GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA
Catania
11 Giugno 2019

I NUOVI FARMACI PER IL TRATTAMENTO DELL'EMICRANIA

*Perché **NON** sono utili*

Salvatore Ferlisi, MD
Università degli Studi di Palermo

EPIDEMIOLOGIA

- L'emicrania colpisce fino al 12% della popolazione generale. È più frequente nelle donne. L'emicrania senza aura è il tipo più comune e rappresenta circa il 75% dei casi
- E' più comune tra i 30 e i 39 anni
- Rappresenta, secondo l'OMS, la terza causa di disabilità al mondo negli under 50

Steiner et al. The Journal of Headache and Pain (2015) 16:58
DOI 10.1186/s10194-015-0544-2

The Journal of Headache and Pain
a SpringerOpen Journal

EDITORIAL Open Access

Headache disorders are third cause of disability worldwide

Timothy J. Steiner[1,2*], Gretchen L. Birbeck[3,4], Rigmor H. Jensen[5], Zaza Katsarava[6,7], Lars J. Stovner[1,8] and Paolo Martelletti[9,10]

Steiner et al. The Journal of Headache and Pain (2016) 17:104
DOI 10.1186/s10194-016-0699-5

The Journal of Headache and Pain

EDITORIAL Open Access

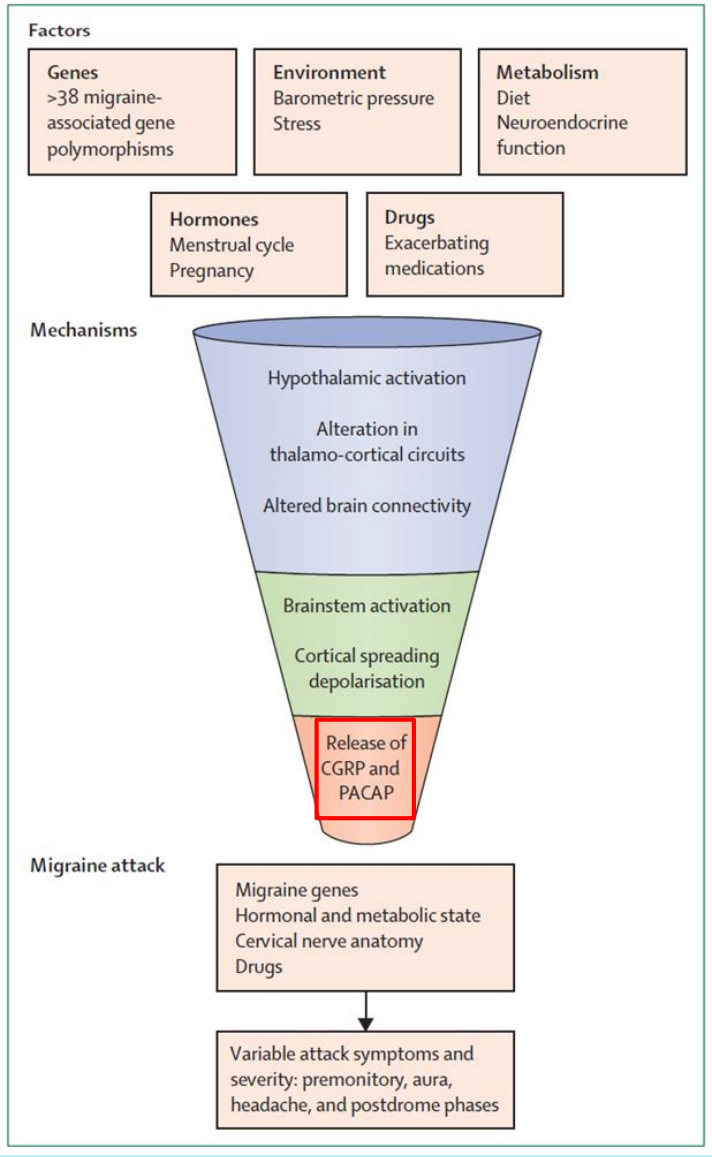
GBD 2015: migraine is the third cause of disability in under 50s

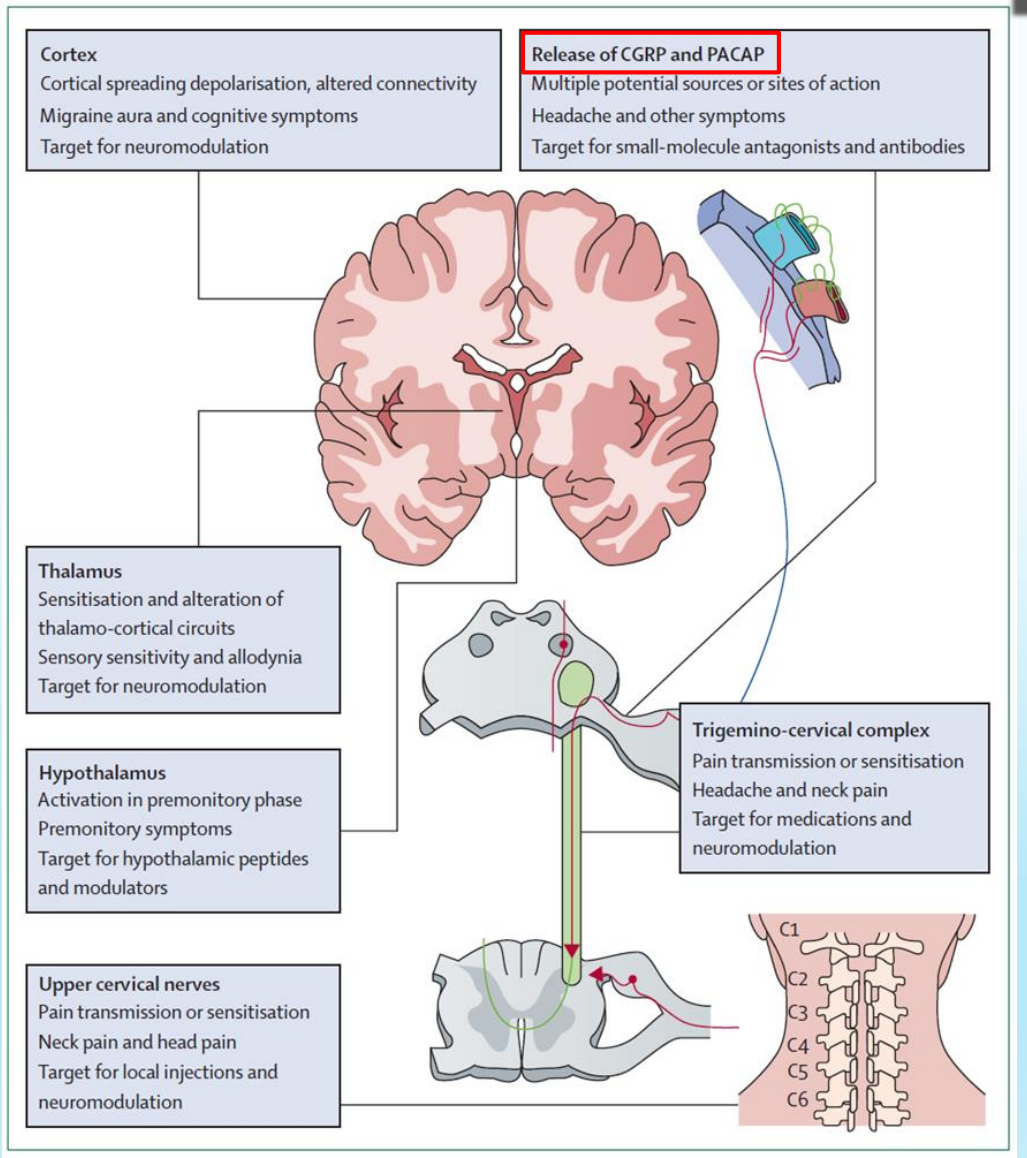
Timothy J. Steiner[1,2*], Lars J. Stovner[1,3] and Theo Vos[4]

Burden of migraine

- WHO GBD Study (2000): Migraine ranked as the **9th** most disabling medical condition in women[1]
- WHO GBD Study (2010): Migraine ranked as the **3rd** most disabling medical condition in women[2]
- WHO GBD Study (2016): Migraine ranked as the **2nd** most disabling medical condition in women[3]
- Migraine accounts for approximately **50%** of the disability burden attributable to all neurological disease worldwide[4]
- CDH (>15 days per month), affects 3–5% of people worldwide[5]
- There is a higher prevalence of CDH in lower socioeconomic populations (e.g.,**10%** Russia and **8%** Georgia)[6,7]

FISIOPATOLOGIA





Lancet Neurol 2018; 17: 174-182

TRATTAMENTO ACUTO

Intensità moderata: paracetamolo, FANS, triptani

Intensità severa: triptani, cortisonici, ergotamina, dopamino-antagonisti

Intensità molto severa: steroidi, oppioidi, antagonisti dopaminergici

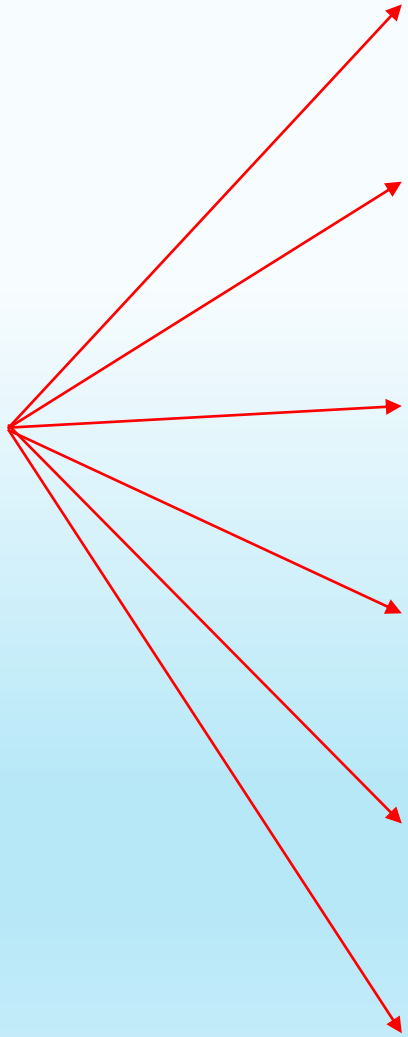
TABLE 1-1 Acute Migraine Treatment Strategies

Strategy	Medications
Acetaminophen and nonsteroidal anti-inflammatory drug strategy for attacks of mild to moderate severity	Acetaminophen (primarily for milder attacks)
	Acetylsalicylic acid
	Ibuprofen
	Naproxen sodium
	Diclofenac potassium
Triptan strategy for moderate and severe attacks	Sumatriptan
	Rizatriptan
	Eletriptan
	Zolmitriptan
	Almotriptan
	Frovatriptan
	Naratriptan
Refractory migraine strategies	Triptan and nonsteroidal anti-inflammatory drug combinations
	Dihydroergotamine
	Various rescue medications (eg, dopamine antagonists)
	Combination analgesics without opioids
	Combination analgesics with opioids (not for routine use)
Strategies for patients with contraindications to vasoconstricting drugs	Nonsteroidal anti-inflammatory drugs
	Dopamine antagonists
	Combination analgesics without opioids
	Combination analgesics with opioids (not for routine use)

Continuum 2015;21:953-972

TRATTAMENTO DI PROFILASSI

Classi farmacologiche



- Antiipertensivi(beta-bloccanti, calcio-antagonisti, ACE-I, sartani)
- Antiepilettici (topiramato, ac. valproico, lamotrigina, pregabalin)
- Antidepressivi (triciclici, SSRIs, SNRIs)
- Tossina Botulinica tipo A
- **Inibitori CGRP**
- Altri (es. ergotaminici)

Exp rev Pharmacother 2017;18:1409-1415

TRATTAMENTI NON INVASIVI

Headache Currents

HEADACHE CURRENTS

An Update on Non-Pharmacological Neuromodulation for the Acute and Preventive Treatment of Migraine

Francesca Puledda, MD; Peter J. Goadsby, PhD

Device	Use	Patient nb	Duration of NS
Supraorbital Nerve NS	Prevention - Episodic	67	20 min
Vagus Nerve NS	Prevention - Episodic	322	12 min
Caloric vestibular NS	Prevention – Episodic	49	?
« Permastoid » NS	Prevention – Episodic	80	45 min

Device	Use	Patient nb	Duration of NS
Vagus Nerve NS	Prevention – Chronic	59	12 min

Device	Use	Patient nb (incl.)	Duration of NS
Supraorbital Nerve NS	Attack (1)	99	60 min
Vagus Nerve NS	Attack (up to 5)	248	4 min
Transcranial Magnetic NS	Attack (mean 3)	164	0.5 min
Remote Electrical NS	Attack (at least 1)	71	20 min

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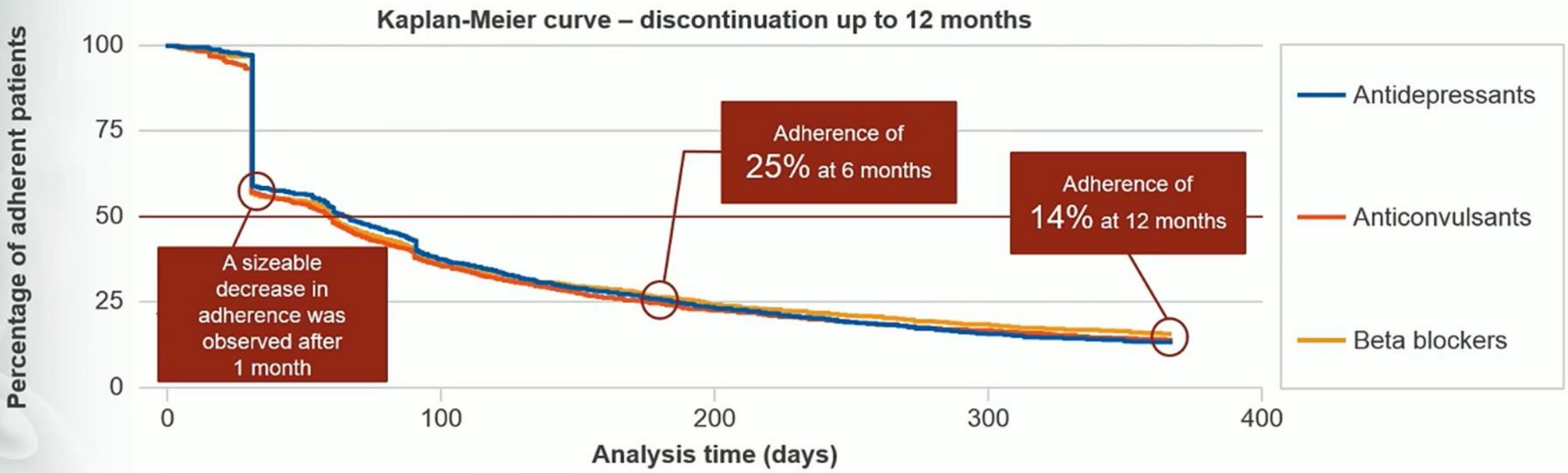
LOW ADHERENCE AS SHOWN BY THE 'TIME TO DISCONTINUATION UP TO 12 MONTHS' FOLLOW-UP FROM THE INITIAL PROPHYLACTIC'

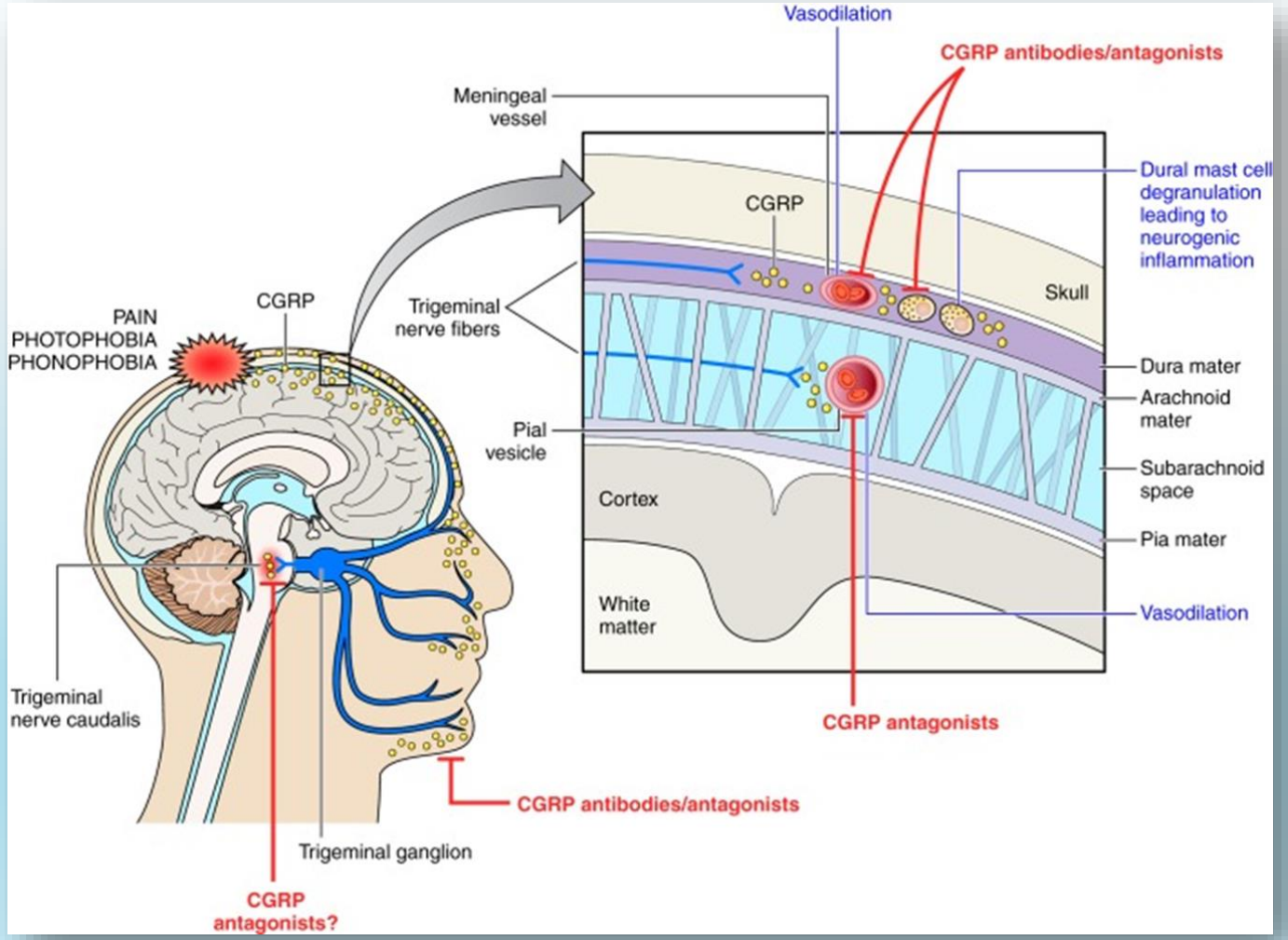


More than 80% of chronic migraine patients discontinued prophylactic treatment within 1 year

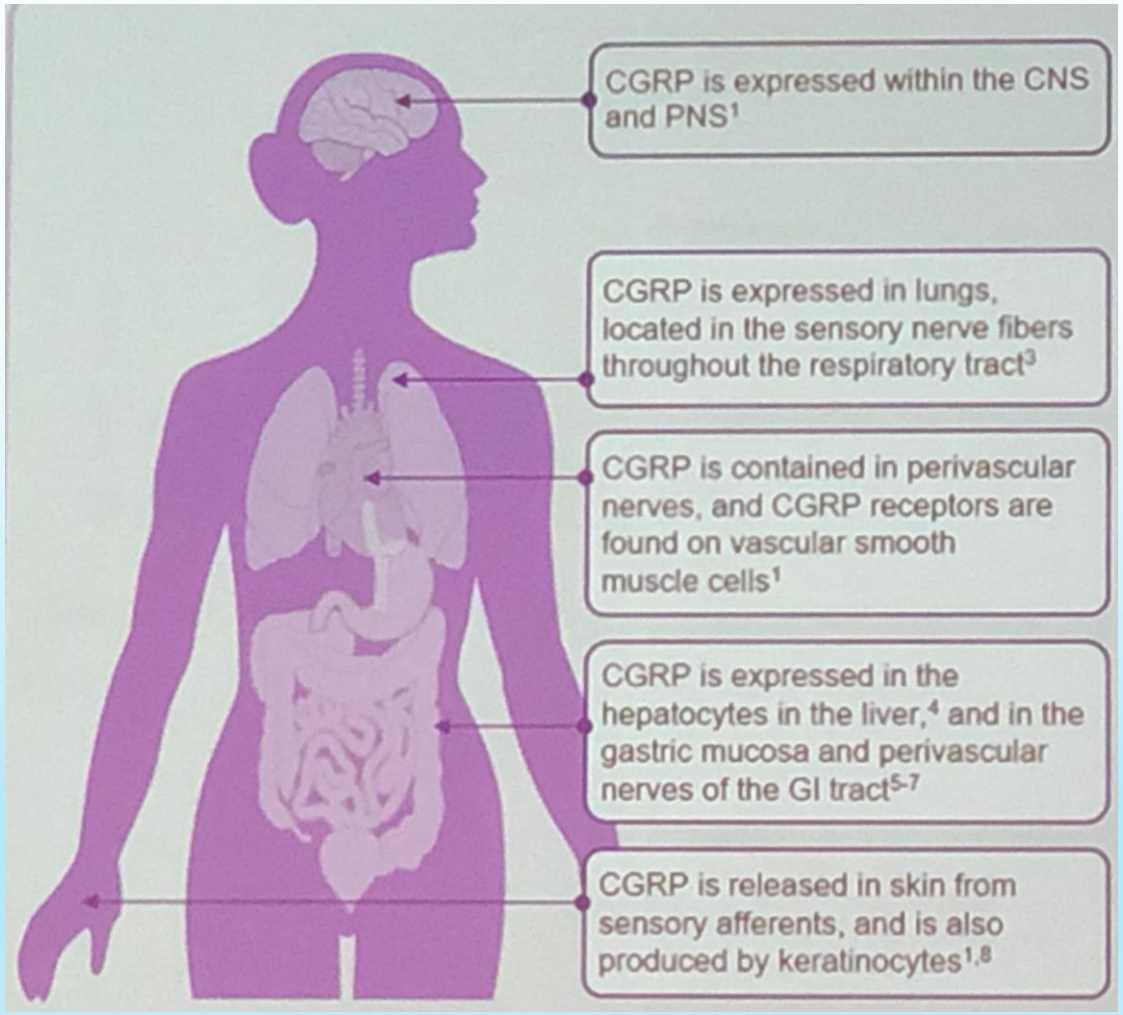
Hepp Z et al. Cephalalgia 2017; 37; 470-85

Calcitonin Gene Related Peptide

- Il peptide correlato al gene della calcitonina (CGRP) è implicato nella ***mediazione della trasmissione del dolore nel sistema trigemino-vascolare***
- Studi randomizzati con diversi anticorpi monoclonali diretti sul ***recettore del CGRP o sul suo ligando*** hanno mostrato risultati promettenti nella prevenzione dell'emicrania
- ***Nel 2018 la FDA statunitense ha approvato gli antagonisti del CGRP ERENUMAB, il FREMANEZUMAB e il GALCANEZUMAB per la prevenzione dell'emicrania***

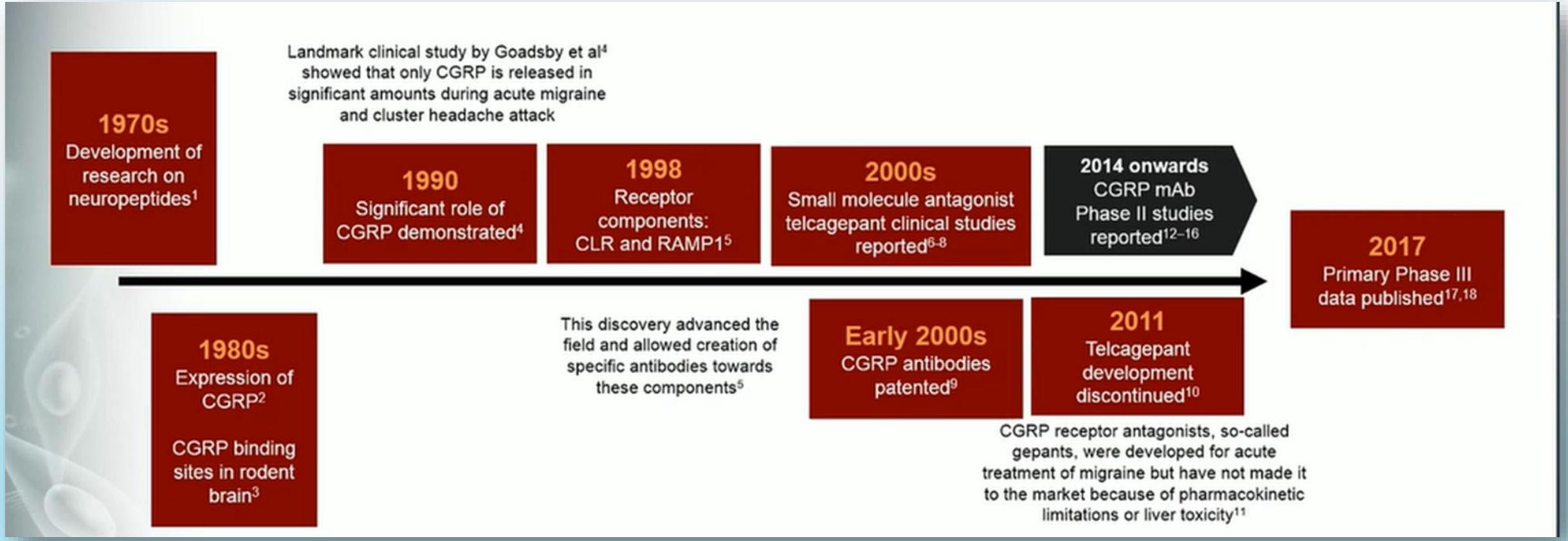


DISTRIBUZIONE DEL CGRP



Adapted from Russell FA, et al. Physiol Rev. 2014; 94: 1099-1142

SVILUPPO NEL TEMPO DEGLI ANTI-CGRP



Anti-CGRP

	Gepants	Anti-CGRP Monoclonal antibodies
Mechanism of action	Blocks CGRP from binding to CGRP receptor	Neutralize CGRP molecule by binding to them directly except Aimovig™, which bind directly to the CGRP receptor
Molecular structure	Small molecule	Human and humanized monoclonal antibody
Route of administration	By mouth	Subcutaneous except eptinezumab, which is given intravenously
Indication of use	Acute treatment of migraines	Prevention of chronic and episodic migraines. Emgality™ and Ajovy™ are being tested for prevention of cluster headaches
Side effects	Liver toxicity	Injection site reactions
FDA approved	None	Emgality™, Ajovy™, Aimovig™

Anticorpi Monoclonali anti-CGRP

Generic name	erenumab-aooe	fremanezumab-vfrm	galcanezumab-gnlm
Mode of delivery	autoinjector	prefilled syringe	autoinjector or prefilled syringe
Mode of action	blocks CGRP receptor	blocks CGRP ligand*	blocks CGRP ligand*
Dosage	70 or 140 mg	225 mg monthly or 675 mg quarterly	240 mg first, then 120 mg monthly
Savings program	Free 2-month trial for all, $0 to $5 copay for up to 1 year for commercial insurance only**	$0 copay up to one year for commercial insurance only**	$0 copay up to one year for commercial insurance only**
Clinical success	1 - 3 fewer migraines/ month	4.3 (given quarterly) - 4.6 (given monthly) fewer/month	3.91 (at 120 mg. dose) – 5.27 (at 240 mg. dose) fewer/month
Listed side effects	Injection site irritation, constipation	Site irritation	Site irritation
Notable results	First drug available		Found to help those who failed Botox
		*ligand = molecule that helps CGRP attach to receptor	**not available to patients on Medicare

Indicati per il trattamento di profilassi in pazienti con almeno 4 giorni di emicrania al mese

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Deen et al. The Journal of Headache and Pain (2017) 18:96
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The Journal of Headache and Pain

REVIEW ARTICLE Open Access

Blocking CGRP in migraine patients – a review of pros and cons

Marie Deen[1*†], Edvige Correnti[2†], Katharina Kamm[3†], Tim Kelderman[4†], Laura Papetti[5†], Eloisa Rubio-Beltrán[6†], Simone Vigneri[7†], Lars Edvinsson[8†], Antoinette Maassen Van Den Brink[6†] and On behalf of the European Headache Federation School of Advanced Studies (EHF-SAS)

Abstract

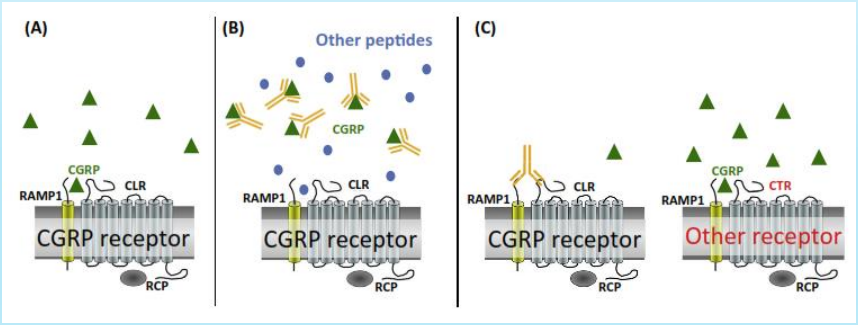
Migraine is the most prevalent neurological disorder worldwide and it has immense socioeconomic impact. Currently, preventative treatment options for migraine include drugs developed for diseases other than migraine such as hypertension, depression and epilepsy. During the last decade, however, blocking calcitonin gene-related peptide (CGRP) has emerged as a possible mechanism for prevention of migraine attacks. CGRP has been shown to be released during migraine attacks and it may play a causative role in induction of migraine attacks. Here, we review the pros and cons of blocking CGRP in migraine patients. To date, two different classes of drugs blocking CGRP have been developed: small molecule CGRP receptor antagonists (gepants), and monoclonal antibodies, targeting either CGRP or the CGRP receptor. Several trials have been conducted to test the efficacy and safety of these drugs. In general, a superior efficacy compared to placebo has been shown, especially with regards to the antibodies. In addition, the efficacy is in line with other currently used prophylactic treatments. The drugs have also been well tolerated, except for some of the gepants, which induced a transient increase in transaminases. Thus, blocking CGRP in migraine patients is seemingly both efficient and well tolerated. However, CGRP and its receptor are abundantly present in both the vasculature, and in the peripheral and central nervous system, and are involved in several physiological processes. Therefore, blocking CGRP may pose a risk in subjects with comorbidities such as cardiovascular diseases. In addition, long-term effects are still unknown. Evidence from animal studies suggests that blocking CGRP may induce constipation, affect the homeostatic functions of the pituitary hormones or attenuate wound healing. However, these effects have so far not been reported in human studies. In conclusion, this review suggests that, based on current knowledge, the pros of blocking CGRP in migraine patients exceed the cons.

- **Distribuzione sistemica del CGRP**
- **Rischioso l'utilizzo in pazienti con comorbidità**
- **Effetti a lungo termine sconosciuti**
- **Possibile insorgenza di stitichezza, alterazione delle funzioni omeostatiche mediate dagli ormoni ipofisari e alterazione della guarigione delle ferite**

Sin

PERCHE' **NON** SOMMINISTRARLI

- QUALI EFFETTI A LUNGO TERMINE ?
- NON ANCORA DIMOSTRATO IL PRECISO SITO D'AZIONE
- SVILUPPO DI AUTOANTICORPI
- MANCANZA DI STUDI COMPARATIVI CON GLI ATTUALI FARMACI DI PROFILASSI
- USO IN GRAVIDANZA
- TRATTAMENTO DELLE COMORBIDITA'
- COSTO DEL FARMACO



Deen et al. The Journal of Headache and Pain (2017) 18:96

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PREZZO !

701,42€

Emgality®
(galcanezumab-gnlm)
120 mg injection

Possibili effetti collaterali a lungo termine

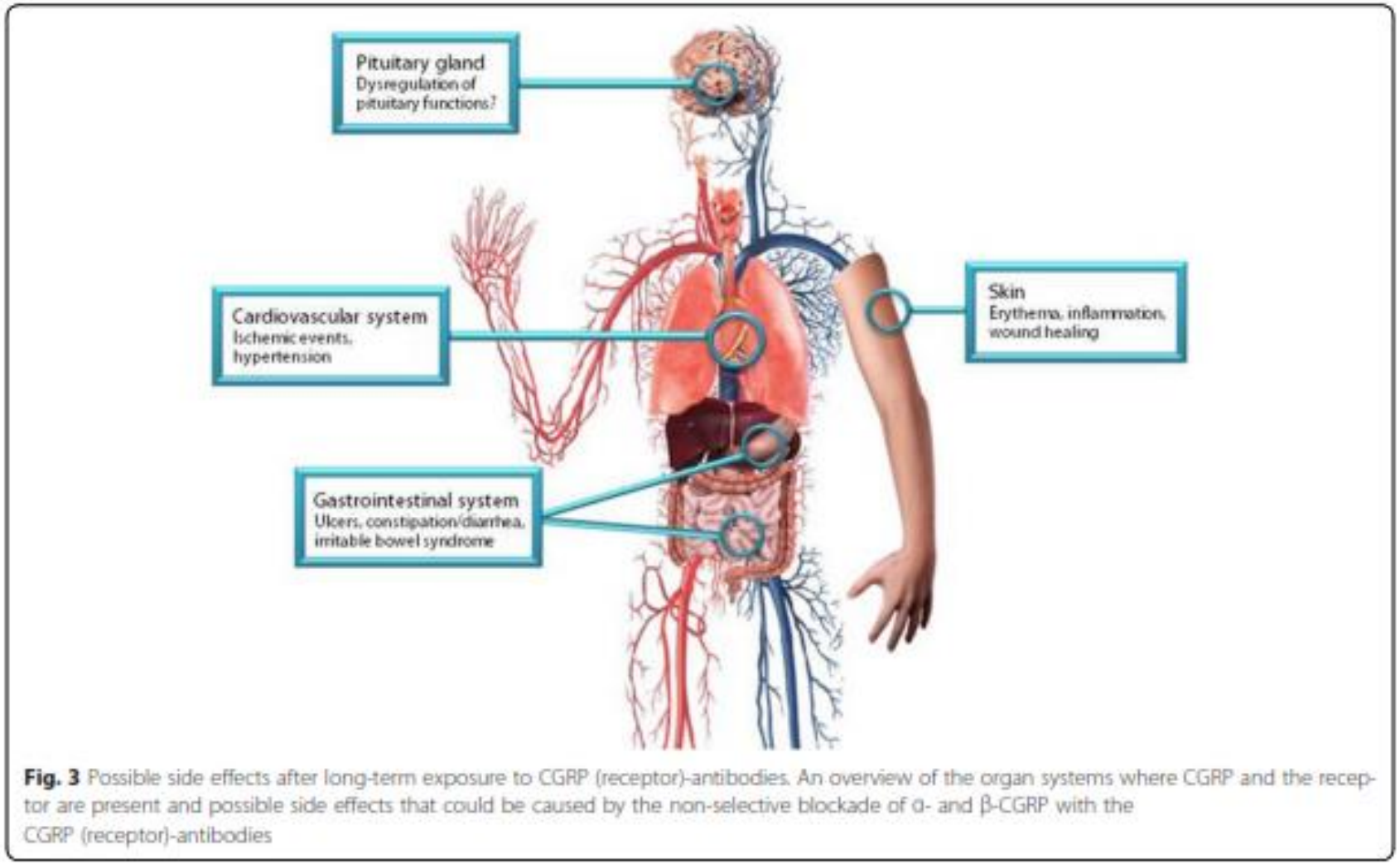

Fig. 3 Possible side effects after long-term exposure to CGRP (receptor)-antibodies. An overview of the organ systems where CGRP and the receptor are present and possible side effects that could be caused by the non-selective blockade of α- and β-CGRP with the CGRP (receptor)-antibodies

Deen et al. The Journal of Headache and Pain (2017) 18:96

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Favoni *et al. The Journal of Headache and Pain* (2019) 20:27
https://doi.org/10.1186/s10194-019-0979-y

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REVIEW ARTICLE Open Access

ischemia. Despite the aforementioned cardiovascular implication, preventive treatment with CGRP antibodies has shown no relevant cardiovascular side effects. Results from long-term trials and from real life are now needed.

point of view: what do we expect from blocking CGRP?

Trends in Pharmacological Sciences CellPress

R attacks. Preliminary efficacy data are promising. However, because CGRP may act as a vasodilatory safeguard during cerebral and cardiac ischemia, CGRP blockade could transform transient mild ischemic events into full-blown infarcts. Here, we review the cerebro- and cardiovascular risks that might be associated with CGRP blockade and which clinical and preclinical studies should be conducted to better assess the potential safety issues of this new promising class of drug.

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Carlos M. Villalón,* and Michel D. Ferrari

CGRP/CGRP Receptor Antibodies: Potential

However, as discussed above, blocking signaling by CGRP and/or the CGRP receptor antibodies may reduce angiogenesis and lymphangiogenesis. CGRP release enhances angiogenesis during ischemia [7], and the same machinery as that in ischemia is active during healing of skin wounds [6,57] and gastric ulcers [5] and in the tumor microenvironment [4]. Furthermore, lymphangiogenesis is enhanced by CGRP in secondary lymphedema, and blockade of CGRP receptor signaling enhances edema formation [8]. These findings suggest that CGRP/RAMP1 acts as a neuronal

Raffaelli *et al. The Journal of Headache and Pain* (2019) 20:66
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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]

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
0(0) 1–10

DOI: 10.1177/0333102419854082
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SAGE

Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine

Messoud Ashina[1], Peter J Goadsby[2], Uwe Reuter[3], Stephen Silberstein[4], David Dodick[5], Gregory A Rippon[6], Jan Klatt[7], Fei Xue[6], Victoria Chia[6], Feng Zhang[6], Sunfa Cheng[6] and Daniel D Mikol[6]

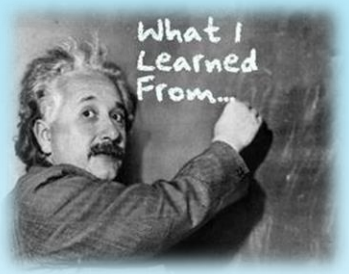
TAKE HOME MESSAGES

- *L'emicrania è una delle principali cause di disabilità a livello mondiale per cui è importante la gestione e il trattamento del paziente*

- *La scoperta degli anticorpi monoclonali nel trattamento di profilassi dell'emicrania rappresenta l'inizio di una nuova era*

- *Nonostante la grande efficacia e il recente successo degli ANTI-CGRP è necessario essere cauti, non tutti i pazienti possono essere canditati al trattamento*

- *Bisogna tenere in considerazione il costo*



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Grazie per l'attenzione

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