SESSIONE 4

UPDATE SUL DOLORE

Terapia dell'emicrania

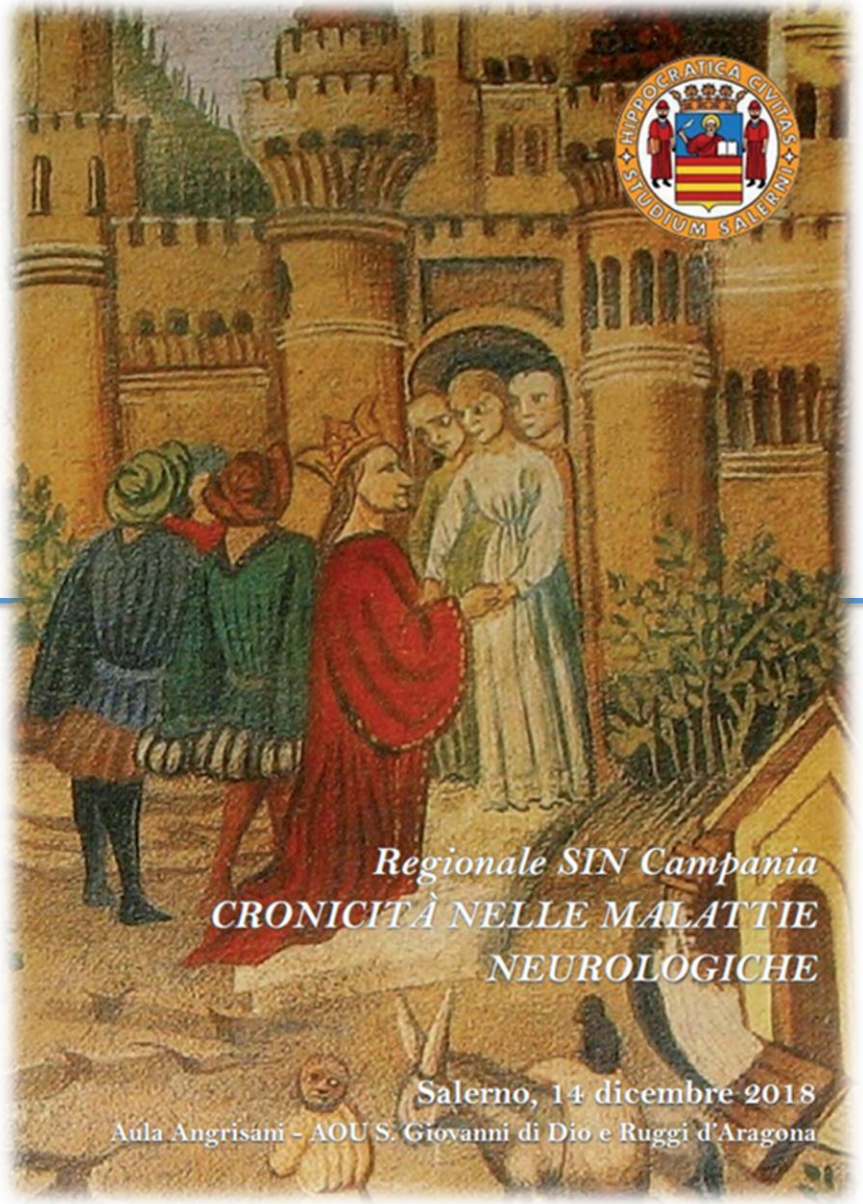
Antonio Russo

Centro Cefalee - I Clinica Neurologica e Neurofisiopatologia

Dipartimento Assistenziale di Medicina Interna e Specialistica

Università degli Studi della Campania "Luigi Vanvitelli"

Napoli



Università degli Studi della Campania *Luigi Vanvitelli*

Sin SOCIETÀ ITALIANA DI NEUROLOGIA

Cefalee I Clinica Neurologica - S.U.N.

Bassa magia cerimoniale ed emicrania (diagnosi e terapia)

Dal punto di vista fisico i problemi provocati alla persona colpita dal malocchio sarebbero violenti mal di testa, nausea, vomito, cattivo umore, ritiro sociale, mancanza di forze nel fare le cose ….

E. De Martino. Sud e magia, 1959

1.1 Emicrania senza aura

A. Almeno 5 attacchi che soddisfino i criteri B-D

B. La cefalea dura 4-72 ore (non trattata o trattata senza successo)

mal di testa….

C. La cefalea presenta almeno due delle seguenti caratteristiche:

1. localizzazione unilaterale
2. dolore di tipo pulsante
3. dolore con intensità media o forte

….violenti

4. aggravata da o che limiti le attività fisiche di routine (per es., camminare, salire le scale)

mancanza di forze nel fare le cose

D. Alla cefalea si associa almeno una delle seguenti condizioni:

1. presenza di nausea e/o vomito

nausea/vomito

2. presenza di fotofobia e fonofobia

ritiro sociale

E. Non meglio inquadrata da altra diagnosi ICHD-3

Sotto-diagnosi e sotto-trattamento dell'emicrania: uno studio italiano

Underdiagnosis and undertreatment of migraine in Italy: a survey of patients attending for the first time 10 headache centres

S Cevoli[1], D D'Amico[2], P Martelletti[3], F Valguarnera[4], E Del Bene[5], R De Simone[6], P Sarchielli[7], MC Narbone[8], L Testa[9], S Genco[10], G Bussone[2] & P Cortelli[1]

Of the 2675 patients who attended HCs for the first time during the study period, **71% received a diagnosis of migraine** (953/1025 completed the study)

Only 26.8% (256) of migraine patients had a previous diagnosis of migraine and they reported a duration of the disease of 7.9±8.3 years (mean and S.D., range 1–41 years).

Healthcare utilization for migraine in the last year by 256 patients with a previous diagnosis of migraine

Number of GP visits	
1–3	108 (42.8%)
>3	52 (20.3%)
	Total 160
Number of neurologist visits	
1–3	93 (36.3%)
>3	5 (1.9%)
	Total 98
Number of ED admissions	
1–3	59 (23%)
>3	3 (1.1%)
	Total 62
Number of hospital admissions	
1–3	11 (4.2%)
>3	1 (0.3%)
	Total 12

Cephalalgia, 2009, 29, 1285–1293

Studio Eurolight: scarsa “medical care” dei pazienti emicranici

Katsarava et al. The Journal of Headache and Pain (2018) 19:10
DOI 10.1186/s10194-018-0839-1

The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

Poor medical care for people with migraine in Europe – evidence from the Eurolight study

Zaza Katsarava[1*], Maka Mania[2], Christian Lampl[3], Johanna Herberhold[4] and Timothy J. Steiner[5,6]

- 1175 (33.8%) of total population (9247) participants reported frequent migraine (> 5 days/month) and might clearly expect benefit from, and therefore had need of, preventative medication.
- Participants with migraine who had consulted specialists (3.1–33.8%) were receiving the best care by these indicators; those treated by GPs (9.5–29.6%) fared less well, and those dependent on self-medication (48.0–84.2%) were, apparently, inadequately treated

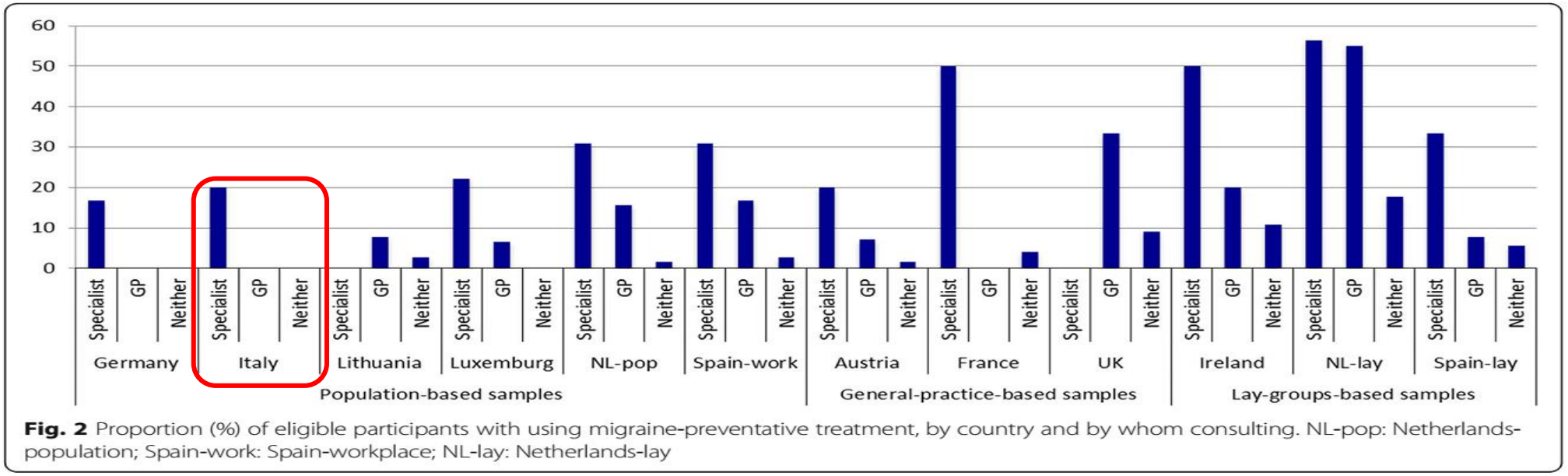


Fig. 2 Proportion (%) of eligible participants with using migraine-preventative treatment, by country and by whom consulting. NL-pop: Netherlands-population; Spain-work: Spain-workplace; NL-lay: Netherlands-lay

Trattamenti farmacologici dell'emicrania

Acute Therapy

Prophylactic Therapy

Preemptive: Used when a known trigger exists (eg, exercise)[158]
Note: Involves administration of an acute therapy (eg, NSAID) before exposure to trigger[158]

Short term: Used when patients are undergoing time-limited exposure to a provoking factor (eg, menstruation)[158]

Maintenance: Used when patients need ongoing treatment (eg, those at risk of CM)[158]

Treatment guidelines typically recommend using prophylactic migraine therapies for patients who have ≥4 migraine attacks per month or experience significant disability from migraine

NSAID = non-steroidal anti-inflammatory drug; CM = chronic migraine.

Marmura MJ, et al. *Headache*. 2015;55:3-20., Silberstein SD. *Continuum*. 2015;21:973-989. 279. Silberstein SD. *Neurology*. 2000;55:754-762.

Linee guida internazionali: profilassi dell'emicrania

Migraine type	Treatment*		Evidence level†	
	Category	Agent	EFNS[106]	AHS/AAN[142]
Episodic	Beta-blockers	Metoprolol	A	A
		Propranolol	A	A
		Timolol	–	A
	Anticonvulsants	Valproic acid	A	A
		Topiramate	A	A
		Gabapentin	C	U
	Calcium channel blockers	Flunarizine	A	–
	Antidepressants	Amitriptyline	B	B
	Other	Candesartan	C	C
		Lisinopril	C	C
		Methysergide	C	–
Chronic	Other	OnabotulinumtoxinA[143]	–	–

* Availability of treatments may vary by region. Some agents may not be indicated for the treatment of migraine or migraine-related symptoms. More information is available elsewhere in this resource. Please consult the label of any treatment option before use.
† Evidence level: A = first choice with evidence of efficacy; B = second choice, less efficacy or more side effects;
C = possible efficacy; U = inadequate evidence.
AAN =American Academy of Neurology; AHS = American Headache Society; EFNS = European Federation of Neurological Societies;
Rx = prescription.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

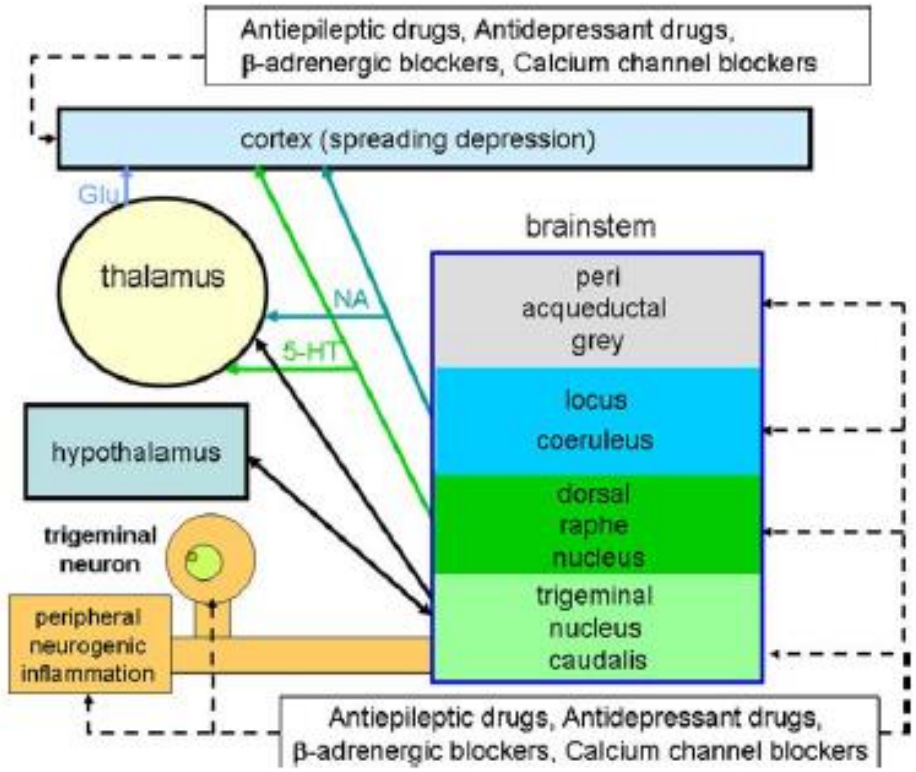
31/05/2018
EMA/375438/2018

Approvate nuove misure volte a evitare l'esposizione a valproato durante la gravidanza

I medicinali a base di valproato sono dunque ora controindicati, ossia non devono essere utilizzati, in ragazze e donne in età fertile, a meno che non si seguano i termini di un particolare **programma di prevenzione della gravidanza**

Evers S, et al. *Eur J Neurol*. 2009;16:968-981. 142. Loder E, et al. *Headache*. 2012;52:930-945. - Simpson DM, et al. *Neurology*. 2016;86:1818-1826.

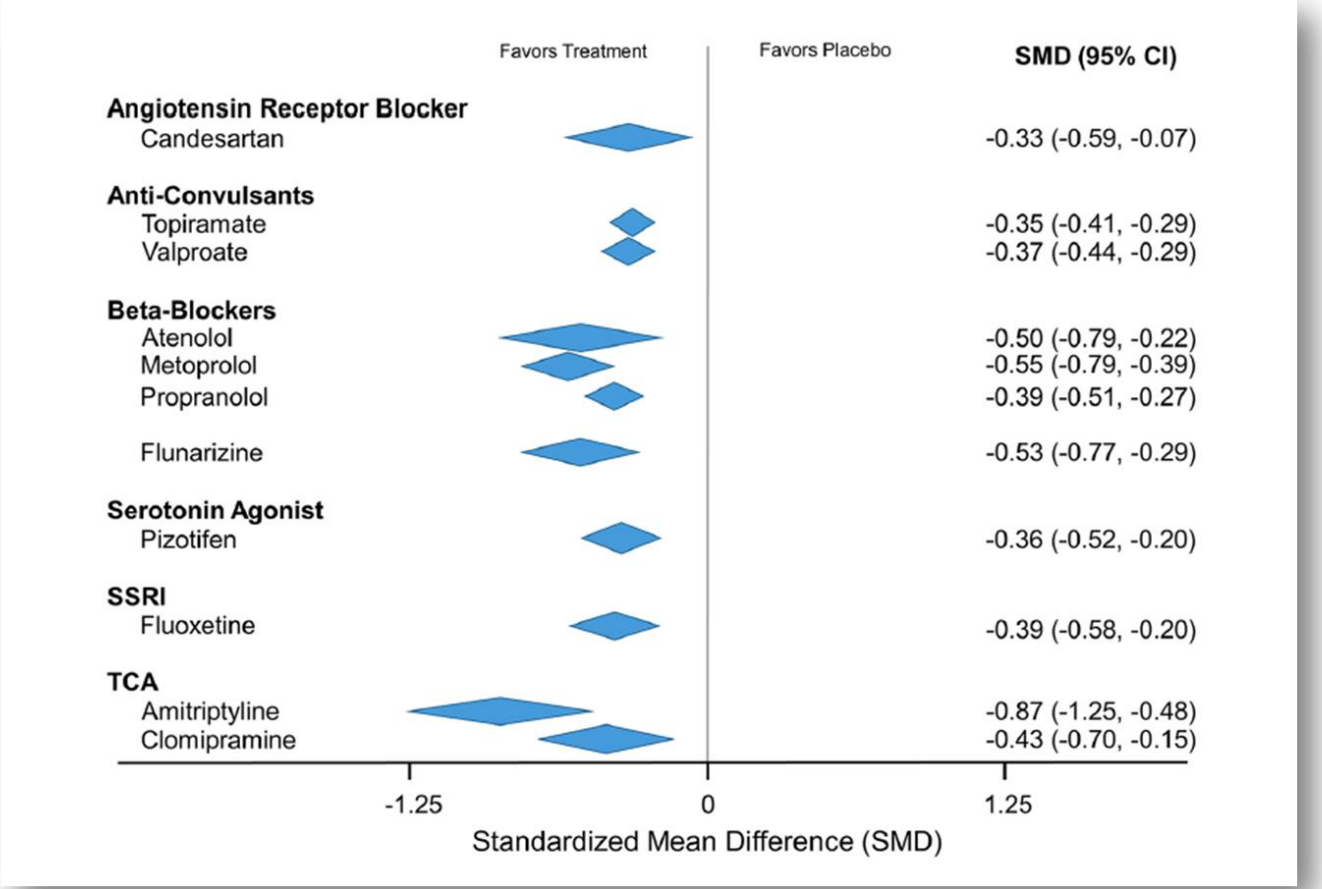
Target dei farmaci degli attuali farmaci per la profilassi dell'emicrania



Target multiple cortical and subcortical neuronal structures:

- reduce spreading depression at the cortical level
- control sensory information in the thalamus
- target multiple sites such as the periaqueductal grey, locus coeruleus, dorsal raphe nucleus, trigeminal nucleus caudalis
- modulate peripheral neurogenic inflammation mediated by trigeminal neurons

Efficacia delle terapie profilattiche di riposizionamento per emicrania



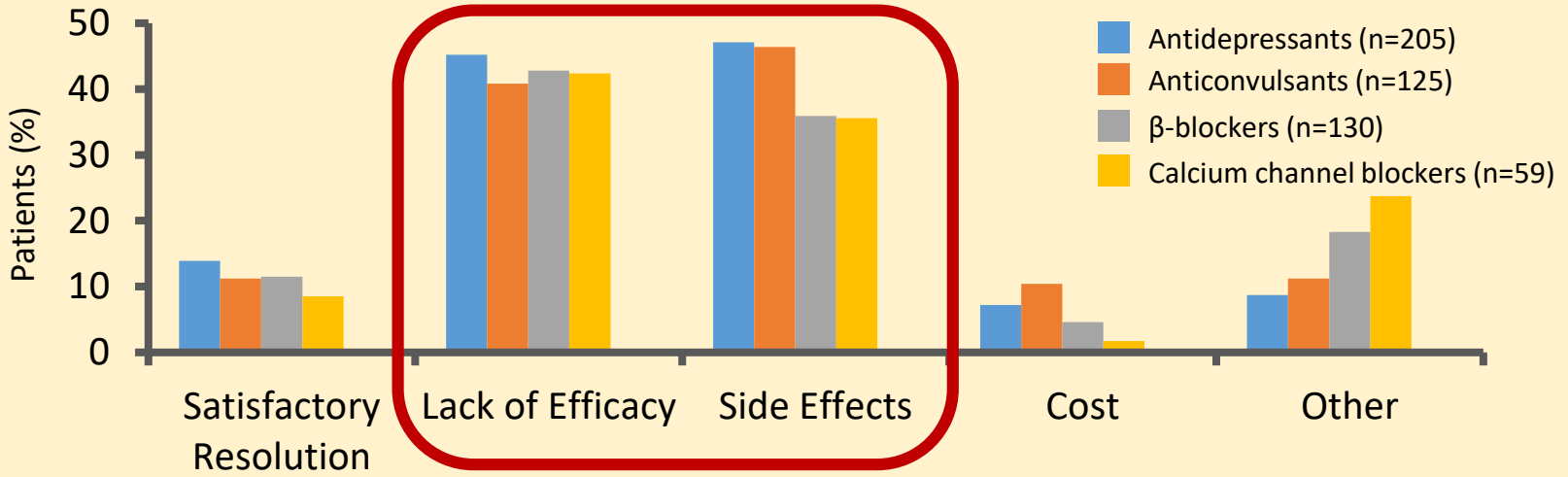
The pooled risk reduction (ARR: 0.15, 95% CI: 0.09– 0.21) suggests that 7 people would need to be treated to produce a 50% reduction in headache burden in one subject

Jackson et al., PLOS ONE 2015; DOI:10.1371/journal.pone.0130733 July 14, 201520152015:

La mancanza di efficacia e una scarsa tollerabilità sono i principali motivi di discontinuazione degli attuali farmaci di profilassi dell'emicrania

International Burden of Migraine Study (IBMS-II)

Patient-Reported Reasons for Discontinuation of Prophylactic Medication



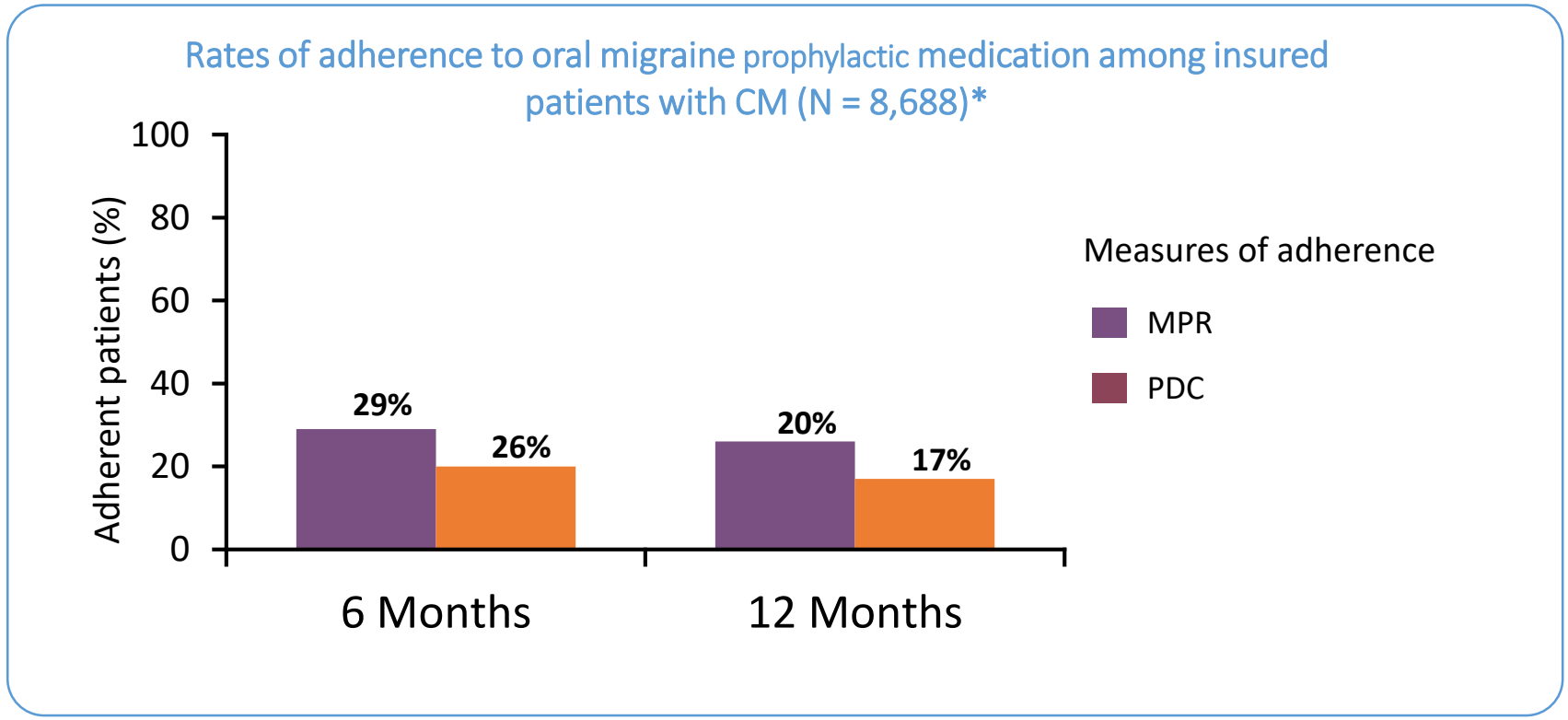
- The second International Burden of Migraine Study (IBMS-II) assessed prophylactic therapy patterns in 1165 patients with EM (n=672) or CM (n=493) from six countries (United States, Canada, United Kingdom, Germany, France, and Australia) in 2010
- Discontinuation of one or more prophylactic medications was reported by 24.0% and 40.8% of EM and CM respondents, respectively
- The most commonly reported reasons for discontinuation were lack of efficacy and side effects

CM = chronic migraine; EM = episodic migraine; IBMS = International Burden of Migraine Study.

Blumenfeld AM, et al. *Headache*. 2013;53:644-655.

Con gli attuali farmaci per profilassi dell'emicrania si ha una bassa "aderenza" al trattamento

- A retrospective analysis of a US claims database (data collected in 2008–2012) found that adherence (defined as ≥80% for MPR and PDC measures) decreased with increased treatment duration in patients with CM (N = 8,688)



*Prophylactic medications analyzed in this retrospective study were limited to specific antidepressants, β-blockers, and anticonvulsants.
CM = chronic migraine; MPR = medication possession ratio; PDC = proportion of days covered.

Hepp Z, et al. *Cephalalgia*. 2015;35:478-488.

La discontinuazione e lo switch dei trattamenti di profilassi dell'emicrania è un fenomeno abbastanza comune

- A retrospective US claims analysis evaluated 8,707 patients with CM who initiated an oral prophylactic between 2008 and 2012
- 75% and 86% of patients had discontinued their initial oral prophylactic regimen at the 6- and 12-month follow-up, respectively
- Switching between oral prophylactic therapies was common, but persistence appeared to worsen as patients cycled through prophylactic regimens

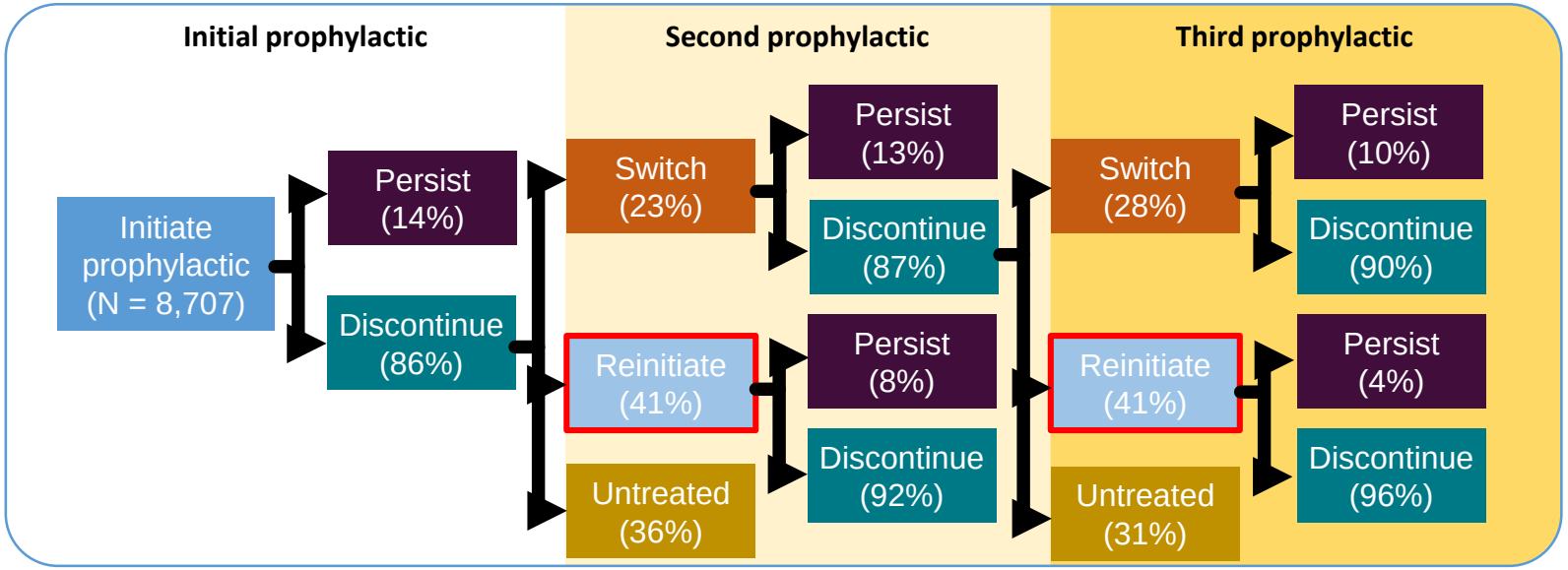


Figure demonstrates persistence/discontinuation at the 12-month follow-up.
Switching: Defined as switching to a new prophylactic therapy within 30 days prior to, or 60 days after, discontinuing previous prophylactic therapy.
Reinitiation: Defined as any prophylactic therapy that was started 60–365 days after discontinuation of the previous prophylactic therapy.
Note that reasons for discontinuation or switching oral prophylaxis in this study could not be determined owing to the design limitations of this claims analysis.

CM = chronic migraine; US = United States.

Hepp Z, et al. *Cephalalgia*. 2017;37(5):470-485.

L’overuse dei trattamenti per uso acuto è stata associato con la cronicizzazione dell’emicrania

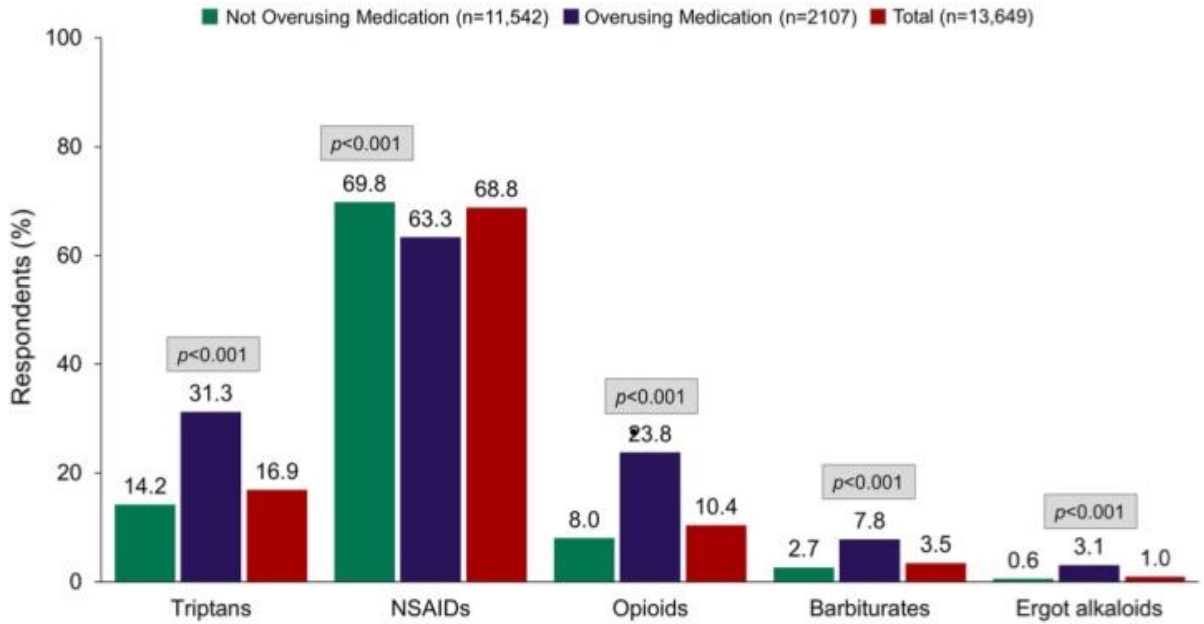
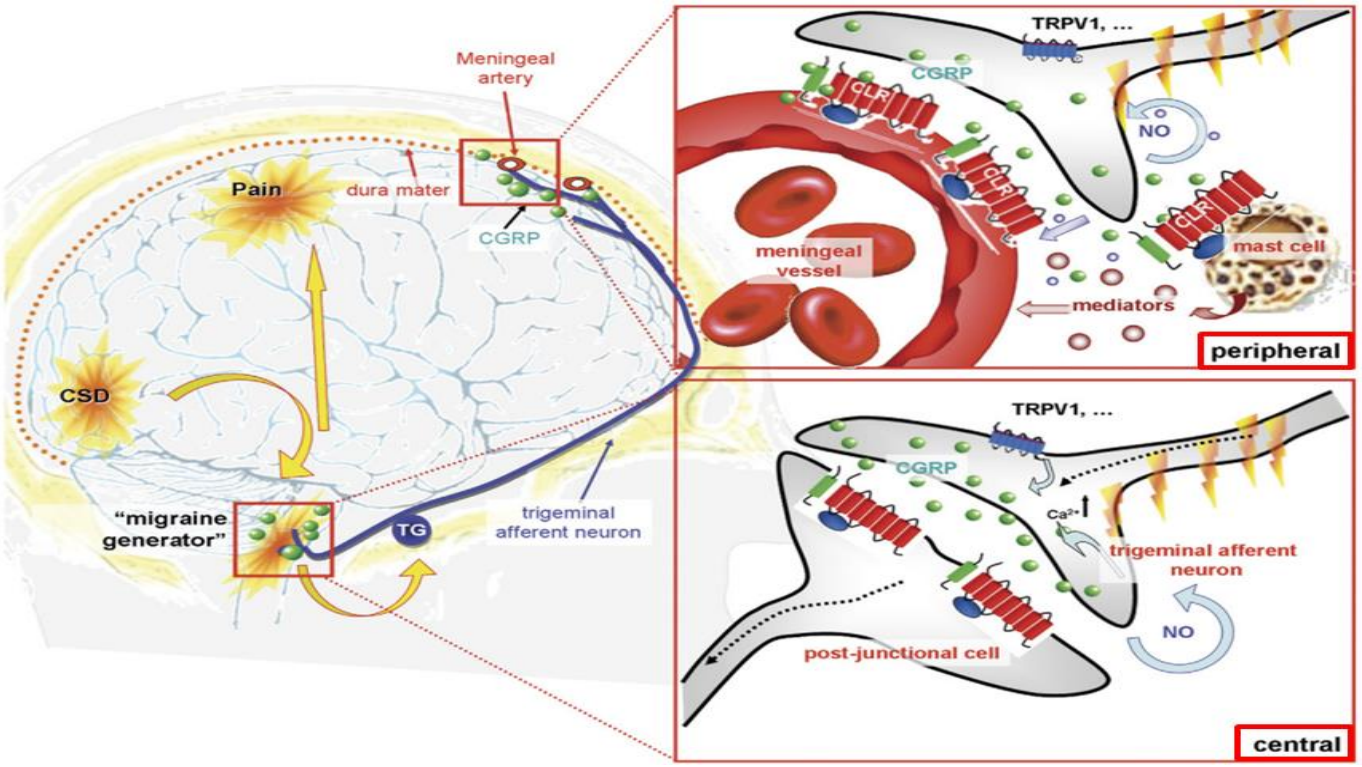
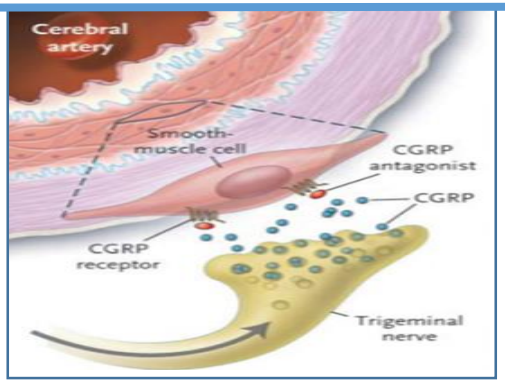


Fig. 1 Medication Overuse by Drug Class Among Respondents with Migraine Currently Using Acute Medication for Headache. Legend: NSAID, nonsteroidal anti-inflammatory drug

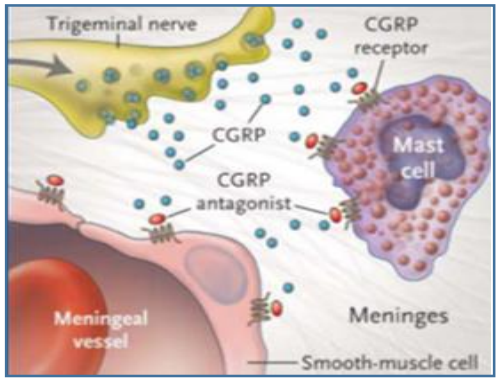
Activation of trigeminal nociceptive neurons release Calcitonin-Gene-Related-Peptide (CGRP)



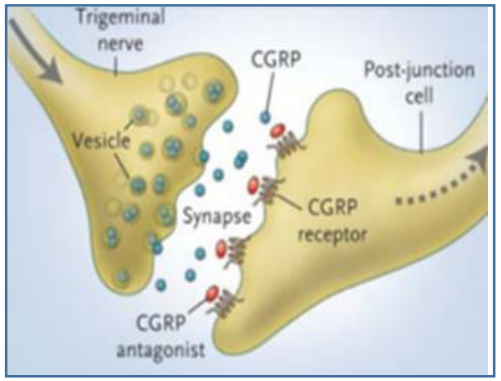
Vasodilatation
activation of vascular CGRPr



Neurogenic inflammation
CGRP-dependent mediators from mast cells



Pain transmission
CGRP-release



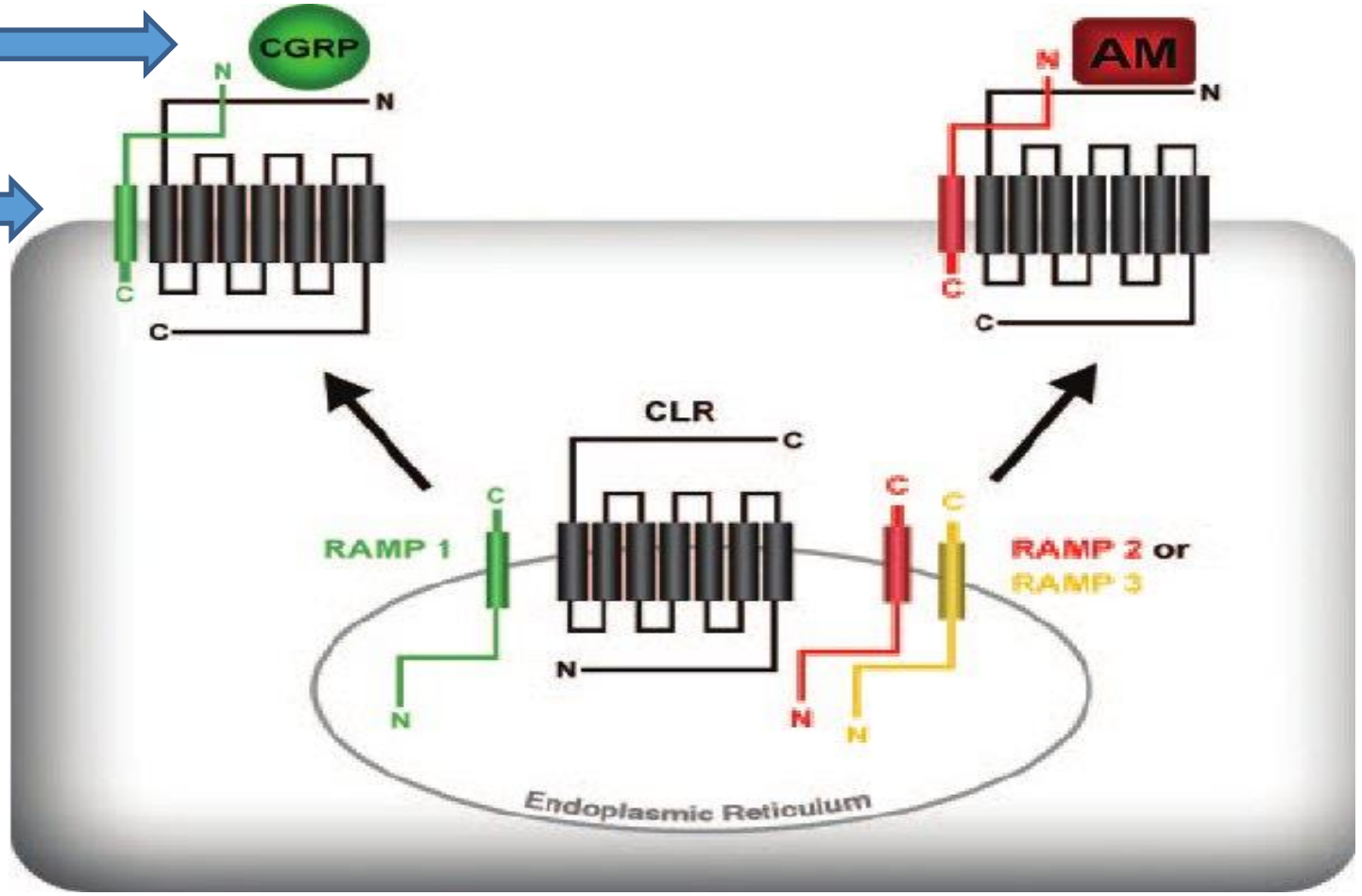
Doods et al., Trend Pharmac. Sciences, 2017; Poyner et al., Pharmacol. Rev. 2002; Katafuchi et al., Peptides 2004 ; Durban et al., N Engl J Med 2004

The CLR – RAMP association determines specificity of ligand

Ab anti CGRP

Ab anti CGRPr

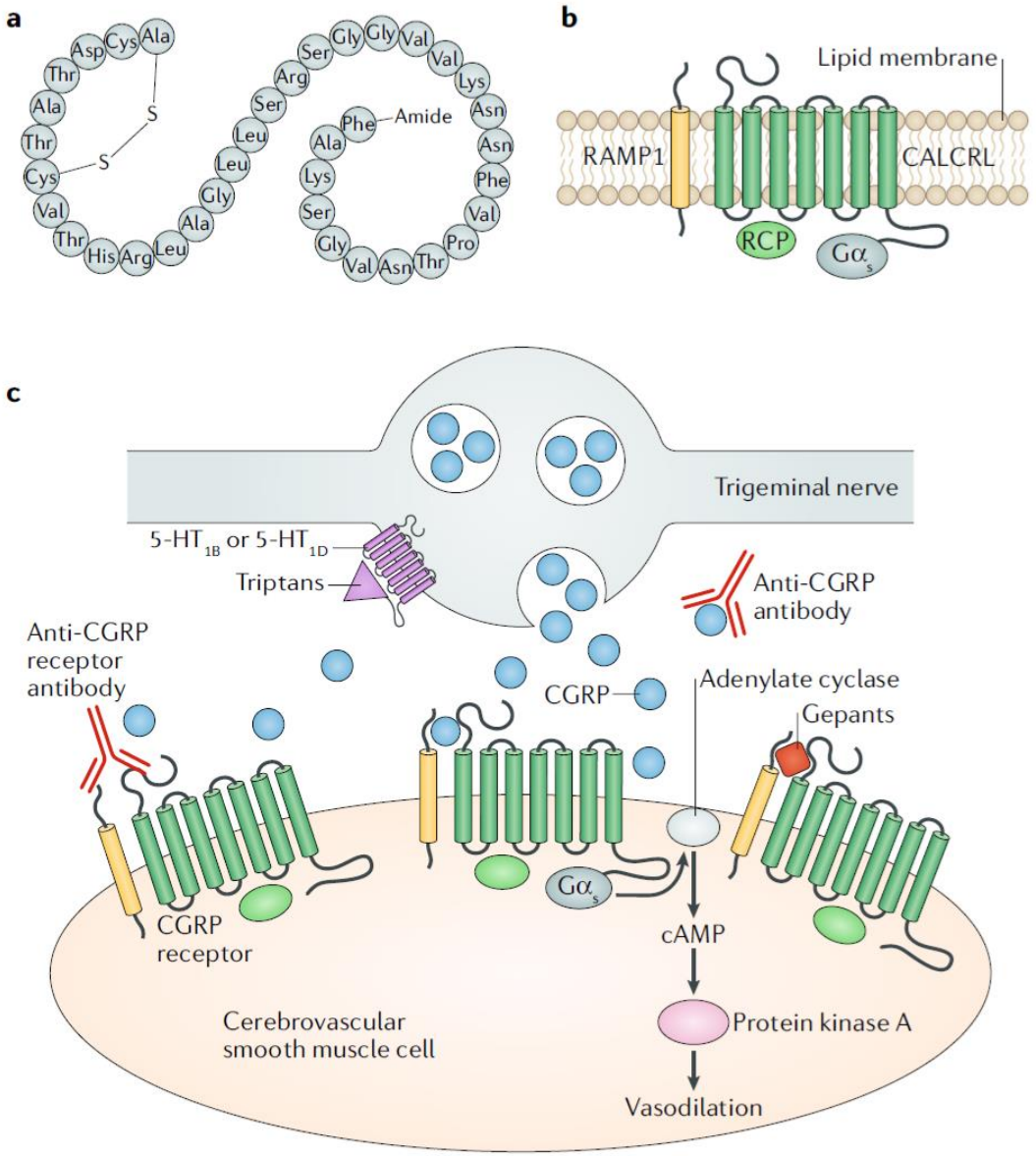
CGRP is a 37-amino acid neuropeptide belonging to a family of peptides which encompasses calcitonin, adrenomedullin and amylin.



CLR = calcitonin-like receptor; RAMP1 = receptor activity-modifying protein 1

Lucas C. et al., Molecular Endocrinology 2007

CARATTERISTICHE Ab MONOCLONALI ANTI CGRP O ANTIRECETTORE CGRP



- Azione specifica sui meccanismi dell'emicrania
- Molecole di grandi dimensioni: non attraversano B.E.E.
- Natura proteica: somministrazione sc, im o ev
- No alterazioni degli enzimi epatici
- Lunga emivita

Edvinsson et al, 2018; Wang et al., 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

Published online: 24 April 2018

Table 1 | **CGRP-related therapies for migraine and other headache disorders**

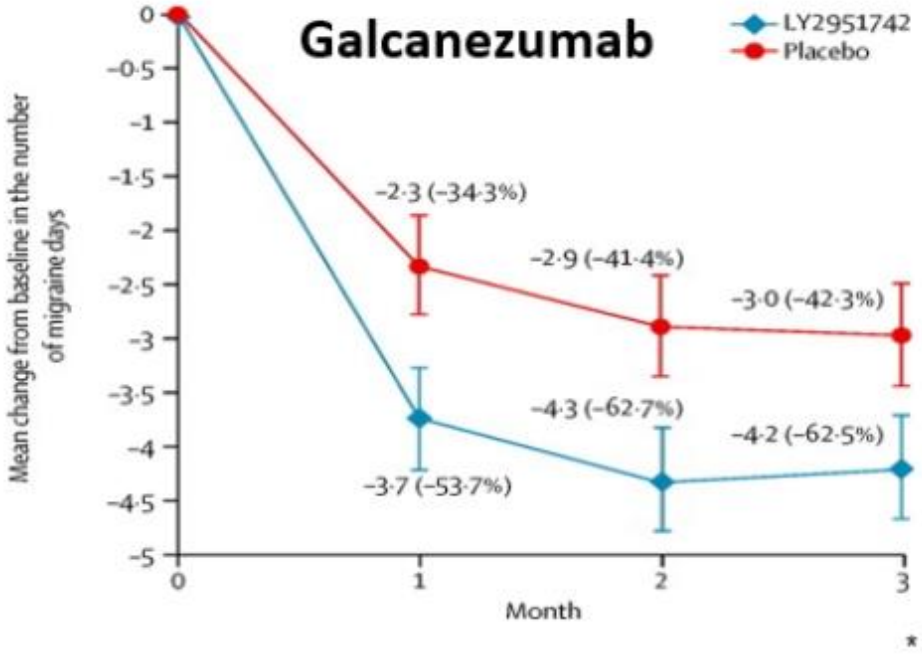
Drug	Indication[a]	Dosing	Mechanism	Drug development status (September 2017)
Preventive therapy				
Erenumab (AMG 334)	Migraine prevention in EM and CM	Monthly, subcutaneous	Monoclonal antibody against CGRP receptor	Phase III trials complete; registration study published[57] and submitted for review to FDA and EMEA
Galcanezumab (LY2951742)	Prevention of EM, CM, eCH and cCH	Monthly, subcutaneous	Monoclonal antibody against CGRP	Positive results[78], now in phase III trials in EM and CM
Fremanezumab (TEV-48125)	Prevention of EM, CM, eCH and ~~cCH~~	Monthly or quarterly, subcutaneous, but intravenous load for cluster headache	Monoclonal antibody against CGRP	Positive results[56], now in phase III trials in EM and CM
Eptinezumab (ALD403)	Prevention of EM and CM	Quarterly, intravenous	Monoclonal antibody against CGRP	Positive results[76] in phase III trials in EM; phase III trial in CM ongoing

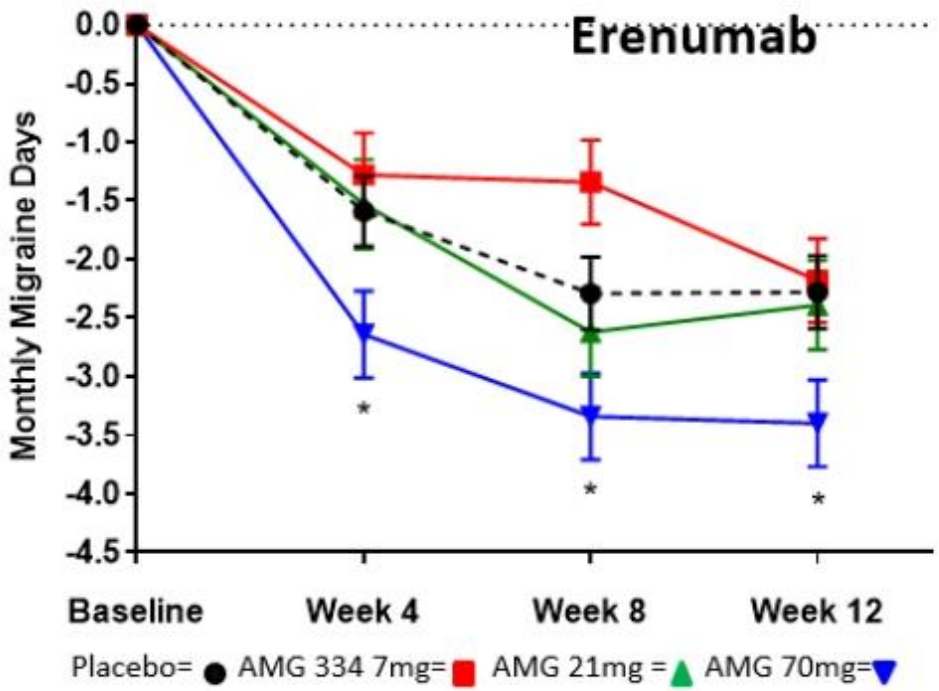
CGRP and Migraine: The Role of Blocking Calcitonin Gene-Related Peptide Ligand and Receptor in the Management of Migraine

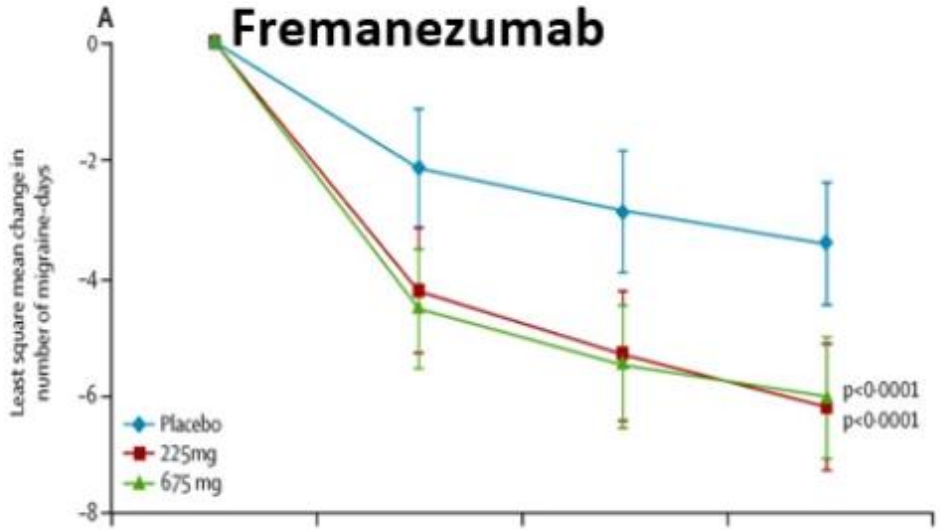
Kasra Maasumi[1] · Rebecca L. Michael[1] · Alan M. Rapoport[2]

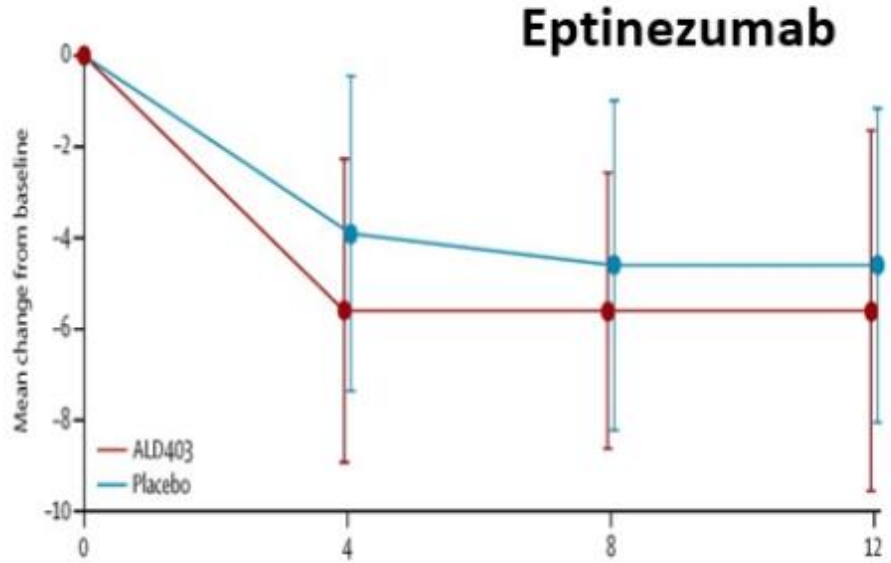
	Erenumab Amgen/Novartis	Galcanezumab Eli Lilly	Eptinezumab Alder	Fremanezumab Teva
Administered	SC	SC	IV	SC
Dose regimen	Monthly	Monthly	Quarterly	Monthly/quarterly
Half-life (days)	21	~ 28	32	31
Target	CGRP receptor	CGRP ligand	CGRP ligand	CGRP ligand
Sequenced from	100% humanized	> 90% humanized	> 90% humanized	> 95% humanized
IgG subtype	IgG2	IgG4	IgG1	IgG2Δa

Maasumi et al., Drugs 2018


Galcanezumab
LY2951742
Placebo
Mean change from baseline in the number of migraine days
0
-0·5
-1
-1·5
-2
-2·5
-3
-3·5
-4
-4·5
-5
-2·3 (-34·3%)
-2·9 (-41·4%)
-3·0 (-42·3%)
-4·3 (-62·7%)
-4·2 (-62·5%)
-3·7 (-53·7%)
0
1
2
3
Month
*


Erenumab
Monthly Migraine Days
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
*
*
*
Baseline
Week 4
Week 8
Week 12
Placebo= AMG 334 7mg= AMG 21mg = AMG 70mg=


A
Fremanezumab
Least square mean change in number of migraine-days
0
-2
-4
-6
-8
Placebo
225mg
675 mg
p<0·0001
p<0·0001

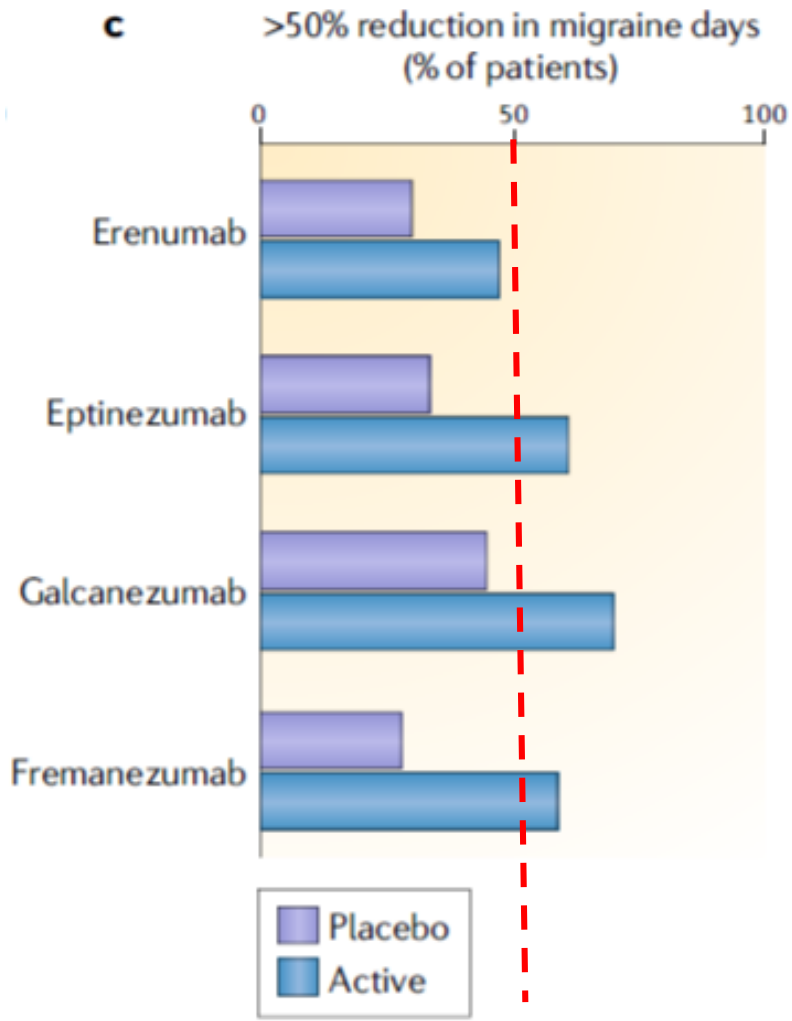

Eptinezumab
Mean change from baseline
0
-2
-4
-6
-8
-10
ALD403
Placebo
0
4
8
12

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

Published online: 24 April 2018



Adverse events reported during the double-blind treatment phases

Event	Placebo (N=319)	Erenumab, 70 mg (N=314)	Erenumab, 140 mg (N=319)
	number of patients (percent)		
Adverse event	201 (63.0)	180 (57.3)	177 (55.5)
Adverse events reported by ≥2% of patients in any trial group			
Nasopharyngitis	32 (10.0)	31 (9.9)	35 (11.0)
Upper respiratory tract infection	18 (5.6)	21 (6.7)	15 (4.7)
Sinusitis	7 (2.2)	7 (2.2)	11 (3.4)
Constipation	4 (1.3)	5 (1.6)	11 (3.4)
Arthralgia	6 (1.9)	7 (2.2)	7 (2.2)
Fatigue	8 (2.5)	6 (1.9)	7 (2.2)
Nausea	6 (1.9)	7 (2.2)	6 (1.9)
Influenza	6 (1.9)	4 (1.3)	8 (2.5)
Urinary tract infection	7 (2.2)	5 (1.6)	7 (2.2)
Back pain	7 (2.2)	6 (1.9)	6 (1.9)
Injection-site pain	1 (0.3)	10 (3.2)	1 (0.3)
Migraine	10 (3.1)	4 (1.3)	3 (0.9)
Hypertension	8 (2.5)	5 (1.6)	0
Adverse event leading to discontinuation of trial regimen	8 (2.5)	7 (2.2)	7 (2.2)
Serious adverse event†	7 (2.2)	8 (2.5)	6 (1.9)

	Placebo (n=282)	Erenumab 70 mg (n=190)	Erenumab 140 mg (n=188)
Adverse events	110 (39%)	83 (44%)	88 (47%)
Serious adverse events	7 (2%)	6 (3%)	2 (1%)
Abdominal adhesions	0	0	1 (<1%)
Abdominal pain	0	0	1 (<1%)
Cartilage injury	0	0	1 (<1%)
Intervertebral disc protrusion	1 (<1%)	1 (<1%)	0
Appendicitis	0	1 (<1%)	0
Costochondritis	0	1 (<1%)	0
Fibroma	0	1 (<1%)	0
Non-cardiac chest pain	0	1 (<1%)	0
Radius fracture	0	1 (<1%)	0
Cholecystitis	1 (<1%)	0	0
Migraine	1 (<1%)	0	0
Pancreatitis	1 (<1%)	0	0
Parotitis	1 (<1%)	0	0
Urinary tract infection	1 (<1%)	0	0
Vomiting	1 (<1%)	0	0

Goadsby et al. N Engl J Med 2017; Tepper et al., *Lancet Neurol*. 2017

CGRP Monoclonal Antibodies for the Preventative Treatment of Migraine

Heike Israel[1] · Lars Neeb[1] · Uwe Reuter[1]

Current Pain and Headache Reports (2018) 22:38

Differences between CGRP mAbs and currently available oral migraine preventative medications

	mAbs for episodic and chronic migraine	Currently available oral medications
Specificity	+	–
Formulation	SC/IV solution	Oral/tablet
Dose titration	–	+
Frequency of intake	Monthly/every 3rd month	Daily
Onset of action	Fast (days)	Slow (weeks)
Side effects (AEs)		
- Effect on weight	–	+
- Mood change	–	+
- Drowsiness/fatigue	–	+
- Cognitive dysfunction	–	+
- Dizziness	–	+

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

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

Uwe Reuter, MD, MBA

Table 2.—Rates of Nonpersistence/Nonadherence to Existing Preventive Agents in Clinical Trials

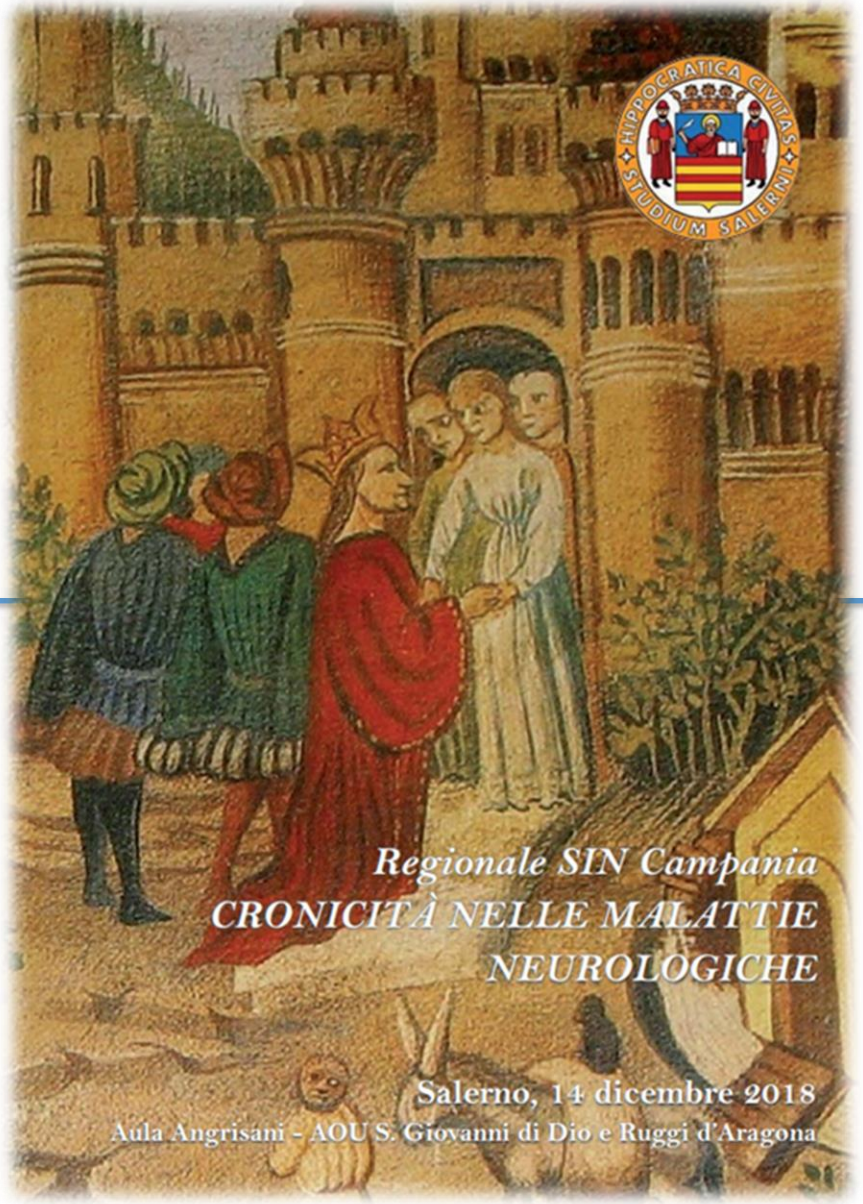
Study	Substance	EM/CM	Double-Blind Period Duration	% Drop-Out (total)	% Drop-Out Due to AEs
Goadsby et al. (2017)[18]	Erenumab 140 mg	EM	6 months	8.5	2.1
Brandes et al. (2004)[19]	Topiramate 100 mg	EM	6 months	47.5	26.7
Silberstein et al. (2017)[20]	Fremanezumab 675 mg monthly	CM	3 months	9.5	1.8
Tepper 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

Abbreviations: AE = adverse event; CM = chronic migraine; EM = episodic migraine.

Immunogenicity

		ADA %	neutralizing ADA (n)	Duration
STRIVE	Erenumab70 mg	8% (n=24)	1	6 mo
	Erenumab 140 mg	3,2% (n=10)	0	6 mo
CM Registration	Erenumab70 mg	6% (n=11)	0	3 mo
	Erenumab 140 mg	2% (n=3)	0	3 mo
EVOLVE	Galcanzumab 120 mg	3,5% (n=7)	7	6 mo
	Galcanzumab 240 mg	5,2% (n=11)	11	6 mo
Halo(CM)	Fremanezumab monthly	None	0	3 mo
	Fremanezumab quat	2	0	3 mo

Grazie per l'attenzione



Università degli Studi della Campania *Luigi Vanvitelli*

Sin SOCIETÀ ITALIANA DI NEUROLOGIA

Cefalee I Clinica Neurologica - S.U.N.