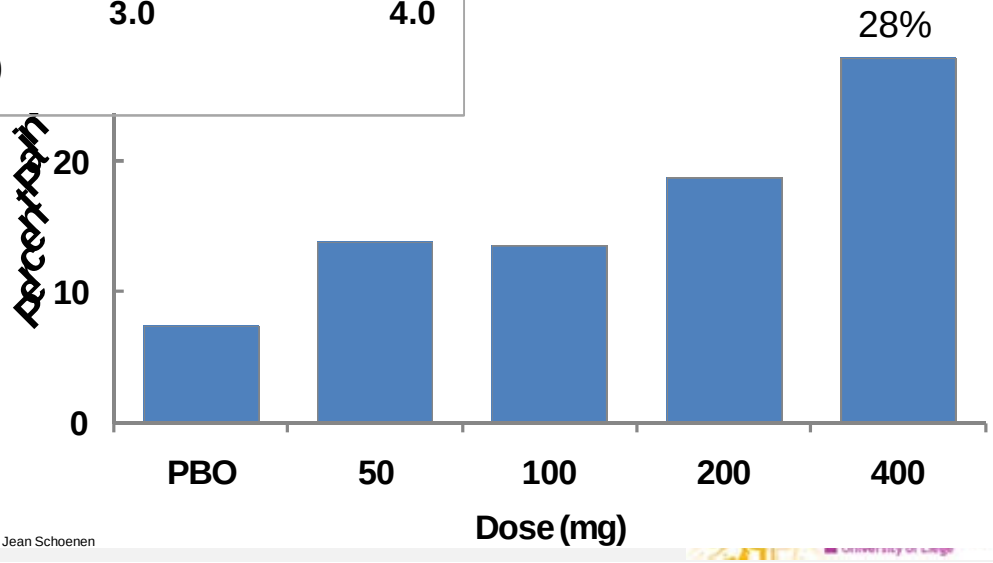
5-HT1F receptor agonist Lasmiditan?Ø

LASMIDITAN (COL-144 MIG-202): Response Time Course (4h)



I.V.: proof of concept
(Ferrari et al. 2010)

Pain Free, 2h



Oral: phase II
(Färkkila et al. Lancet Neurology 2012)

No triptan-like side effects !

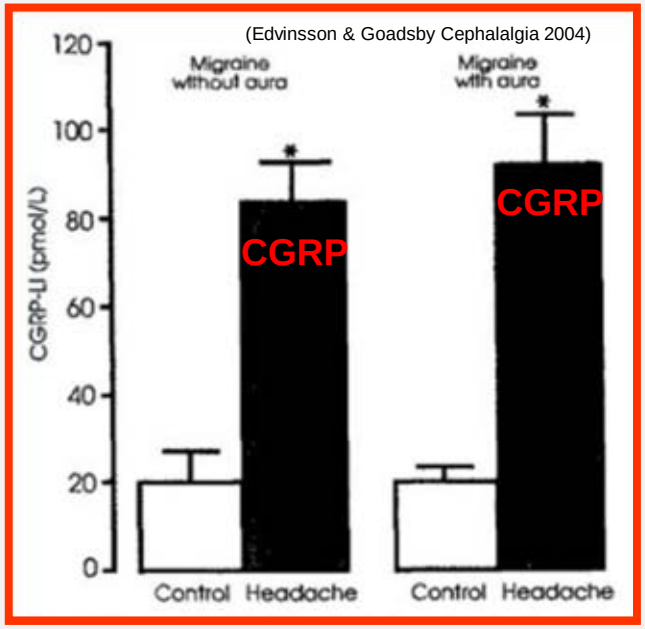
Acute therapy: gepants & ditans

Novel drugs (not marketed)

- **CGRP** rec antagonists: the “
  (BIBN-4096BS, MK-0974/telcag[illegible], MK-3207, BI-44370…)
- **5-HT1F** agonists: the “ditans”
  (….COL-144/lasmiditan…)

? Hepatotoxicity ?

No vascular effects



Receptor	Craniovas-cular	Coronary	Trigeminal periph. terminal	Trigeminal neuron (ganglion)	TNC	Main effect
5-HT1B	+++	+++	-	++	-	vasoconstrictory ?Š?Š trigeminal activation
5-HT1D	±	±	++ autorecepto r	++	++	?” trigeminal activation ?mPPE
5-HT1F	-	-	?	++	++ (pre-synaptic)	?ú?ú PPE ?Û trigeminal activation

Recommendations for intake

- Start with low dose
- Explain side effects (weight gain, dizziness etc.)
- Most side effects disappear after some weeks
- Evening dosage
- At least two months of intake before efficacy is known
- Intake at least six months
- Reduction after about one year

Exercise as migraine prophylaxis: A randomized study using relaxation and topiramate as controls

Cephalalgia
0(0) 1–11

DOI: 10.1177/0333102411419681
cep.sagepub.com
SAGE

Emma Varkey[1], Åsa Cider[1,2], Jane Carlsson[1] and Mattias Linde[1,3,4]

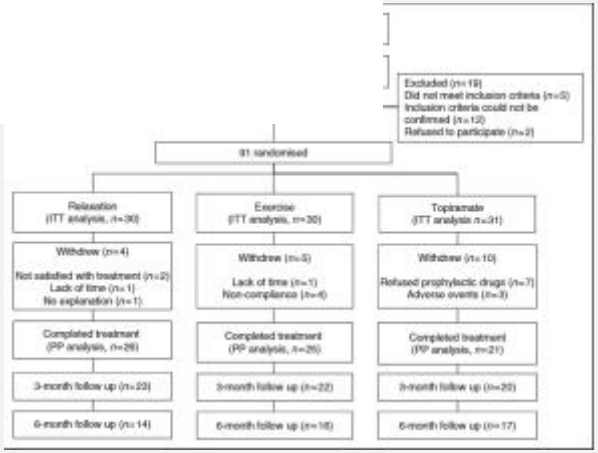


Table 1. Baseline demographic characteristics of the intention-to-treat (ITT) and the per-protocol (PP) populations

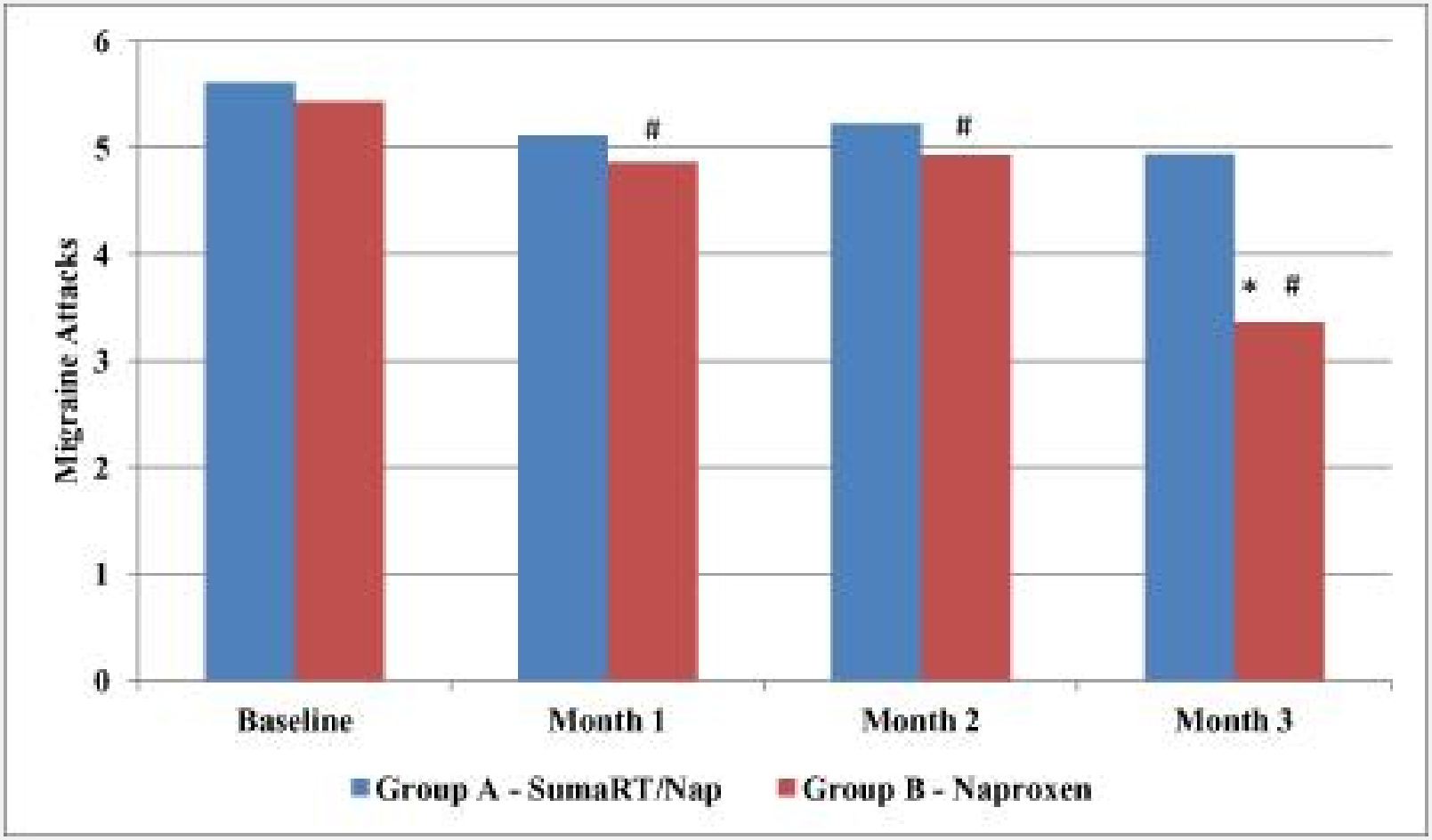
Characteristic	Relaxation ($n=30$)	Exercise ($n=30$)	Topiramate ($n=31$)	Total ITT ($n=91$)	Total PP ($n=72$)
Age (years)	41.5 ± 11. 4	47.0 ± 10.8	44.4 ± 9.2	44.3 ± 10.6	44.4 ± 11.3
Sex					
Male	2 (7)	5 (17)	2 (6)	9 (10)	6 (8)
Female	28 (93)	25 (83)	29 (94)	82 (90)	66 (92)

Table 3. Participants who responded to the different treatments

	ITT			PP		
Response	Relaxation ($n=30$)	Exercise ($n=30$)	Topiramate ($n=31$)	Relaxation ($n=26$)	Exercise ($n=25$)	Topiramate ($n=21$)
Responders (≥50% improvement)	7 (23)	9 (30)	8 (26)	7 (27)	7 (28)	8 (38)
Somewhat improved (25–49% improvement)	5 (17)	5 (17)	3 (10)	5 (19)	5 (20)	3 (14)
Not clinically improved (≤25% improvement)	18 (60)	16 (53)	20 (65)	14 (54)	13 (52)	10 (48)

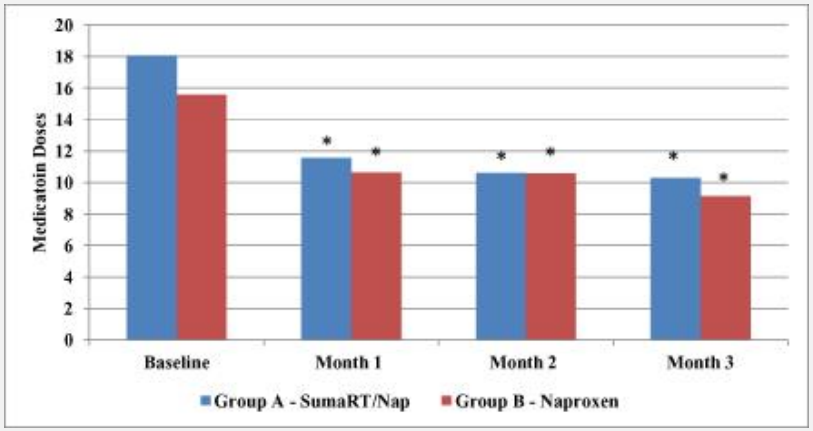
Values are *n* (%). ITT: $p=0.86$; PP: $p=0.93$.

SumaRT/Nap vs Naproxen Sodium in Treatment and Disease Modification of Migraine: Attacks/month



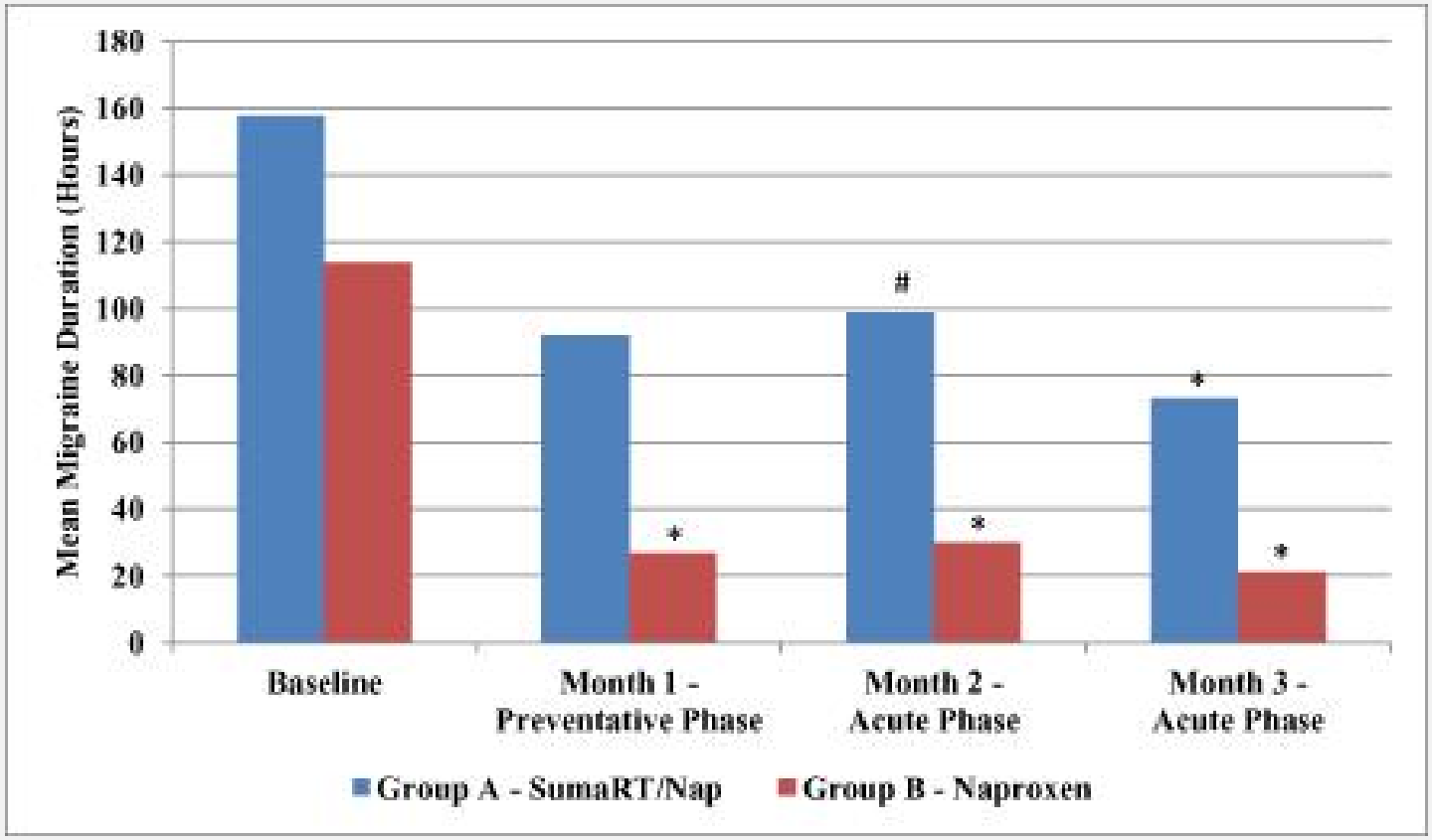
Headache: The Journal of Head and Face Pain
10 SEP 2013 DOI: 10.1111/head.12211
http://onlinelibrary.wiley.com/doi/10.1111/head.12211/full#head12211-fig-0002

SumaRT/Nap vs Naproxen Sodium in Treatment and Disease Modification of Migraine: A Pilot Study



Headache: The Journal of Head and Face Pain
10 SEP 2013 DOI: 10.1111/head.12211
http://onlinelibrary.wiley.com/doi/10.1111/head.12211/full#head12211-fig-0005

Treatment of Chronic Migraine: A 3?Month Comparator Study of Naproxen Sodium vs SumaRT/Nap: Migraine attack duration

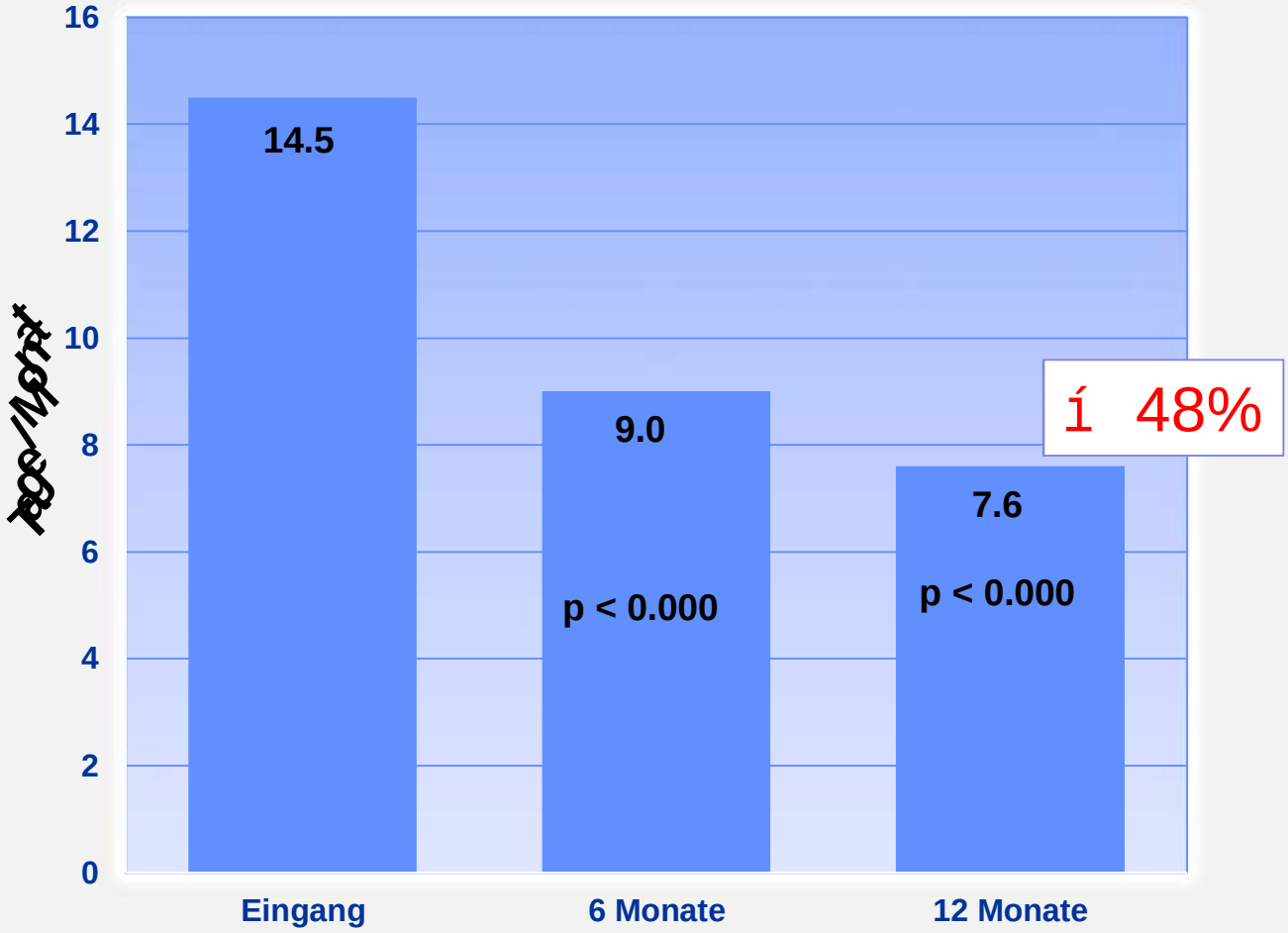


Headache: The Journal of Head and Face Pain
10 SEP 2013 DOI: 10.1111/head.12210
http://onlinelibrary.wiley.com/doi/10.1111/head.12210/full#head12210-fig-0002

KOPFSCHMERZKLINIK BERLIN

PRIMARY OUTCOME MEASURE

≥ 50% headache frequency reduction



(Wallasch T. Kopfschmerzklinik Berlin-St Gallen)