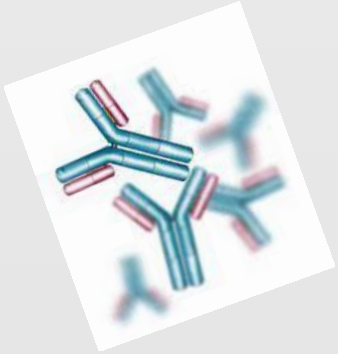


Emicrania: una patologia endemica da riconsiderare

Vicenza, 20 febbraio 2020

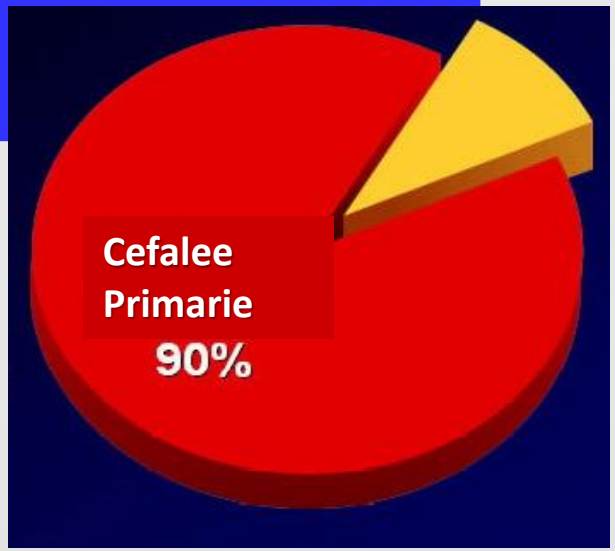
GEPANTI, DITANI ED ANTICORPI MONOCLONALI anti-CGRP NELL'EMICRANIA

Giorgio Zanchin

Già Direttore Clinica Neurologica e Centro Regionale Cefalee

Università di Padova

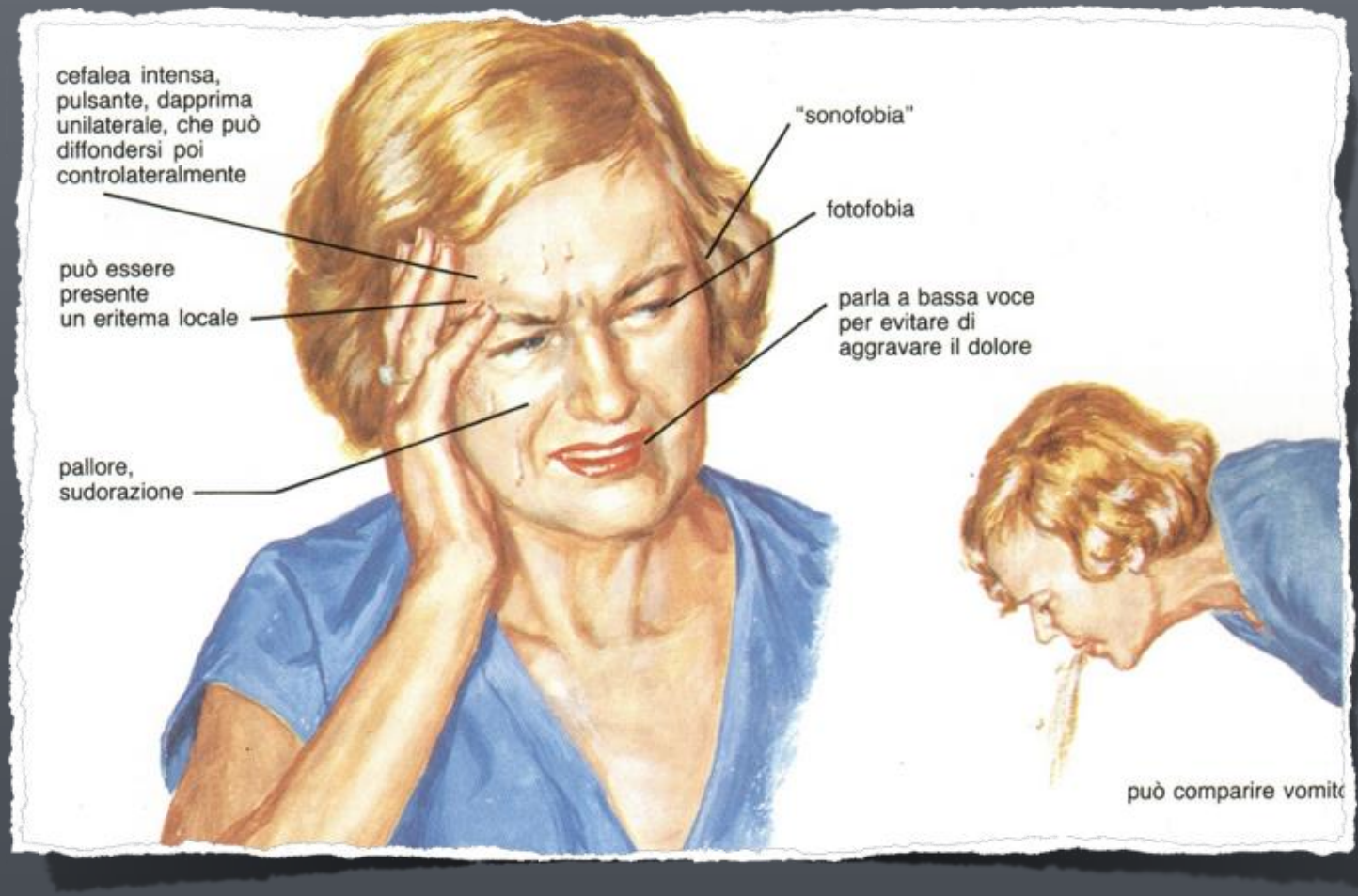
Cos’è l’emicrania



- E’ una cefalea primaria

- Si manifesta con attacchi ricorrenti di dolore tipicamente unilaterale, pulsante, di moderata o forte intensità, che peggiora con l’attività fisica di routine ed è accompagnato da nausea e/o vomito, fotofobia e fonofobia

cos'e' l'emicrania?

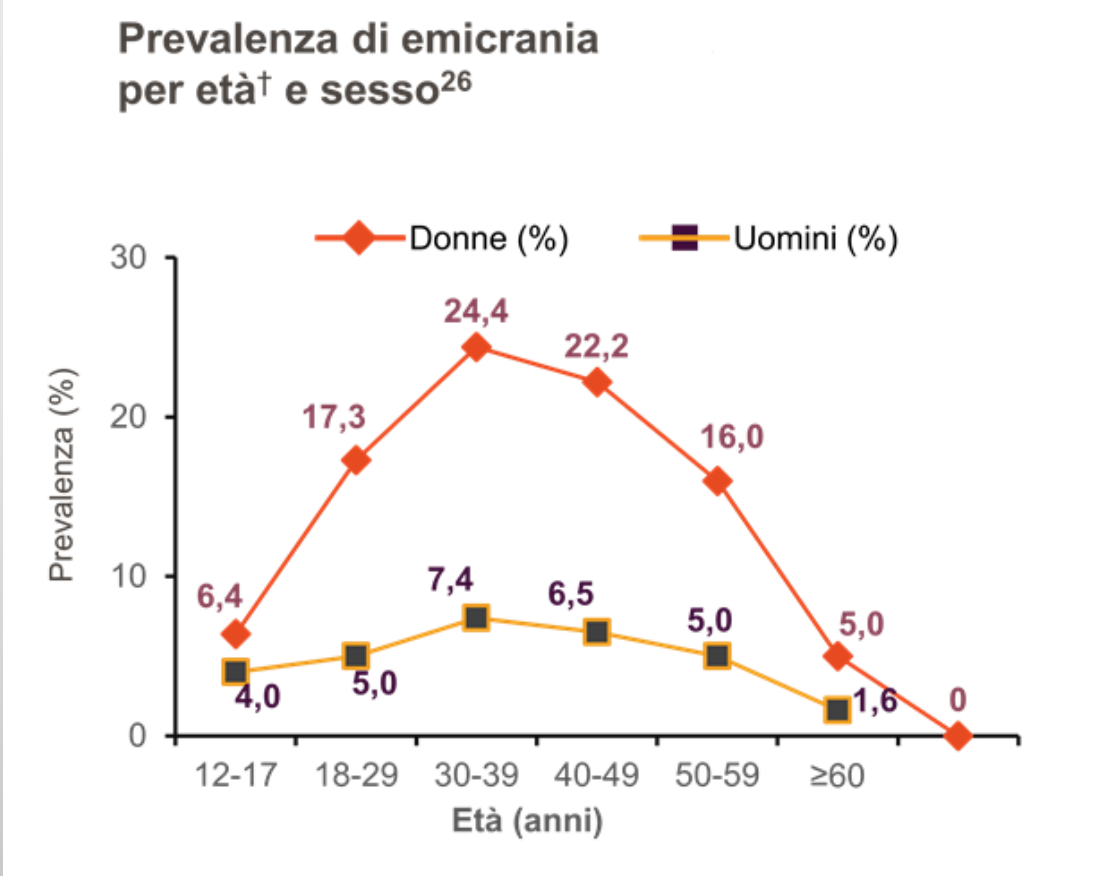


cos'e' l'emicrania?

- una **malattia cronica** con attacchi di cefalea
- fisiopatologia complessa
- disordine ereditario dell'eccitabilita' neuronale che in risposta ad un insieme complesso di fattori ambientali determina l'attivazione del sistema trigemino-vascolare alla base della crisi algica

Haut SR, Bigal ME, Lipton RB. Lancet Neurol 2006;5:148-57.
Silberstein SD. Lancet 2004;363:381-91.

L'EMICRANIA E' LA PRIMA CAUSA DI ANNI VISSUTI CON DISABILITA' NEGLI INDIVIDUI AL DI SOTTO DI 50 ANNI NEL MONDO



* Attuale = periodo di 6 mesi - 1 anno; † Curve di prevalenza specifiche per età aggiustate in base ai fattori demografici.

25. Bigal ME, et al. *Neurology*. 2006;67:246-251. 26. Lipton RB, et al. *Neurology*. 2007;68:343-349.
28. Woldeamanuel YW, Cowan RP. *J Neurol Sci*. 2017;372:307-315.

% di pazienti che ha ricevuto diagnosi specialistica

RESULTS

THEMES - DIAGNOSIS AND ASSESSMENT

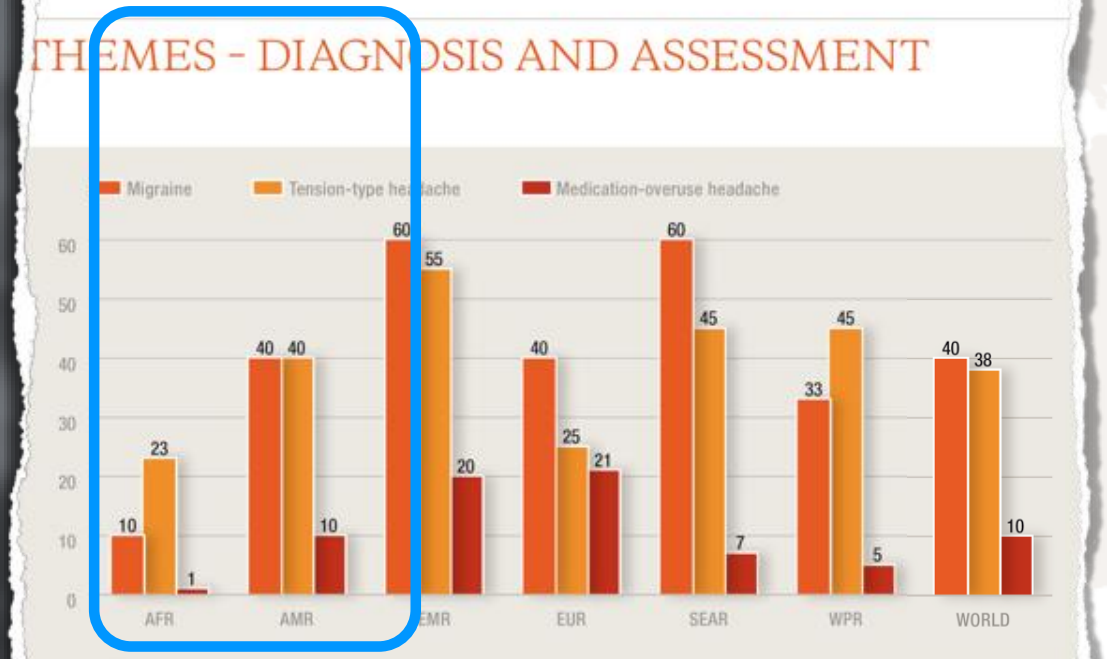


FIG. 5.1 Estimated percentages of people with specific headache disorders who have been professionally diagnosed, worldwide and by WHO region (medians of individual responses)

ATLAS

OF HEADACHE DISORDERS AND RESOURCES IN THE WORLD 2011

A collaborative project of World Health Organization and *Lifting The Burden*

elevata % di pazienti non diagnosticati

World Health Organization

Lifting The Burden
The Global Campaign against Headache

emicrania: l'impatto economico

COSTI (tipologie)	EMICRANIA EPISODICA (costo medio annuo/paziente)	EMICRANIA CRONICA (costo medio annuo/paziente)
complessivi per paziente	523.6 ± 825.8	2250.1 ± 1796.1
sostenuti dal SSN	468.3 ± 801.8	2110.4 ± 1756.9
ricoveri	242.6 ± 753.5	1242.9 ± 1251.2
valutazioni cliniche	101.6 ± 185.4	113.3 ± 163.6
trattamenti	115.9 ± 15.2	762.1 ± 1105.1

VALORI IN €

Adattato da Berra et al. The Journal of Headache and Pain (2015) 16:50

EMICRANIA
ICHD –III 2018

EPISODICA

- **MENO DI 15 GIORNI/MESE**

Meno di 4 giorni di disabilità/mese

TERAPIA SINTOMATICA

4 più giorni di disabilità/mese

TERAPIA SINTOMATICA

TERAPIA PREVENTIVA

CRONICA

- **FREQUENZA UGUALE O MAGGIORE DI 15 GIORNI/MESE DA ALMENO 3 MESI**
- **8 GIORNI/MESE CON CARATTERISTICHE EMICRANICHE**

TERAPIA SINTOMATICA

TERAPIA PREVENTIVA

SOSPENSIONE DEL FARMACO D'ABUSO/DISINTOSSICAZIONE

GESTIONE DELL'ATTACCO EMICRANICO

FARMACI SINTOMATICI PER L'EMICRANIA

ASPECIFICI

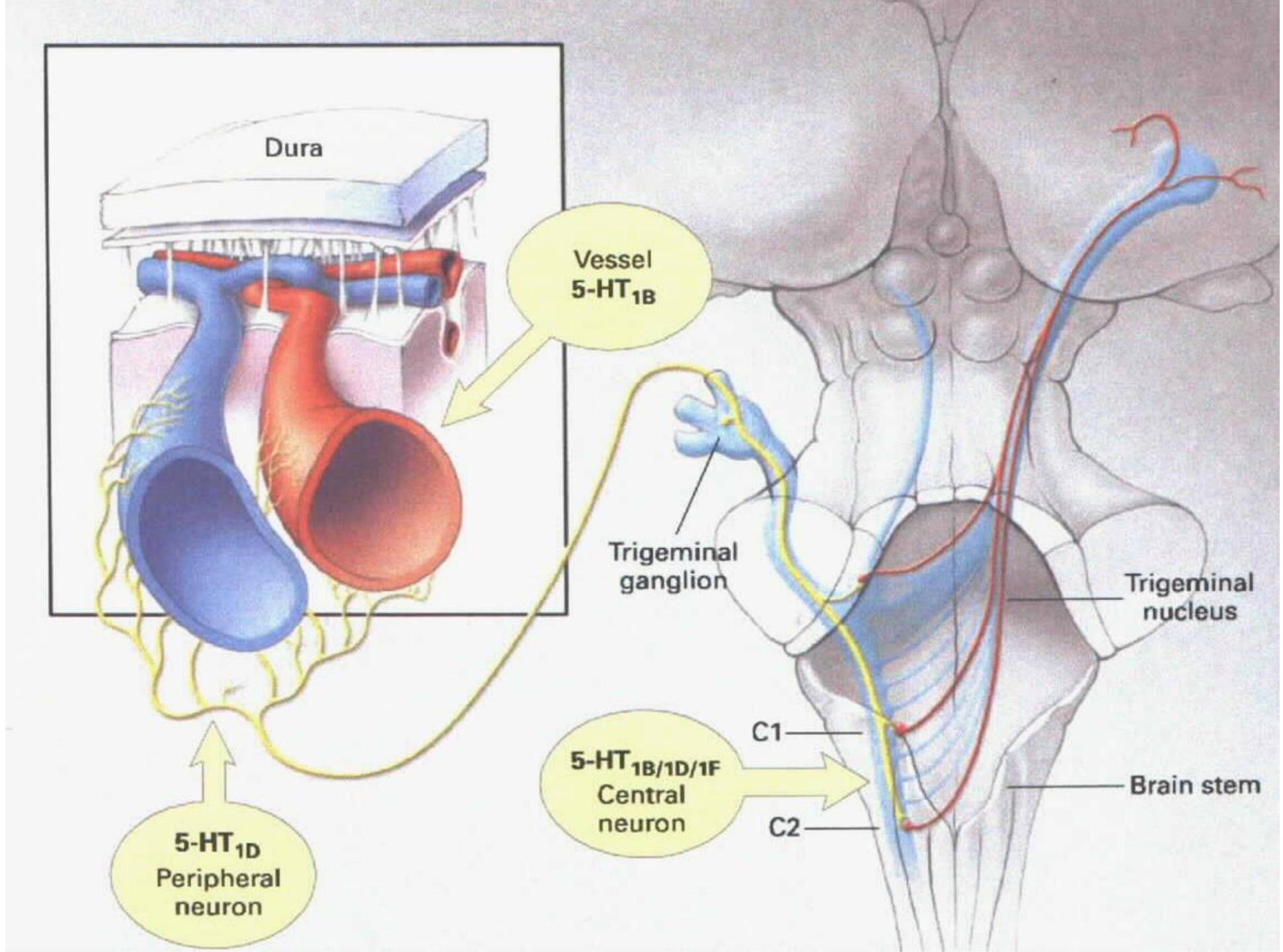
- ANALGESICI E FANS
- ANALGESICI DI COMBINAZIONE
- ANALGESICI OPPIODI SINGOLI E DI COMBINAZIONE
- ANTIEMETICI

SPECIFICI

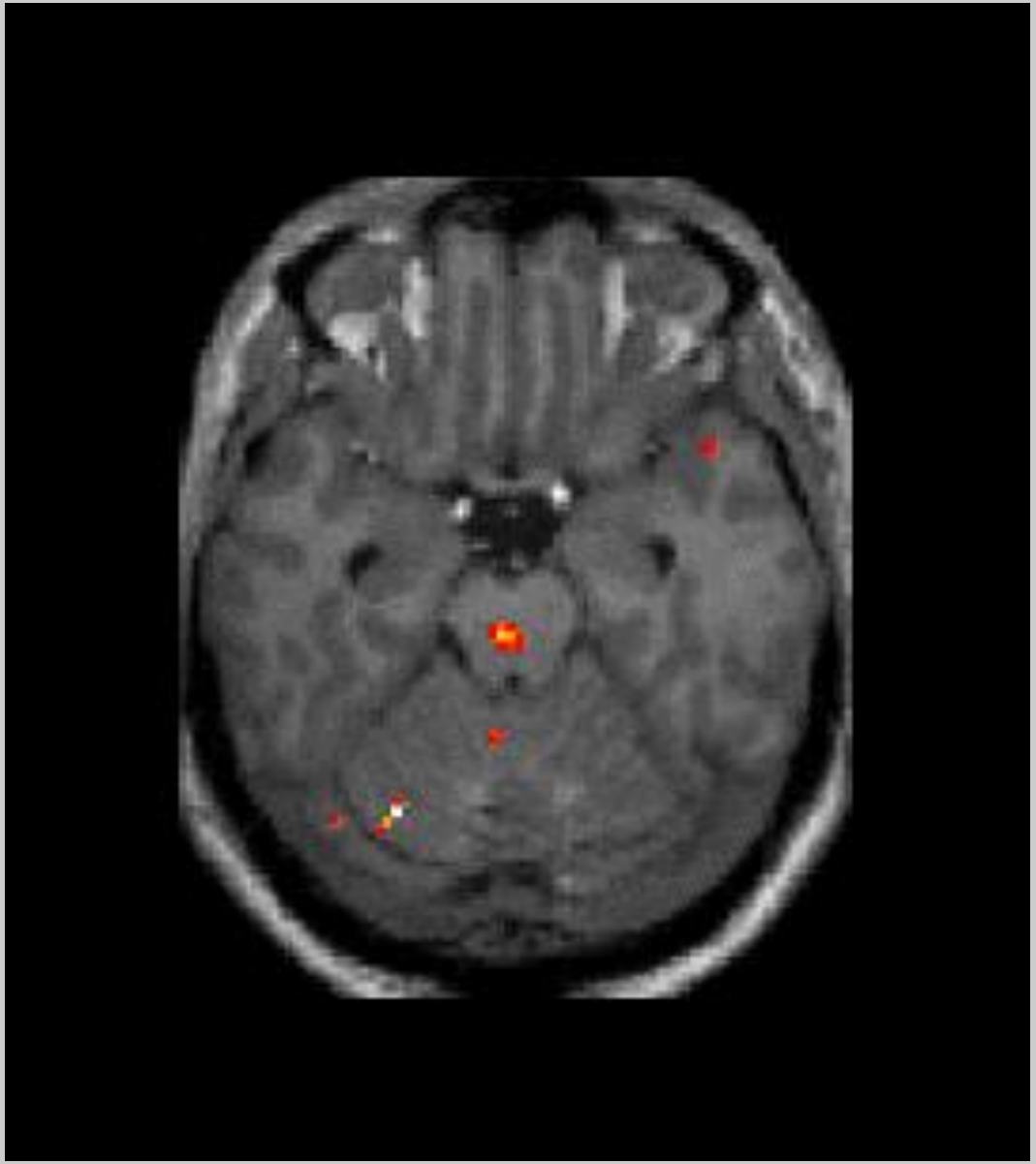
- ALCALOIDI DELL'ERGOT ED ERGOT DERIVATI

selettivi

non selettivi


Dura
Vessel
5-HT1B
Trigeminal ganglion
Trigeminal nucleus
C1
5-HT1B/1D/1F
Central neuron
C2
Brain stem
5-HT1D
Peripheral neuron

Brainstem activation specific to migraine headache



Bahra et al. (2001)

EMICRANIA :TRIPTANI

LINEE GUIDA TERAPEUTICHE SISC

CONTROINDICAZIONI

Cardiopatia ischemica

Vasospasmo coronarico

Patologia cerebrovascolare

Ipertensione non controllata

Emicrania basilare

Emicrania emiplegica

EVENTI AVVERSI

Senso di pressione/costrizione toracica

Mialgia

Sonnolenza

Senso di caldo/freddo alla testa/arti

Parestesie

Instabilità/vertigini

Despite relative success in helping patients manage attacks, there are several unmet needs with acute treatment[1,2,3]

Il 40% degli emicranici non è soddisfatto della terapia sintomatica

- Trial and error approach
- Medication overuse headaches
- Use of rescue treatment
- Response Rate
- Efficacy
- Tolerability
- Progression

1. Bigal ME. Med Gen Med 2006; 8: 31
2. Lipton RB et al. Headache 2015; 55(S2): 103–122
3. Silberstein SD. Clin Pharmacol Ther 2013; 93: 78–85

Lasmiditan

Properties of Lasmiditan

Chemistry of Lasmiditan Lasmiditan is a novel 5-HT receptor agonist with high affinity and selectivity for the 5-HT_{1F} receptor. The chemical structure of lasmiditan is different from triptans, thereby is included in a novel drug class called "ditans". The chemical difference between lasmiditan and triptans is based on the replacement of the indole structure of triptans, which is identical to the neurotransmitter 5-HT, by a pyridinoyl-piperidine scaffold [49].

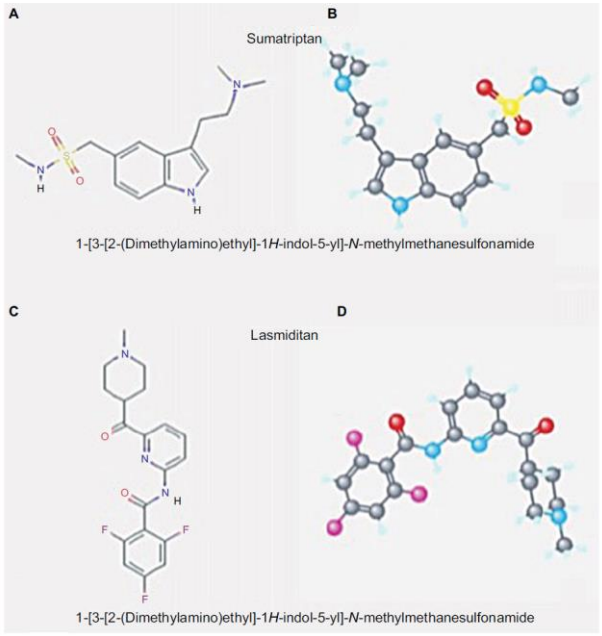


Figure 1 Comparison of chemical structure of sumatriptan and lasmiditan: 2D structure (**A** and **C**) and 3D conformer (**B** and **D**).

Neurotherapeutics
https://doi.org/10.1007/s13311-018-0615-6

REVIEW

Targeted 5-HT_{1F} Therapies for Migraine

Marta Vila-Pueyo[1]

Table 8 Summary of the phase II and phase III clinical trials performed to date with lasmiditan

Study ID	Administration	Summary	Participants (received lasmiditan)	Status	Date started–finished	Reference
Phase II						
COL MIG-201	Intravenous	Randomised, multicentre, placebo-controlled, double-blind, group-sequential, adaptive treatment-assignment, proof-of-concept and dose-finding study in the acute treatment of migraine	130 (88)	Completed	2006–2007	[63, 73–75]
COL MIG-202	Single oral (50, 100, 200 or 400 mg)	Randomised, multicentre, placebo-controlled, double-blind, parallel-group, dose-ranging outpatient study in the acute treatment of migraine	512 (86)	Completed	2009–2010	[63, 76, 77]
Phase III						
COL MIG-301 (SAMURAI)	Single oral tablet (100 or 200 mg)	Prospective, randomised, double-blind, placebo-controlled study in subjects with disabling migraine (Migraine Disability Assessment (MIDAS) score ≥ 11)	2231 (617)	Completed	2015–2016	[78]
COL MIG-302 (SPARTAN)	Single oral tablet (50, 100 or 200 mg)	Prospective, randomised, double-blind, placebo-controlled study in subjects with disabling migraine (MIDAS score ≥ 11)	3007	Ongoing, not recruiting	2016–2017	[79]
COL MIG-305 (GLADIATOR)	Single oral tablet with second dose for rescue (100 or 200 mg)	Prospective, randomised, open-label study in subjects with migraine who have completed COL MIG-301 or COL MIG-302 to evaluate the safety, tolerability and efficacy of long-term intermittent use of lasmiditan 100 mg and 200 mg as the first and second dose for the acute treatment of migraine	2580*	Recruiting	2015–2018*	[80]

*Indicates estimated enrolment or estimated finishing date

CGRP: neuropeptide con ruolo chiave nella fisiopatologia dell'emicrania

Il CGRP è un neuropeptide di 37 aminoacidi codificato dal gene della calcitonina.[1]

Diffusamente distribuito a livello del sistema nervoso centrale e periferico[1]; presente a livello del sistema trigeminale[1]

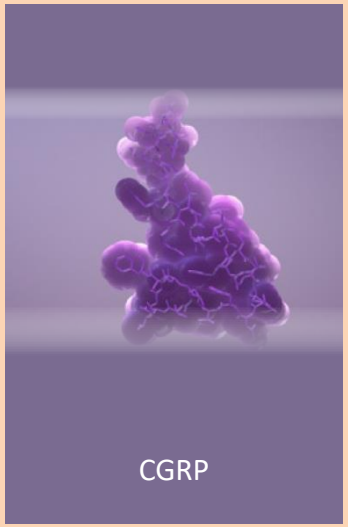
L'attivazione trigeminale provoca il rilascio del CGRP da parte dei terminali nervosi perivascolari[2]

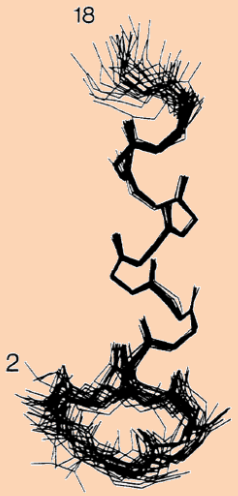
Il CGRP gioca un ruolo chiave in diversi meccanismi patogenetici dell'emicrania e nella percezione del dolore:[8]

- vasodilatazione
- Infiammazione neurogena
- Degranulazione dei mastociti
- Attivazione del segnale sensitivo
- Sensibilizzazione periferica e centrale

Durante l'attacco emicranico I livelli sierici di CGRP sono elevati[3-5]

Gli antagonisti selettivi del CGRP o del suo recettore sono efficaci nel trattamento dell'emicrania[6]





Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH_2[7,8]

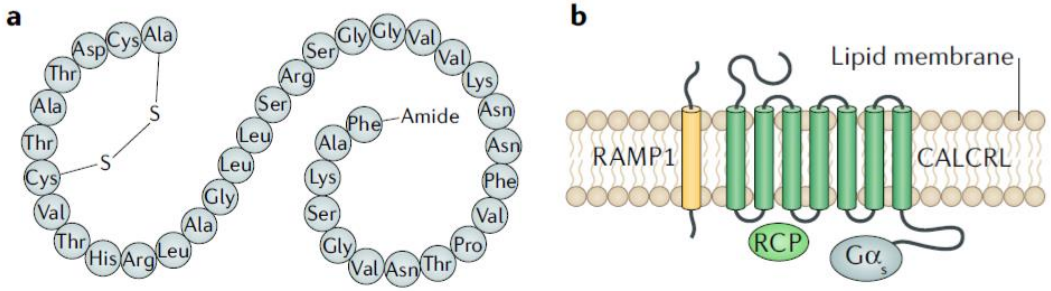
1. Ho TW, et al. *Nat Rev Neurol.* 2010;6(10):573-582. 2. Durham PL. *Headache*. 2006;46:S3-S8. 3. Goadsby PJ, et al. *Ann Neurol*. 1990;28(2):183-187. 4. Edvinsson L, Goadsby PJ. *Eur J Neurol*. 1998;5:329-341. 5. Cernuda-Morollón E, et al. *Neurology*. 2013;81(14):1191-1196. 6. Giamberardino MA, Martelletti P. *Expert Opin Emerg Drugs*. 2015;20(1):137-147. 7. Breeze AL. *Biochemistry*. 1991;30(2):575-582. 8. Russell FA, et al. *Physiol Rev.* 2014;94:1099-1142.

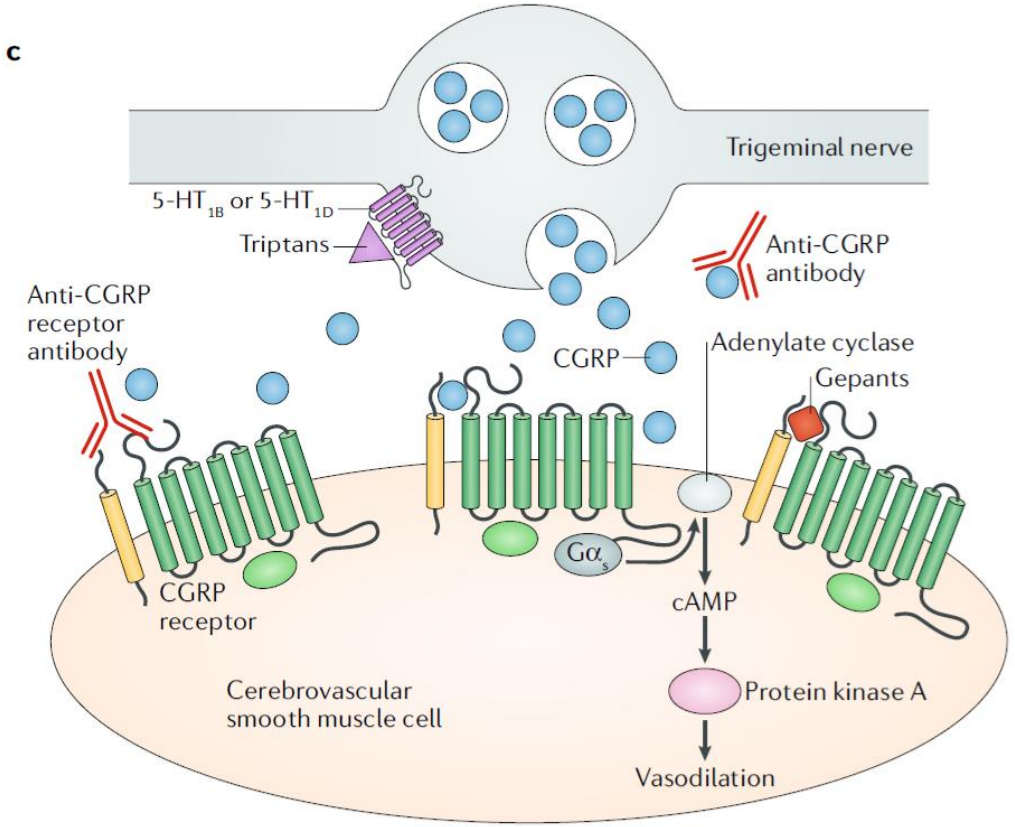
Published online: 24 April 2018

CGRP as the target of new migraine therapies — successful translation from bench to clinic

Lars Edvinsson[1,2], Kristian Agmund Haanes[2], Karin Warfvinge[1,2] and Diana N. Krause[1,3]*

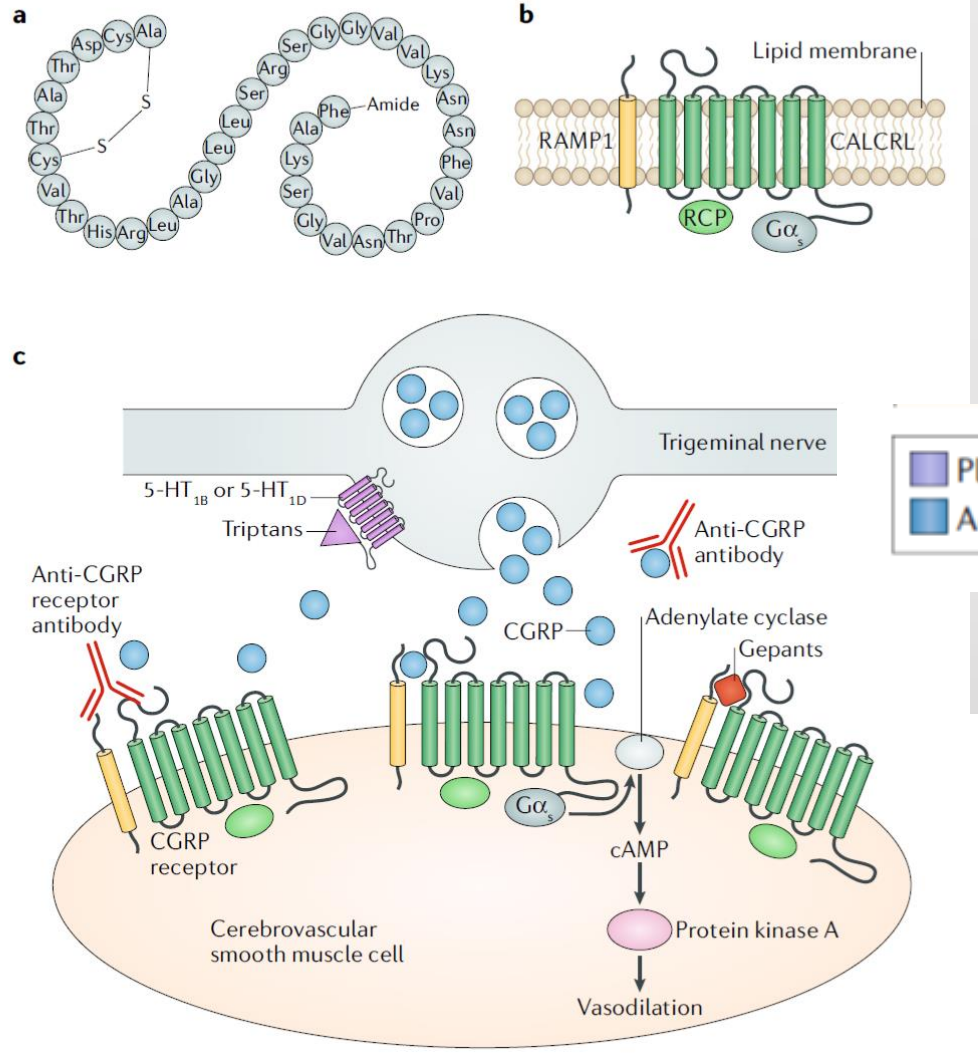
NATURE REVIEWS | NEUROLOGY

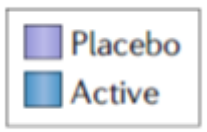




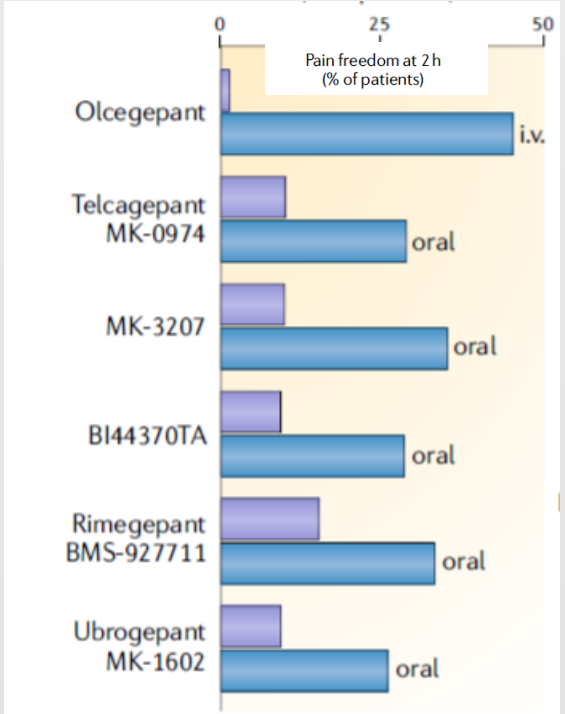
CGRP: peptide composto da 37 aminoacidi prodotto nelle terminazioni dei neuroni sensitivi in numerosi siti del SN

Il complesso recettoriale comprende due proteine di membrana: la CALCRL e la RAMP1 la cui interfaccia rappresenta la sede di legame e che devono essere coespresse per consentire il funzionamento.
Del complesso recettoriale fanno parte due proteine citoplasmatiche (una proteina G che contiene la subunità Ga che attiva la adenilciclasi e la RCP che amplifica l'attivazione della proteina G ed ottimizza la trasduzione del segnale).





GEPANTI



2,5 mg ev- Scarsa biodisponibilità dopo somministrazione orale

300 mg os- Aumento delle transminasi se assunto frequentemente

200 mg- os. Aumento delle transminasi se assunto frequentemente

400 mg- os Dopo il 2011 non sono state fornite notizie

150 mg- os Efficacia sovrapponibile a quella di sumatriptan 100 mg

100 mg-os efficacia sostenuta a 48 ore

Targeted CGRP Small Molecule Antagonists for Acute Migraine Therapy

Philip R. Holland[1] · Peter J. Goadsby[2]

Neurotherapeutics (2018) 15:304–312

Small molecule antagonist	Also known as	References	Current developmental stage	Ongoing clinical trials
Olcegepant	BIBN4096BS	[53, 56]	Discontinued	N/A
Telcagepant	MK-0974	[57–63]	Discontinued	N/A
MK-3207		[64]	Discontinued	N/A
Ubrogepant	MK-1602	[65]	Ongoing	[66–68]
BI 44370 TA		[69]	Unknown	
Rimegepant	BMS-927711 BHV3000	[70]	Ongoing	[71–73]

N/A = not available

Edvinsson et al, 2018

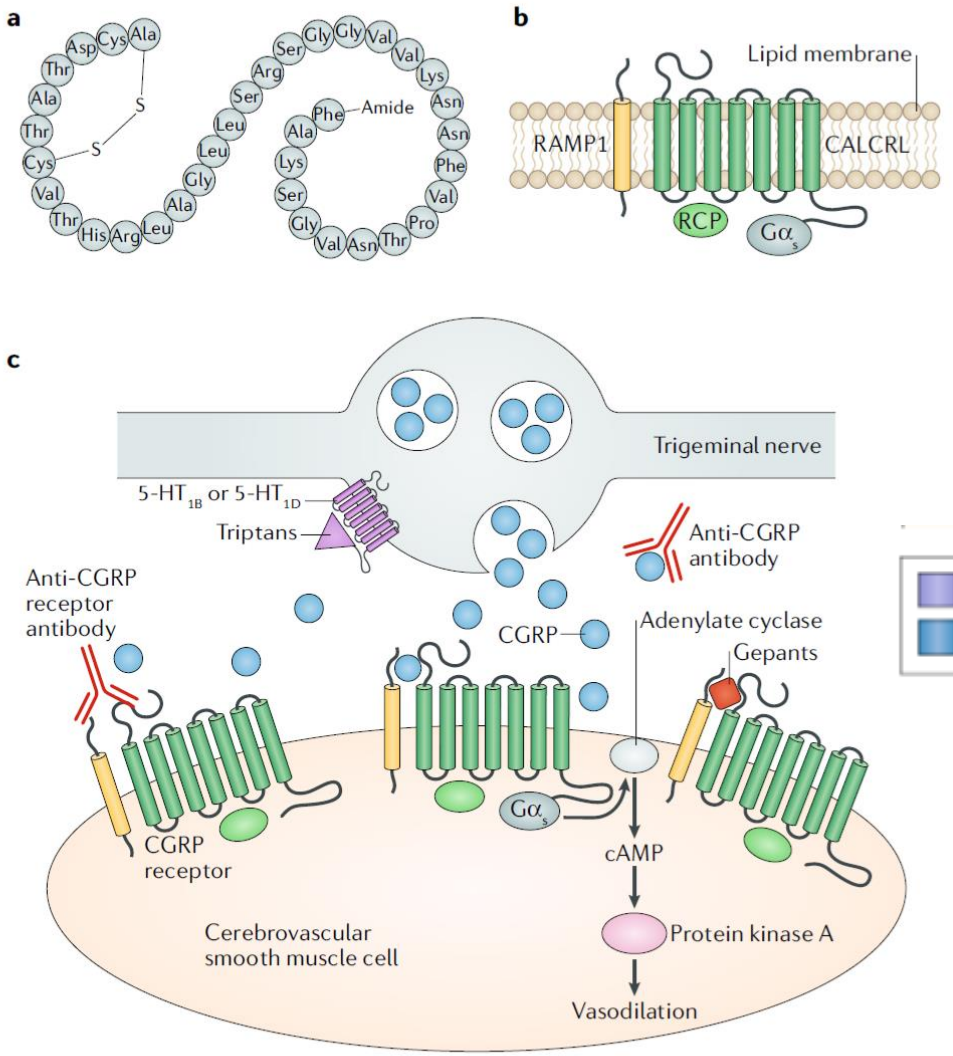
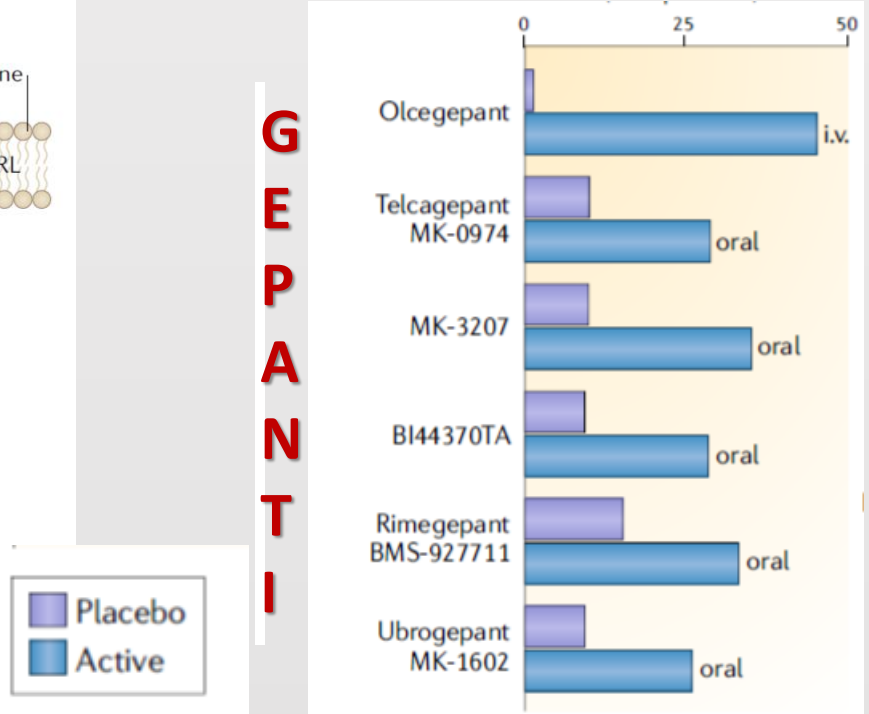


Fig. 2 | **Components of CGRP transmission and sites of action for CGRP-related migraine therapies. a** | Amino acid structure of human α-type calcitonin gene-related peptide (CGRP). **b** | The CGRP receptor complex, which consists of the two integral membrane proteins calcitonin receptor-like receptor (CALCRL) and receptor activity-modifying protein 1 (RAMP1) and two cytoplasmic proteins, receptor coupling protein (RCP) and the α-subunit of the G_s protein ($G\alpha_s$). **c** | The targets for CGRP-related migraine therapies illustrated in a CGRP-containing trigeminal nerve varicosity that innervates a cerebrovascular smooth muscle cell. 5-HT, 5-hydroxytryptamine receptor.

Edvinsson et al, 2018

GEPANTI



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Targeted CGRP Small Molecule Antagonists for Acute Migraine Therapy

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EFFETTI COLLATERALI PIU' COMUNI

- Nausea
- Vertigini
- Fatica
- Bocca secca
- Sonnolenza

SISC

Symposium Florence 2020

Friday 14 February
Saturday 15 2020 Hotel Baglioni, Florence

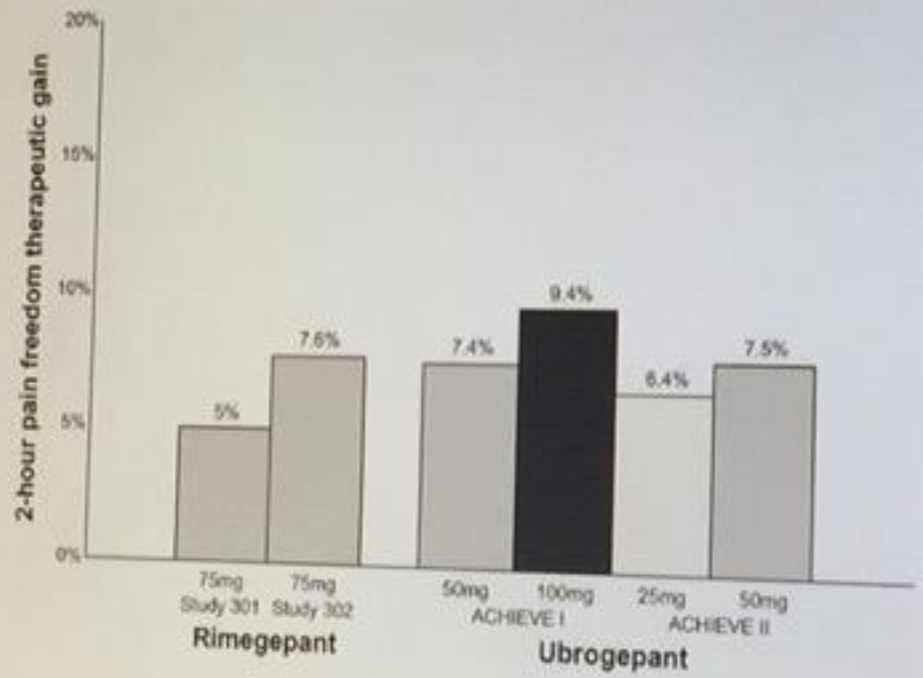
HEADACHE & CGRP

Cristina Tassorelli

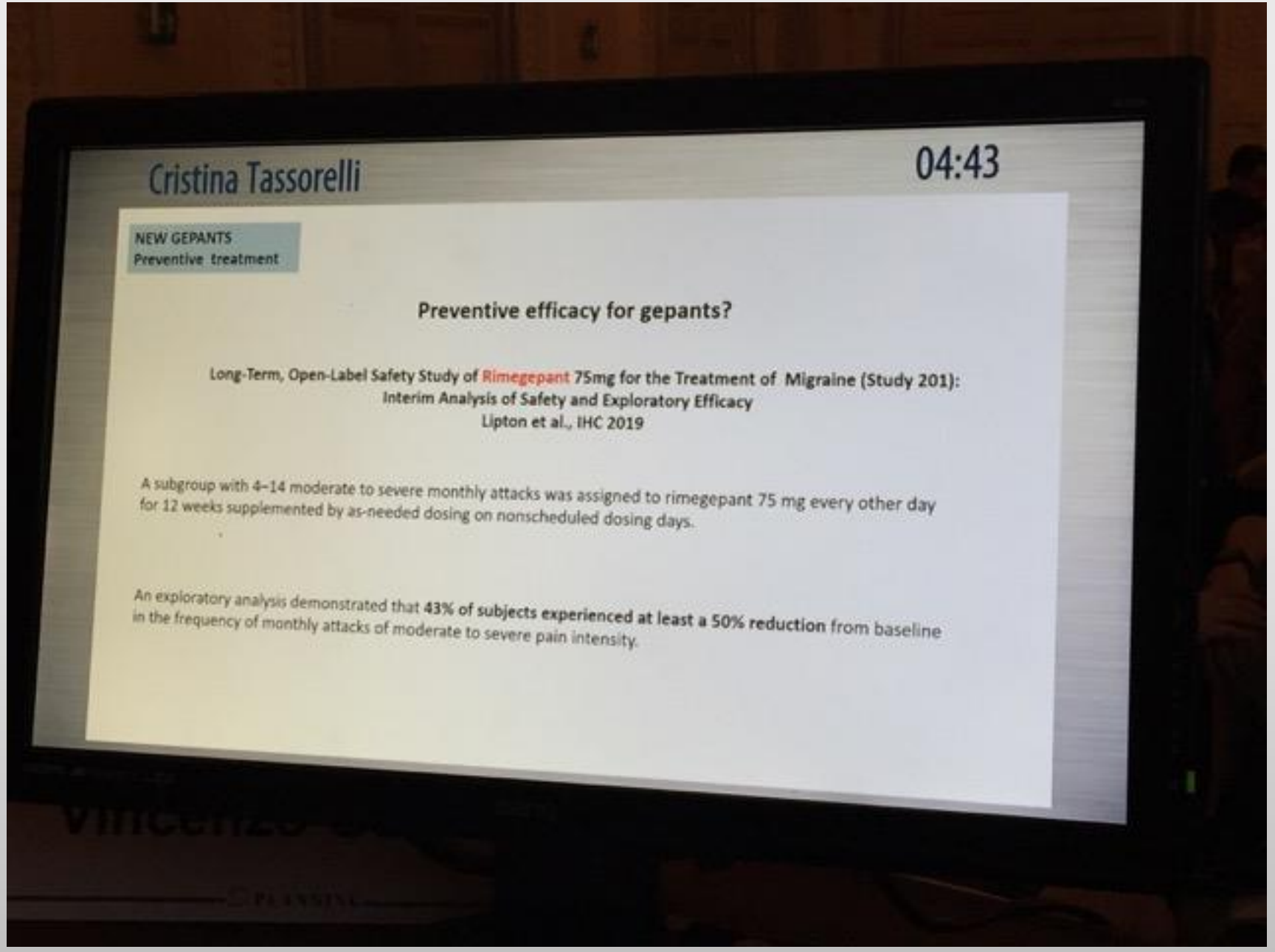
14:18

NEW GEPANTS
Acute treatment

Therapeutic gain vs placebo - 2-hour pain freedom



Do et al., IHP 2019


Cristina Tassorelli
04:43
NEW GEPANTS
Preventive treatment
Preventive efficacy for gepants?
Long-Term, Open-Label Safety Study of Rimegepant 75mg for the Treatment of Migraine (Study 201):
Interim Analysis of Safety and Exploratory Efficacy
Lipton et al., IHC 2019
A subgroup with 4–14 moderate to severe monthly attacks was assigned to rimegepant 75 mg every other day for 12 weeks supplemented by as-needed dosing on nonscheduled dosing days.
An exploratory analysis demonstrated that 43% of subjects experienced at least a 50% reduction from baseline in the frequency of monthly attacks of moderate to severe pain intensity.

Cristina Tassorelli

Possible indications for gepants

Acute treatment in subjects with contraindications to triptans and poor response to other analgesics

Preventive treatment as an alternative to CGRP targeting mABs in subjects who prefer to avoid a long-lasting block of the CGRP pathway or have a preference for an oral route of drug intake

In patients at higher risk to develop chronic migraine or medication overuse headache

Terapia preventiva dell'emicrania

- Terapia farmacologica
  - Betabloccanti
  - Calcioantagonisti
  - Antidepressivi
  - Antiepilettici
  - Tossina Botulinica
  - Altri farmaci

- Modificazioni dello stile di vita
- Dieta
- Nutraceutici
- Esercizio fisico aerobico
- Terapia cognitivo-comportamentale
- Tecniche di rilassamento
- Biofeedback
- Agopuntura
- Neurostimolazione

INDICAZIONI PER LA PROFILASSI

TERAPIA DI PROFILASSI ***LINEE GUIDA TERAPEUTICHE SISC***

Quando

Più di 2 crisi parzialmente o totalmente disabilitanti della durata complessiva di almeno 4 giorni

Perchè

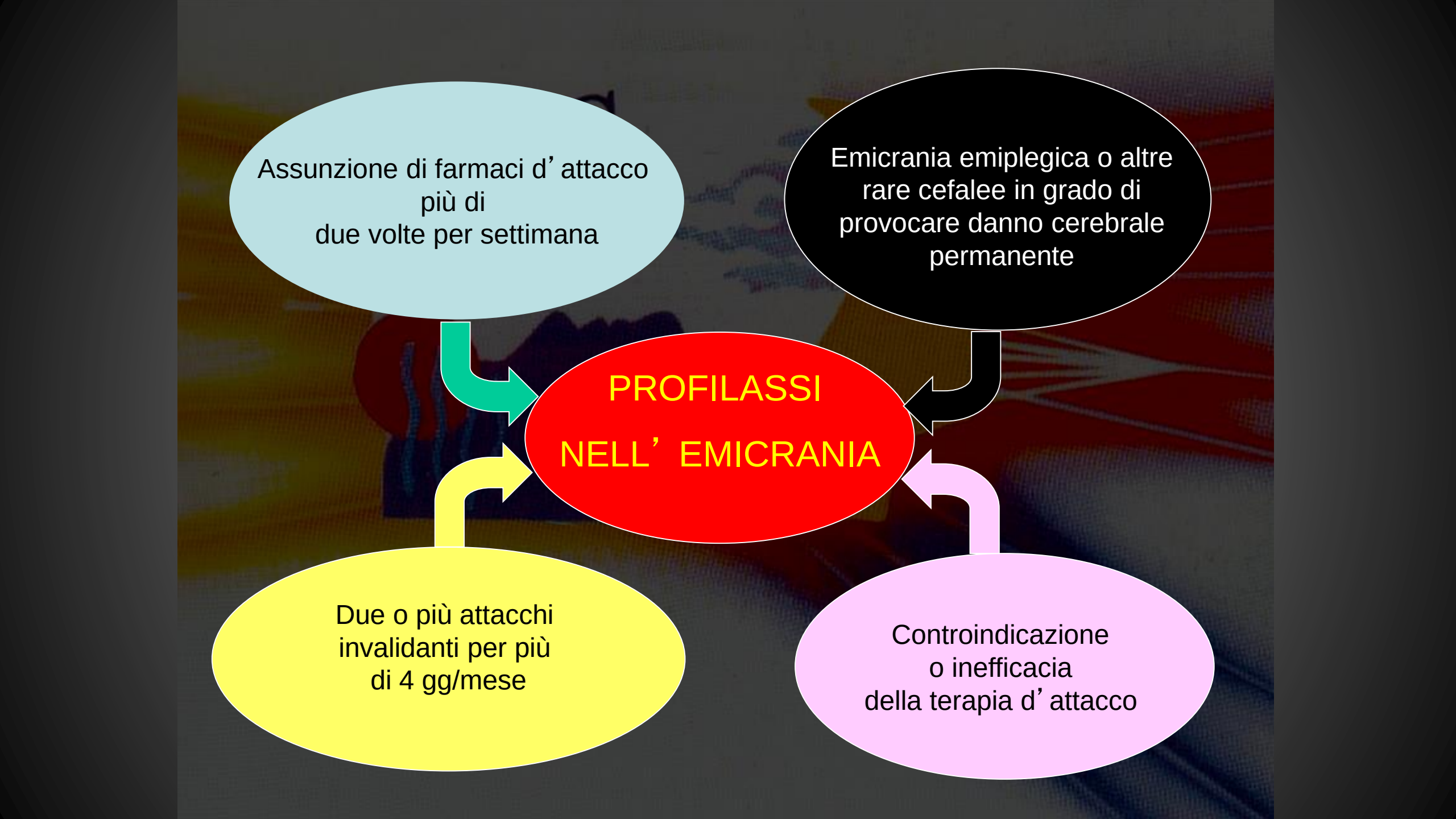
Riduzione del 50% di frequenza ed intensità delle crisi

Come

Minima quantità di farmaco che presenta i minori effetti indesiderati

Considerare comorbidità

Impiego non inferiore ai 3 mesi a dose adeguata


Assunzione di farmaci d’attacco più di due volte per settimana
Emicrania emiplegica o altre rare cefalee in grado di provocare danno cerebrale permanente
PROFILASSI NELL’EMICRANIA
Due o più attacchi invalidanti per più di 4 gg/mese
Controindicazione o inefficacia della terapia d’attacco

emicrania: ruolo della PROFILASSI

- ridurre la disabilità e migliorare la qualità di vita
- miglioramento della qualità di vita riducendo:
  - ★ giorni di cefalea
  - ★ durata della cefalea
  - ★ intensità della cefalea
- i benefici avvengono col tempo e non si possono avere immediatamente

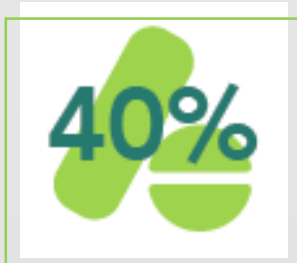
Silberstein SD, et al. Clin Ther 2006;28:1002–11
Dodick DW and Silberstein SD Pract Neurol 2007;7:383–93

FARMACI E COMORBIDITA'

TERAPIA DI PROFILASSI *LINEE GUIDA TERAPEUTICHE SISC*

	INDICATO	CONTROINDICATO
DEPRESSIONE	AMITRIPTILINA	FLUNARIZINA BETA BLOCCANTI
ANSIA ATTACCHI DI PANICO	AMITRIPTILINA SSRI	BETA BLOCCANTI
EPILESSIA	ACIDO VALPROICO - LAMOTRIGINA GABAPENTIN - TOPIRAMATO	AMITRIPTILINA
ASMA - ALLERGIA		BETA BLOCCANTI
IPERTENSIONE	BETA BLOCCANTI VERAPAMILE	DIIDROERGOTAMINA
OBESITA'	TOPIRAMATO VERAPAMILE	PIZOTIFENE – FLUNARIZINA AMITRIPTILINA – ACIDO VALPROICO
GLAUCOMA		PIZOTIFENE AMITRIPTILINA

TERAPIA PREVENTIVA DELL'EMICRANIA



dei pazienti emicranici **potrebbe avere beneficio** dalla terapia preventiva

Dei pazienti emicranici **utilizza** una terapia preventiva

80% dei pazienti che inizia ad assumere una terapia preventive, non la assume dopo **12** mesi

AMPP study - Lipton RB et al. Neurology. 2007;68:343-349
Hepp Z et al. Cephalalgia. 2017;37(5):470-485

SUBJECT REVIEW

J Manag Care Pharm. 2014;20(1):22-33

Systematic Review of Migraine Prophylaxis Adherence and Persistence

Zsolt Hepp, PharmD; Lisa M. Bloudek, PharmD, MS; and Sepideh F. Varon, PhD

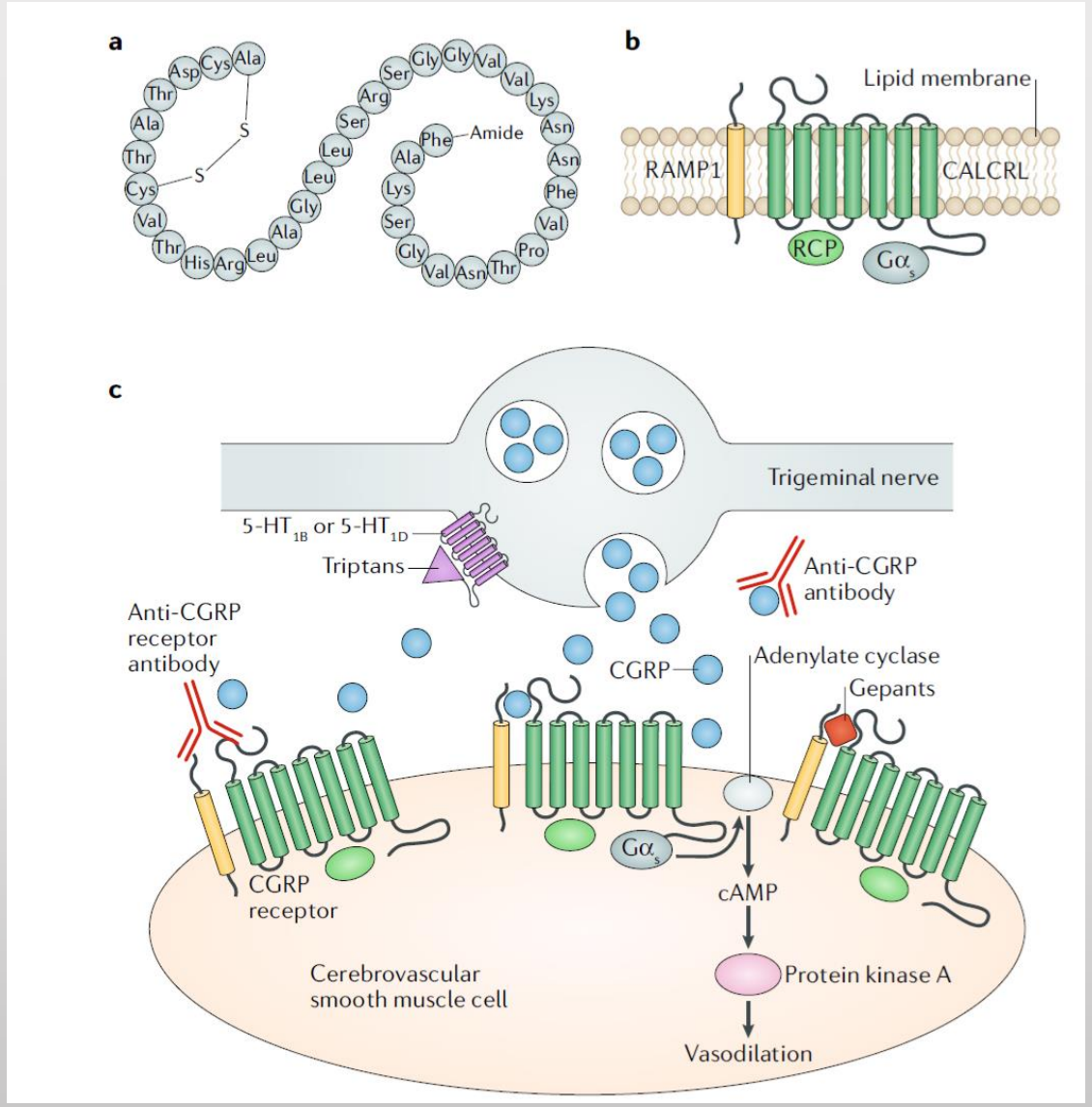
788 studi clinici

33 inclusi

CAUSE DI INTERRUZIONE DEL TRATTAMENTO				
	TOPIRAMATO %	AMITRIPTILINA %	PROPRANOLOLO %	PLACEBO %
EVENTI AVVERSI	23,70	16,74	7,77	6,96
SCELTA DEL PAZIENTE	5,56	18,56	1,21	6,25
PERSI AL FOLLOW UP	3,43	6,30	2,95	3,77
ALTRE CAUSE	8,45	9,53	6,97	15,45

Limiti delle attuali terapie preventive

- Molecole non specifiche
- Scarsa aderenza/persistenza
- Inefficacia
- Effetti indesiderati



Edvinsson et al, 2018

CARATTERISTICHE DEGLI **ANTICORPI MONOCLONALI** ANTI CGRP O ANTIRECETTORE CGRP

- Azione specifica sui meccanismi dell'emicrania
- Sono molecole di grosse dimensioni che non attraversano la b.e.e.
- Per la loro natura proteica devono essere somministrate sc, im, ev
- Non determinano alterazioni degli enzimi epatici
- Hanno una lunga emivita
- Non presentano interazioni farmacologiche

Wang W, Wang EQ, Balthasar JP (2008) Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 84:548–558

SISC

Symposium Florence 2020

Friday 14 February
Saturday 15 2020 Hotel Baglioni, Florence

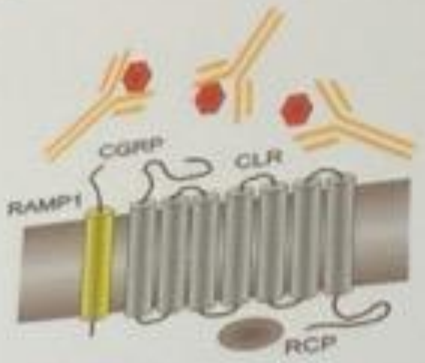
HEADACHE & CGRP

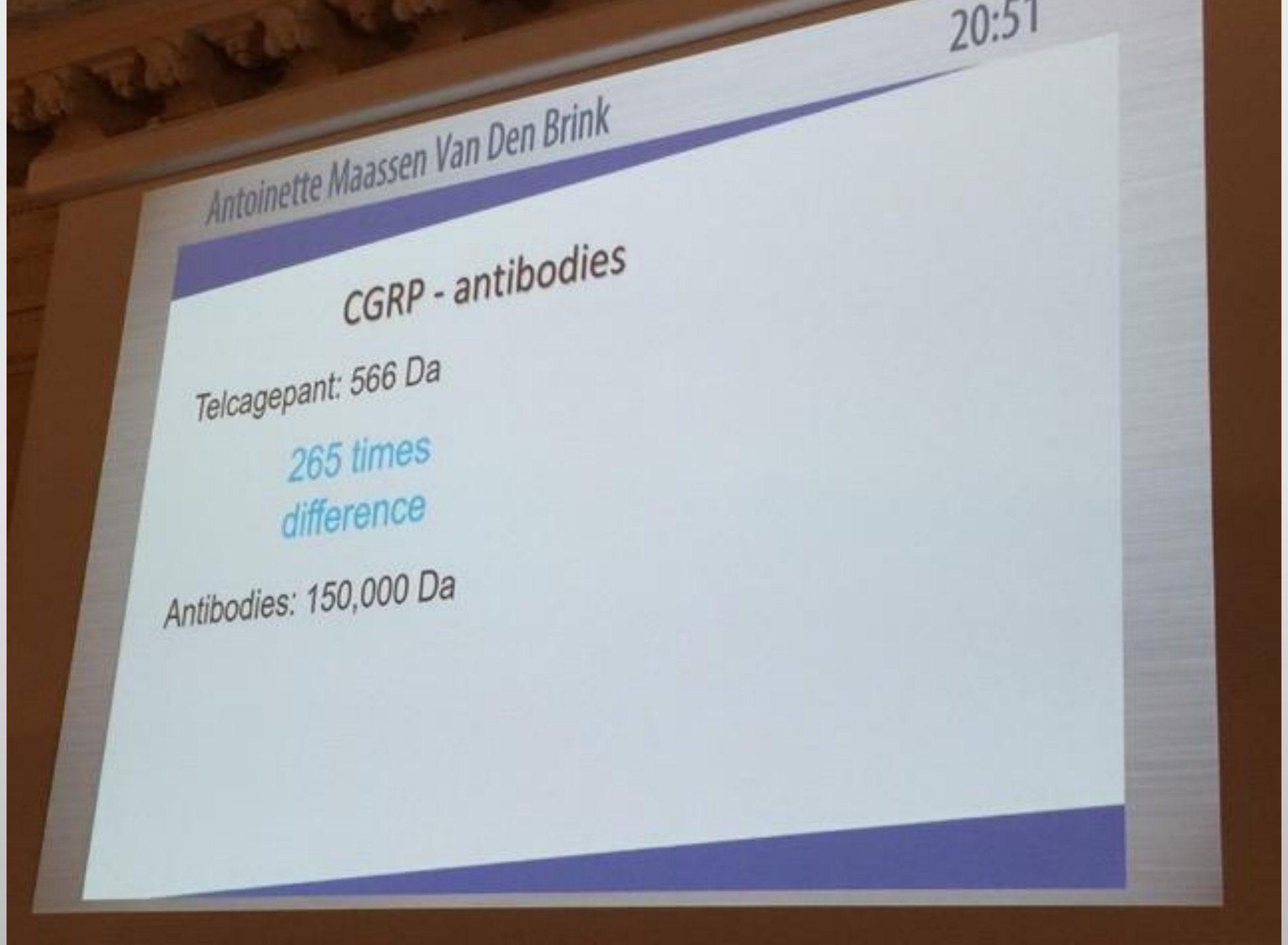
CGRP (receptor) antibodies

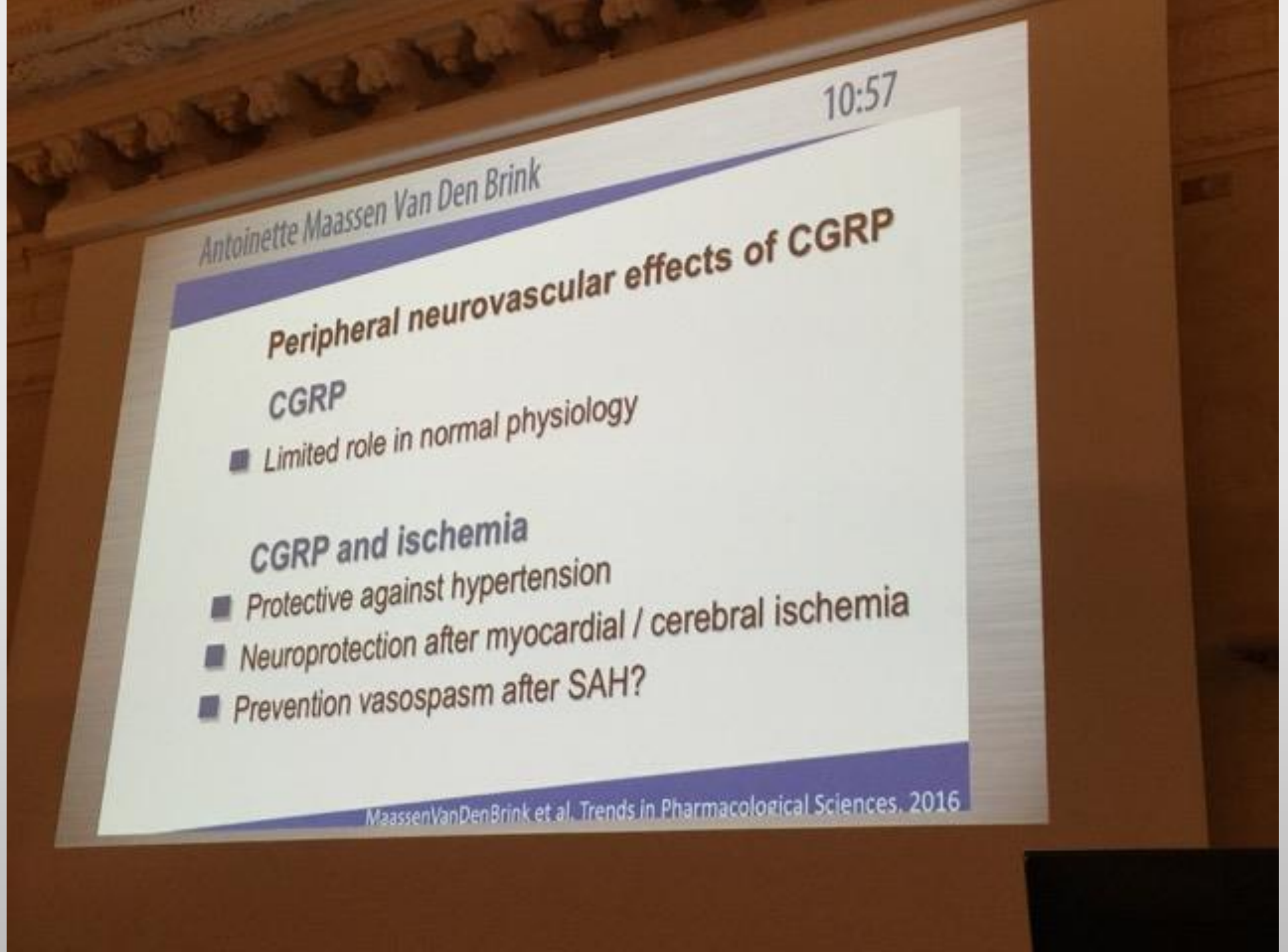
Antibodies against CGRP or its receptor:

- Eptinezumab (Alder)
  Fremanezumab (Teva)
  Galcanezumab (Lilly)
  binding to peptide CGRP

- Erenumab (Amgen / Novartis)
  binding to CGRP receptor




Antoinette Maassen Van Den Brink
20:51
CGRP - antibodies
Telcagepant: 566 Da
265 times
difference
Antibodies: 150,000 Da


10:57
Antoinette Maassen Van Den Brink
Peripheral neurovascular effects of CGRP
CGRP
Limited role in normal physiology
CGRP and ischemia
Protective against hypertension
Neuroprotection after myocardial / cerebral ischemia
Prevention vasospasm after SAH?
MaassenVanDenBrink et al. Trends in Pharmacological Sciences. 2016

CGRP and Migraine: The Role of Blocking Calcitonin Gene-Related Peptide Ligand and Receptor in the Management of Migraine

Kasra Maasumi[1] · Rebecca L. Michael[1] · Alan M. Rapoport[2]

Drugs Published online: 04 June 2018

ANTAGONISTI DEL CGRP NELLA TERAPIA PREVENTIVA DELL'EMICRANIA				
	ERENUMAB	GALCANEZUMAB	EPTINEZUMAB	FREMANEZUMAB
SOMMINISTRAZIONE	SC	SC	EV	SC
REGIME POSOLOGICO	MENSILE	MENSILE	TRIMESTRALE	MENSILE/ TRIMESTRALE
EMIVITA (GIORNI)	21	≈28	32	31
TARGET	recettore CGRP	ligando CGRP	ligando CGRP	ligando CGRP
SEQUENZIATO DA	100% umanizzato	>90% umanizzato	>90% umanizzato	95% umanizzato
SOTTOTIPO IgG	IgG2	IgG4	IgG1	IgG2Δa

ANTICORPI ANTICGRP RESPONDERS (GUADAGNO TERAPEUTICO)°			
	≥50% (GT)	≥75% (GT)	100% (GT)
ERENUMAB • EMICRANIA EPISODICA • EMICRANIA CRONICA**	50% (23%) 41% (18%)	22% (14%) 21% (13%)	5,8% (2,2%) 4.3% (4,9%)
FREMANEZUMAB • EMICRANIA EPISODICA • EMICRANIA CRONICA	48% (20%) 38-41% (20-23%)	9,6-12,4% (4.2-6,9%)	
GALCANEZUMAB • EMICRANIA EPISODICA • EMICRANIA CRONICA	62% (24%) 28% (15%)	39% (20%) 7-9% (4,5%)	16% (9%) 4.3% (4,9%)
EPTINEZUMAB • EMICRANIA EPISODICA**	75% (22%)	44% (9%)	26% (11%)

° DATI PRESENTATI NEL WORKSHOP «L'EMICRANIA: DALLA FISIOPATOLOGIA ALL'ORGANIZZAZIONE DELLA CURA»
50° CONGRESSO SOCIETA' ITALIANA DI NEUROLOGIA, BOLOGNA 12/10/2019
** RCT Fase II-b

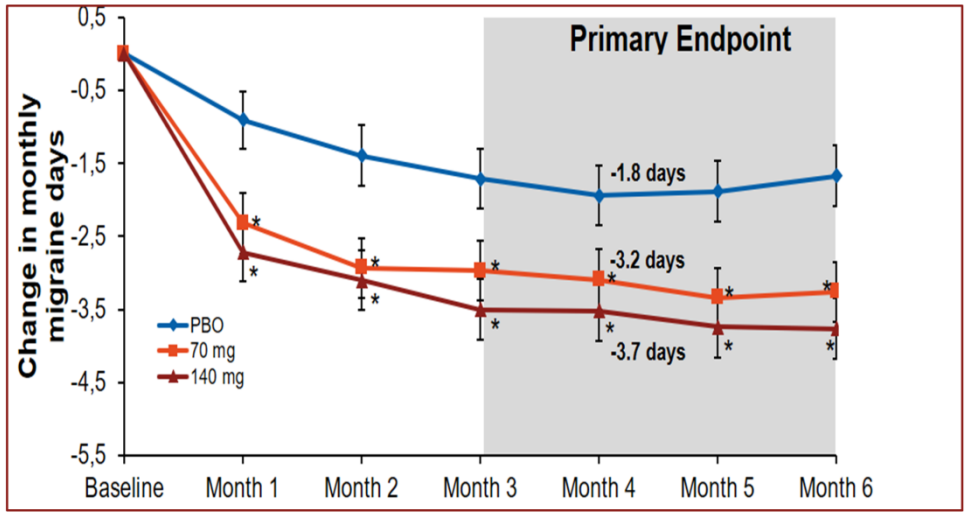
Overview of Erenumab (AMG 334) studies

Study	N pts	Design	Main objective | Primary endpoint
Single-dose study of AMG 334 in healthy subjects and migraine patients[1*]	60	DB, pbo-controlled	• Serum PK assessments • Adverse events
Multiple-dose study of AMG 334 in healthy subjects and migraine patients[1*]	48	DB, pbo-controlled	• Serum PK assessments • 24-hour continuous ambulatory BP
Effects of erenumab (AMG 334) and concomitant sumatriptan on blood pressure in healthy subjects[1,2]	34	DB, pbo-controlled	• Change in MAP • Sumatriptan PK
Pharmacokinetic drug interaction study of erenumab (AMG 334) and a combined oral contraceptive in healthy female subjects[3]	24	Multicenter, open-label, single-arm, PK drug interaction study	• AUC_{tau} and C_{max} for EE, NGMN, and NG
Phase IIa Study[1] (NCT02575833)	89	DB, pbo-controlled	• Effects in stable angina patients
EM Phase II study (20120178)[1*]	483	DB, pbo-controlled OLE	• Dose finding EM • Change from baseline in MMD
STRIVE: EM Phase III study (20120296)[3,4]	955	DB, pbo-controlled	• Pivotal EM trial • Change from baseline in MMD
ARISE: EM Phase III study (20120297)[1-3]	577	DB, pbo-controlled	• Supportive ph3 EM trial • Change from baseline in MMD
CM Phase II study (20120295)[4-6]	667	DB, pbo-controlled OLE	• Pivotal CM trial • Change in MMD from baseline
CAMG334A2301 (LIBERTY)	246	DB, pbo-controlled	• Ph3b study in 2-4 treatment failure patients • 50% responder rate in weeks 9-12

>3000 pts

Erenumab is efficacious in reducing the monthly migraine days versus placebo, with a decrease in acute migraine-specific medication intake

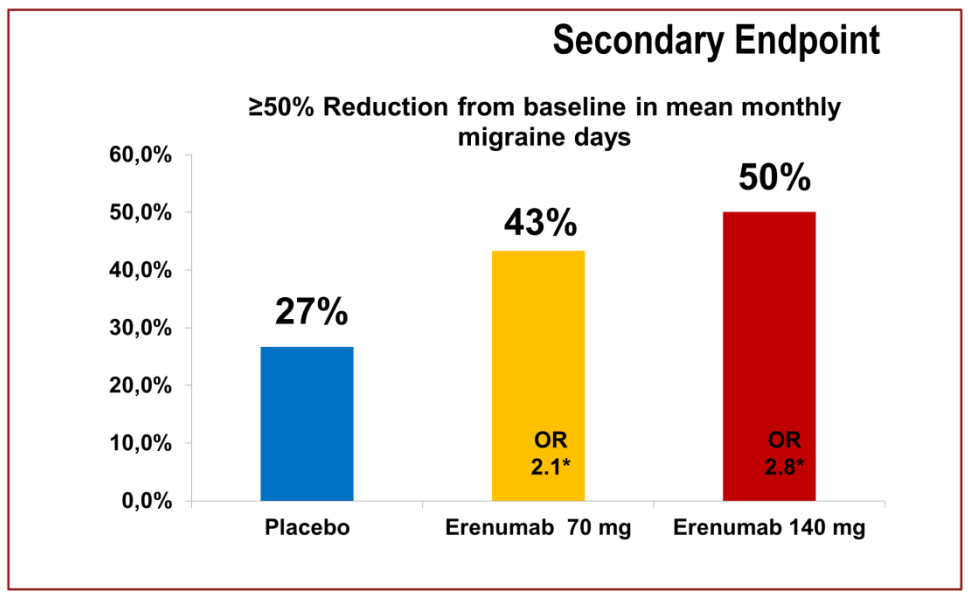
EM phase III, STRIVE

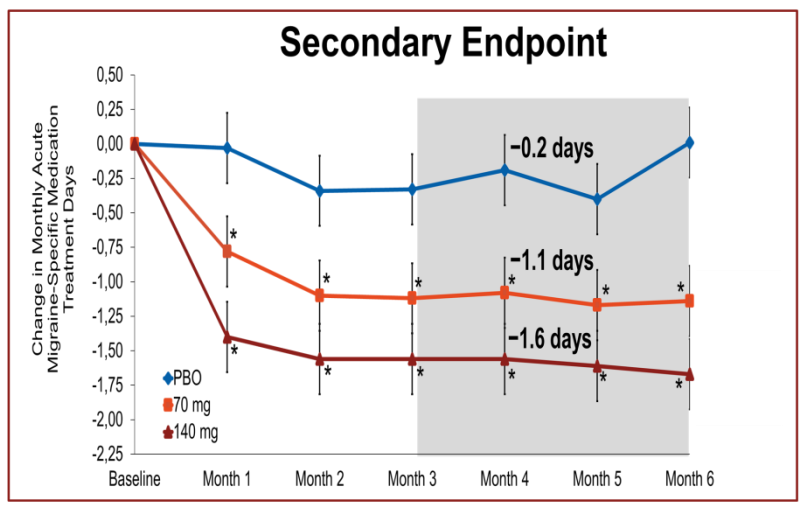


PBO n=319, erenumab 70 mg n=317, erenumab 140 mg n=319

Baseline monthly migraine days, mean (SD)
PBO: 8.2 (2.5)
erenumab 70 mg: 8.3 (2.5)
erenumab 140 mg: 8.3 (2.5)

Baseline monthly migraine-specific medication use days, mean (SD):
PBO: 3.4 (3.4),
Erenumab 70 mg: 3.2 (3.4),
erenumab 140 mg: 3.4 (3.5)





* p<0.001 for each group vs placebo, not adjusted for multiplicity; Endpoint averaged over months 4, 5, and 6.
EM = episodic migraine; OR = odds ratio; PBO = placebo.
Goadsby PJ, et al. N Engl J Med 2017; 377:2123-2132

Safety and tolerability profile of erenumab, evaluated in about 2500 patients, is similar to placebo

Pooled analysis

- The safety and tolerability profiles of erenumab are well established, having been evaluated in about 2.500 patients with migraine. More than 2.200 pts received erenumab for at least 6 months and more than 1.300 for at least 1 year*[б,ь]
- Across four placebo-controlled, randomized trials in EM and CM, the type and frequency of overall adverse events (AEs), treatment-emergent AEs (TEAEs), and serious AEs (SAEs) were similar across treatment groups, and there were no clear dose-dependent AEs[1,2,ю,я]
- The low rates of discontinuation due to AEs reported with erenumab were similar to those observed with placebo[ю,я]

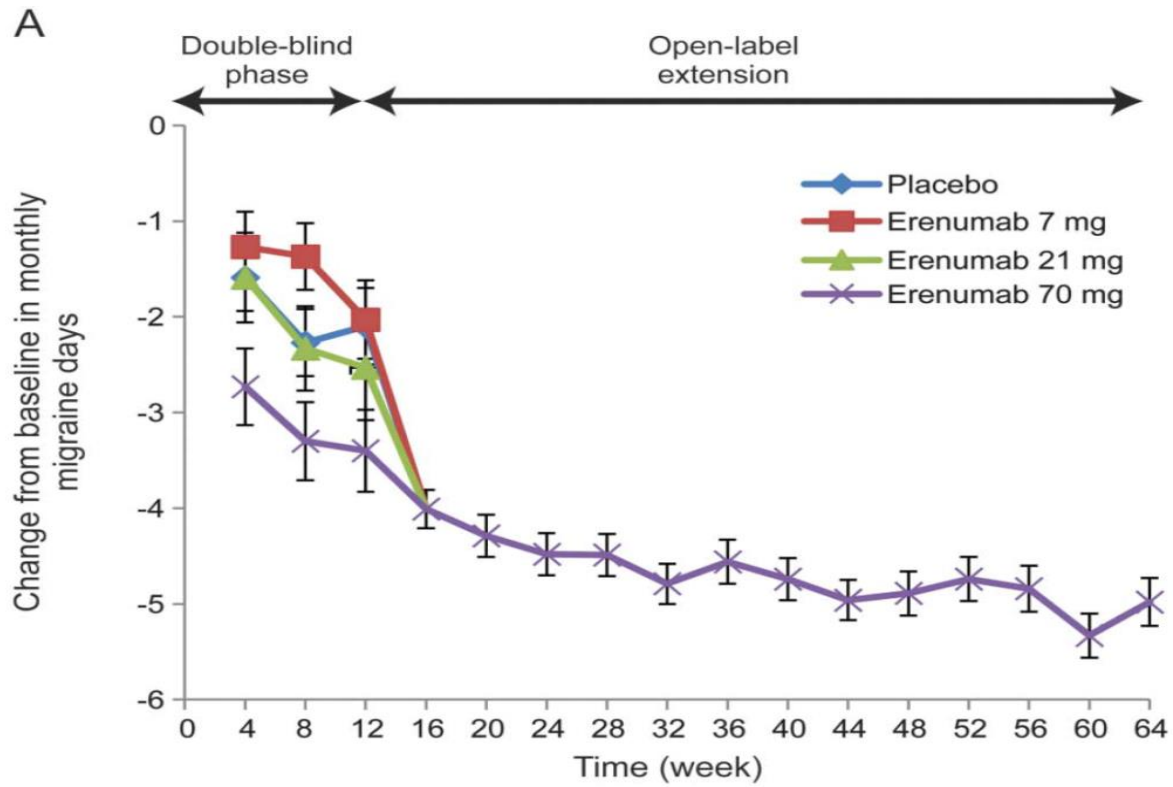
	Placebo (n = 1,043)	Erenumab 70 mg (n = 893)	Erenumab 140 mg (n = 507)
AEs of any grade, % (n)[ю]	**49 (511)**	**47.3 (422)**	**46.0 (233)**
TEAEs, % (n)[ю]			
Nasopharyngitis	7.3 (76)	5.9 (53)	5.5 (28)
Constipation	1.1 (11)	1.3 (12)	3.2 (16)
Upper respiratory tract infection	3.0 (31)	4.5 (40)	2.8 (14)
Injection site pain	1.7 (18)	3.7 (33)	1.6 (8)
Fatigue	1.7 (18)	2.2 (20)	2.0 (10)
Nausea	2.6 (27)	2.4 (21)	2.0 (10)
SAEs, % (n)[я]	**1.5 (16)**	**1.7 (15)**	**1.0 (5)**
AEs leading to discontinuation of investigational product, % (n)[я]	**1.0 (10)**	**1.7 (15)**	**2.0 (10)**

*Includes patients from a 12-week placebo-controlled safety pool who have received at least one dose of erenumab from registrational studies 20120178, 20120295, 20120296, and 20120297.б

1. Goadsby PJ, et al. *N Engl J Med*. 2017;377:2123-2132; 2. Tepper S, et al. *Lancet Neurol*. 2017;16:425-434;
б. Data on file, Amgen. [Integrated Summary of Safety 5.4.5.3. Table 14-5.1.1, AMG 334];
ь. Data on file, Amgen. [Integrated Summary of Safety 5.4.5.3. Table 14-5.2.1, AMG 334];
ю. Data on file, Amgen. [Integrated Summary of Safety 5.3.5.3. Table 14-6.2.1 AMG 334];
я. Data on file, Amgen. [Integrated Summary of Safety 5.3.5.3. Table 14-6.1.1. AMG 334].

The efficacy of erenumab persists throughout 1 year of continuous treatment

EM phase II OLE



383 pts entered in the OLE; 80% completed the 64 weeks period.
Mean (SD) MMD were 8.8 (2.6) at parent study baseline and 3.7 (4.0) at week 64.

Ashina M et al, Neurology. 2017 Sep 19;89(12):1237-1243

NOVARTIS

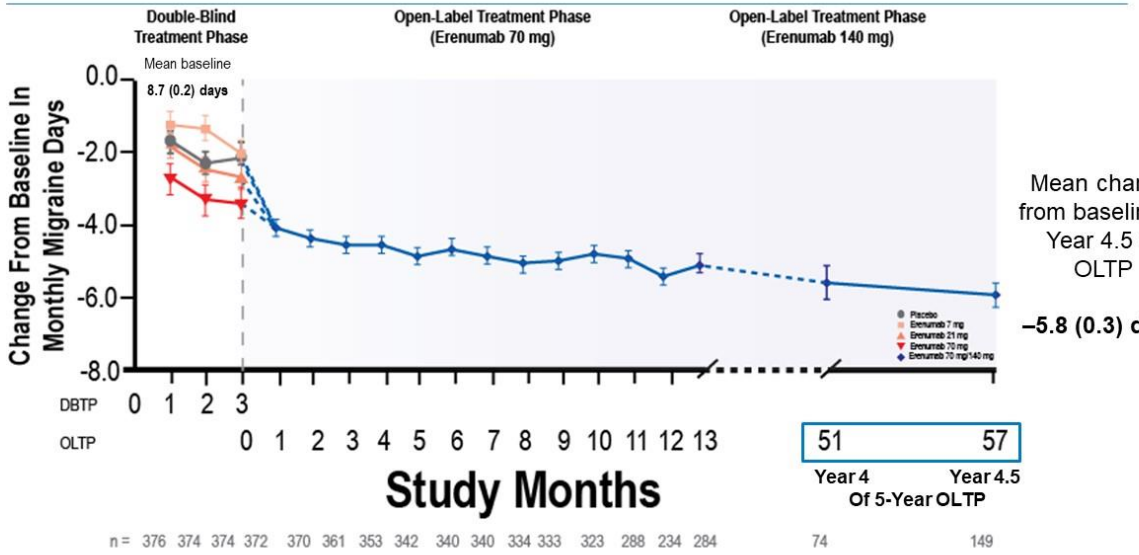
Sustained Efficacy and Long-Term Safety of Erenumab in Patients With Episodic Migraine: 4+-Year Results of a 5-Year, Open-Label Treatment Period

Messoud Ashina,[1] Peter J. Goadsby,[2] Uwe Reuter,[3] Stephen Silberstein,[4] David W. Dodick,[5] Denise E. Chou,[6] Shaloo Pandhi,[7] Fei Xue,[6] Feng Zhang,[6] Sunfa Cheng,[6] Daniel D. Mikol[6]

[1]Department of Neurology, Danish Headache Center, Rigshospitalet Glostrup, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [2]NIHR-Wellcome Trust King's Clinical Research Facility, King's College, London, UK; [3]Department of Neurology, Charité Universitätsmedizin Berlin, Berlin, Germany; [4]Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA; [5]Department of Neurology, Mayo Clinic, Scottsdale, AZ, USA; [6]Amgen Inc., Thousand Oaks, CA, USA; [7]Novartis Pharma AG, Basel, Switzerland

American Headache Society, 61st Annual Meeting; Philadelphia, PA; July 11–14, 2019

Change From Baseline in Monthly Migraine Days (MMD)



Mean change from baseline at Year 4.5 of OLTP

–5.8 (0.3) days

Only includes patients enrolled in the OLTP; Data are mean (SE); n = total number of patients with observed monthly migraine days at each visit, majority of patients started efficacy assessments per protocol amendment at Month 57 (Year 4.5) visit in OLTP; All patients completed Month 57 (Year 4.5) visit in OLTP at time of analysis; 13 study months (4 week) in a calendar year. OLTP, open-label treatment phase

Exposure-Adjusted Incidence Rates of AE (per 100 Patient-Years)

	Double-Blind Treatment Phase Pooled Data From 4 Studies		Open-Label Treatment Phase of This Study
	Placebo (N = 1043)	Total Erenumab (70 mg/140 mg) (N = 1400)	Total Erenumab (70 mg/140 mg) (N = 383)
All AEs, n [r]	551 [280.2]	727 [249.0]	339 [124.9]
Grade ≥ 3	40 [12.8]	58 [12.4]	81 [7.3]
Serious AEs	20 [6.3]	28 [5.9]	46 [3.8]
AEs leading to discontinuation of investigational product	13 [4.1]	27 [5.7]	18 [1.4]
Fatal AEs*	0 [0.0]	0 [0.0]	1 [< 0.1]

AE, adverse event; n, number of patients reporting at least 1 occurrence of event; r, exposure-adjusted rate per 100 patient-years (n/e×100)
*Fatality, previously reported, due to arteriosclerosis occurred in patient with history of hypertension and left anterior hemiblock (ECG), who on autopsy showed evidence of severe coronary artery disease and presence of cardiac stimulants (liver tissue) - considered not related to investigational product by investigator
†Events with ≥ 4.2 patients per 100 patient-years in the erenumab 70 mg/140 mg group

- Overall exposure-adjusted incidence rates of AEs during the OLTP were similar to or lower than those observed during the DBTP with no apparent dose-relationship, no increases over time, and no new AE over time
- Most frequent AEs in OLTP were nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, back pain, and urinary tract infection, and arthralgia

A Review of Monoclonal Antibody Therapies and Other Preventative Treatments in Migraine

Uwe Reuter, MD, MBA

(*Headache* 2018;58:48-59)

STUDIO	SOSTANZA	EM/CM	DURATA IN MESI	% DROP OUT TOTALE	% DROP OUT PER AE
Goadsby et al. (2017)[18]	Erenumab 140 mg	EM	6 months	8.5	2.1
Brandes et al. (2004)[19]	Topiramate 100 mg	EM	6 months	47.5	26.7
Silberstein et al. (2017)[20]	Fremanezumab 675 mg monthly	CM	3 months	9.5	1.8
Tepper et al. (2017)[21]	Erenumab 140 mg	CM	3 months	2.1	1.1
Silberstein et al. (2007)[22]	Topiramate 100 mg	CM	3 months	44.2	10.9
Diener et al. (2010)[23]	Botulinum toxin 155IE	CM	6 months	10.4	2.3
Aurora et al. (2010)[24]	Botulinum toxin 155IE	CM	6 months	13.2	3.2

ABBREVIAZIONI: AE=EVENTI AVVERSI, CM=EMICRANIA CRONICA, EM=EMICRANIA EPISODICA

Raffaelli et al. The Journal of Headache and Pain (2019) 20:66
https://doi.org/10.1186/s10194-019-1018-8

The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

Erenumab and galcanezumab in chronic migraine prevention: effects after treatment termination

Bianca Raffaelli[1,2*], Valeria Mussetto[1], Heike Israel[1], Lars Neeb[1] and Uwe Reuter[1]

Abstract

Background: Monoclonal antibodies (mAbs) targeting the CGRP pathway are safe and efficacious therapies for the prevention of migraine. In this study we assessed the effects of discontinuation of preventive erenumab and galcanezumab treatment in patients with chronic migraine.

Methods: This retrospective pooled analysis included completers of the open-label extension study phase for the preventive treatment of chronic migraine with galcanezumab (NCT02614261; 9 months) and erenumab (NCT02174861; 12 months) in a single headache center. We compare migraine data until week 12 after open-label treatment completion, when patients did not have any pharmacological preventive medication, to study baseline values of the double-blind trial period, and to the last 4 weeks of the open-label extension. The assessment included changes in monthly migraine days, headache hours, days with severe headache and acute headache medication use.

Results: Data from 16 patients after galcanezumab ($n = 9$) and erenumab ($n = 7$) open-label treatment completion were analyzed. The mean number of monthly migraine days was 18.38 ± 3.74 at baseline, and 12.19 ± 4.53 in the last 4 weeks of the open-label extension ($p < 0.001$). Monthly migraine days remained significantly reduced compared to baseline during the entire 12-week observation period after open-label termination ($p = 0.002$), with a reduction of 5.38 ± 4.92 in weeks 1–4 ($p = 0.001$), 4.75 ± 4.15 in weeks 5–8 ($p = 0.001$), and 3.93 ± 5.45 in weeks 9–12 ($p = 0.014$). There was no significant difference in monthly migraine days between the 12 weeks after open-label termination and the last 4 weeks of the open-label phase ($p = 0.228$). All other analyses revealed numerical improvement through week 12 in comparison to baseline.

Conclusions: In this small, self-selected cohort, the results indicate a therapeutic effect of monoclonal antibodies targeting the CRGP pathway in chronic migraine prevention after treatment termination up to 12 weeks.

Keywords: Calcitonin gene-related peptide, Chronic migraine, Erenumab, Galcazenumab, Migraine, Prevention

SISC

Symposium Florence 2020

Friday 14 February
Saturday 15 2020 Hotel Baglioni, Florence

HEADACHE & CGRP

03:40

Angelo Torrente

Materials and methods

PoliPa 32

PoliMe 13

PoliBa 16

BoninoMe 26

PoliCz 15

NapoliVan 72

Outcome studied:

- Headache days per month
- Abortive drugs consumption per month
- Side effects
- HIT6 and MIDAS questionnaire

Data analyzed at

- baseline (t0)
- 3-month therapy (t3)

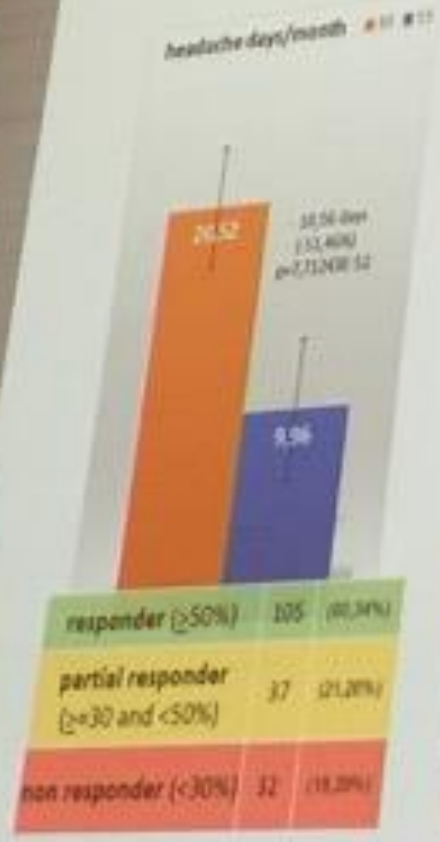
Two dosages:

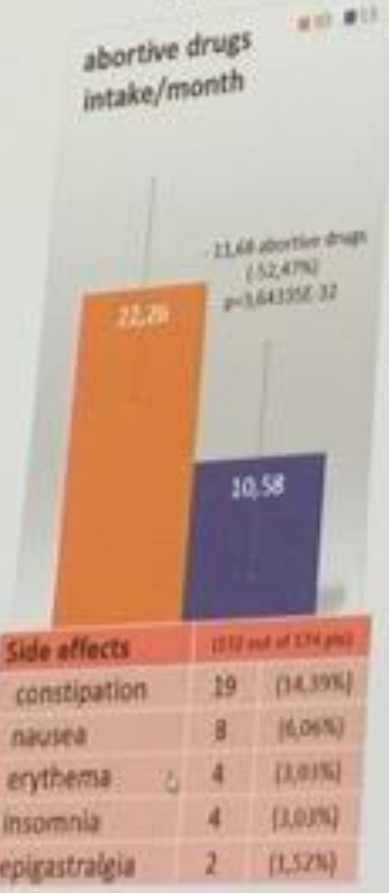
- 70 mg
- 140 mg

Population		
total		174
sex	female	143
	male	31
mean age (years old)		48±10
mean n° of preventive treatments		3,61
Chronic migraineurs		164
Episodic migraineurs		10
MOH		122 / 133
Dosages	70 mg	150
	140 mg	24

Angelo Torrente

Results





responder (≥50%)	105	(60,34%)
partial responder (≥=30 and <50%)	37	(21,28%)
non responder (<30%)	32	(18,39%)

Side effects	(132 out of 174 pts)	
constipation	19	(14,39%)
nausea	8	(6,06%)
erythema	4	(3,03%)
insomnia	4	(3,03%)
epigastralgia	2	(1,52%)

6 pts

70 → 140 mg

EMICRANIA: DIFFERENZE FRA ANTICORPI MONOCLONALI E TERAPIA PREVENTIVA TRADIZIONALE

	ANTICORPI ANTI CGRP	TERAPIA TRADIZIONALE
SPECIFICITA’	+	+
FORMULAZIONE	SC/EV	OS
TITOLAZIONE	-	+
FREQUENZA DI ASSUNZIONE	MENSILE/TRIMESTRALE	GIORNALIERA
INIZIO D’AZIONE	RAPIDA(GIORNI)	LENTA
EFFETTI COLLATERALI		
• EFFETTI SUL PESO	-	+
• CAMBIAMENTI D’UMORE	-	+
• SONNOLENZA/FATICA	-	+
• DISFUNZIONE COGNITIVA	-	+
• VERTIGINI	-	+

Israel et al. Current Pain and Headache Reports (22018)22:38

aifa

AIMOVIG - fascia Cnn

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

Aimovig è indicato per la profilassi dell'emicrania in adulti che hanno almeno 4 giorni di emicrania al mese.

4.2 Posologia e modo di somministrazione

Il trattamento deve essere iniziato da medici esperti nella diagnosi e nel trattamento dell'emicrania.

AGENZIA ITALIANA DEL FARMACO

Sacco et al. The Journal of Headache and Pain (2019) 20:6
https://doi.org/10.1186/s10194-018-0955-y

The Journal of Headache and Pain

CONSENSUS ARTICLE Open Access

European headache federation guideline on the use of monoclonal antibodies acting

Table 19 Recommendations about the use of anti-calcitonin gene-related peptide monoclonal antibodies in subjects with migraine

Clinical question	Recommendation	Strength of the recommendation
1. When should treatment with anti-CGRP monoclonal antibodies be offered to patients with migraine?		
	In patients with episodic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab In patients with chronic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab	Experts' opinion
2. How should other preventive treatments be managed when using anti-CGRP monoclonal antibodies in patients with migraine?		
	In patients with episodic migraine, before starting erenumab, galcanezumab or fremanezumab we suggest to stop oral preventive drugs unless the patient had a previous history of chronic migraine before prevention; in this case, we suggest to add the anti-CGRP monoclonal antibody to the ongoing treatment and to re-assess the need of treatment withdrawal In patients with chronic migraine who are on treatment with any oral drug with inadequate treatment response we suggest to add erenumab, fremanezumab, or galcanezumab and to consider later withdrawal of the oral drug In patients with chronic migraine who are on treatment with onabotulinumtoxinA with inadequate treatment response we suggest to stop onabotulinumtoxinA before initiation of erenumab, fremanezumab, or galcanezumab In patients with chronic migraine who are on treatment with erenumab, fremanezumab, or galcanezumab and who may benefit from additional prevention we suggest to add oral preventive drugs	Experts' opinion

CONSENSUS ARTICLE Open Access

European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention

Sacco et al. The Journal of Headache and Pain (2019) 20:6

Quando prescrivere gli anticorpi anti CGRP?

- Pazienti con emicrania episodica o cronica, non responsivi ad almeno 2 trattamenti preventivi, o che non possono assumere altri trattamenti preventivi per comorbidità, effetti collaterali, scarsa compliance

PROPOSTA

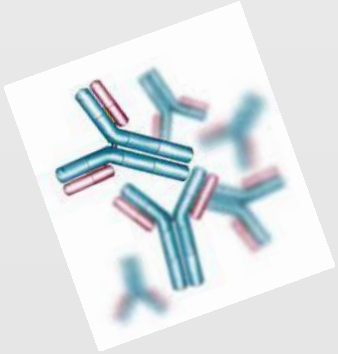
Parere clinico e place in therapy

- i pazienti con emicrania episodica ad alta frequenza (8-14 giorni/mese di emicrania), che dimostrino una risposta insufficiente o che risultino intolleranti ad almeno 2 terapie per la profilassi con livello di raccomandazione I (linee guida SISC), o che presentino controindicazioni a tutte le terapie disponibili

- i pazienti con emicrania cronica (≥15 giorni/mese di emicrania), che dimostrino una risposta insufficiente o mancata risposta a almeno 3 trattamenti profilattici per l'emicrania, di cui uno corrispondente ad almeno 3 sedute di terapia con tossina botulinica A, o che presentino controindicazioni a tutte le terapie disponibili. La mancata risposta è definita da una riduzione <30% dei giorni/mese di cefalea

Conclusioni

- *I mAbs rappresentano la prima classe di farmaci specificamente studiati per la terapia di profilassi dell'emicrania*
- *Presentano un ampio spettro di azione essendosi dimostrati efficaci nelle forme di emicrania episodica e cronica, nelle forme con abuso farmacologico e nell'emicrania refrattaria*
- *Presentano un ottimo profilo di tollerabilità e sicurezza nel breve e nel medio periodo*



Emicrania: una patologia endemica da riconsiderare

Vicenza, 20 febbraio 2020

GEPANTI, DITANI ED ANTICORPI MONOCLONALI anti-CGRP NELL'EMICRANIA

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