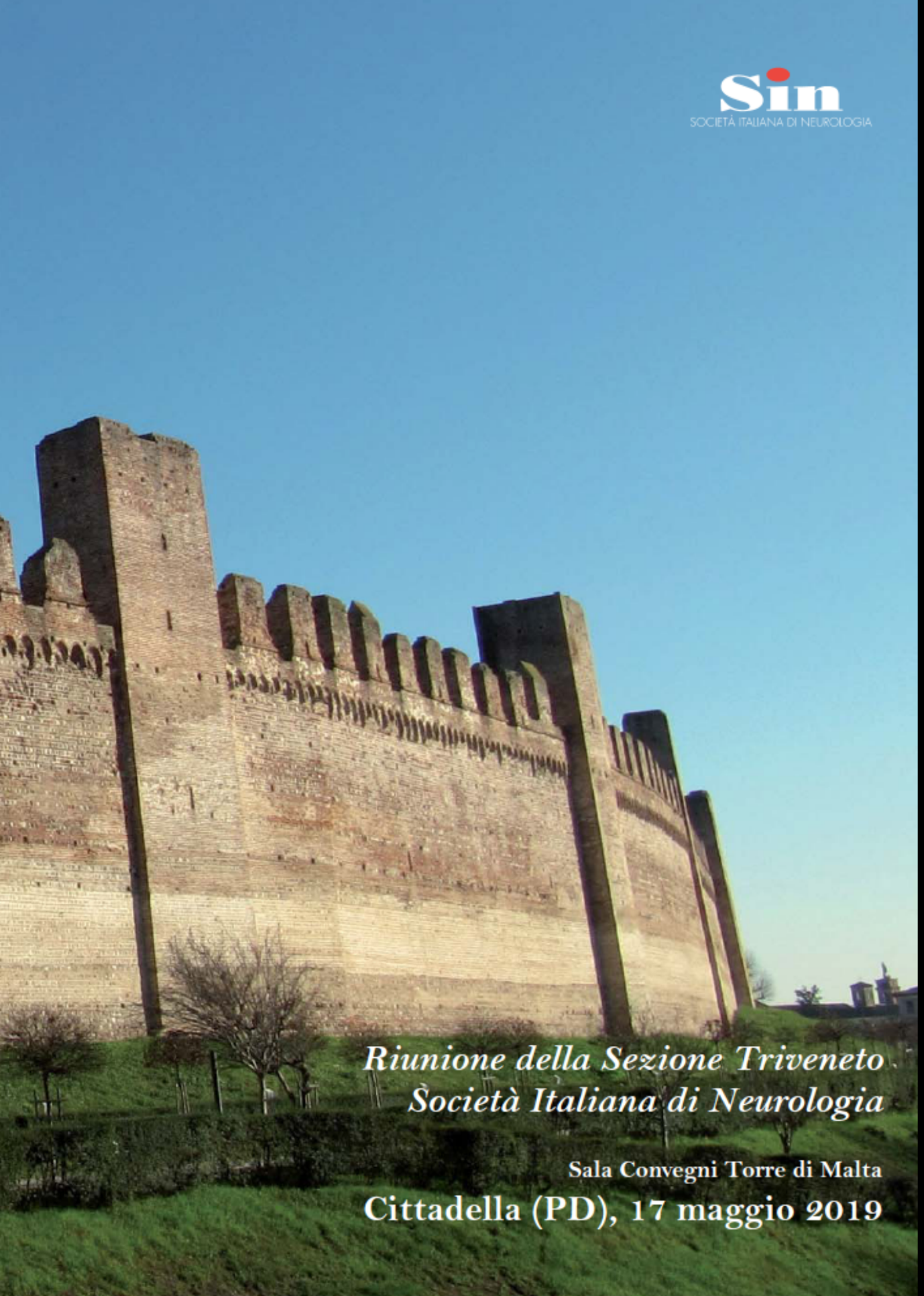


Riunione della Sezione Triveneto

Società Italiana di Neurologia

17 maggio 2019

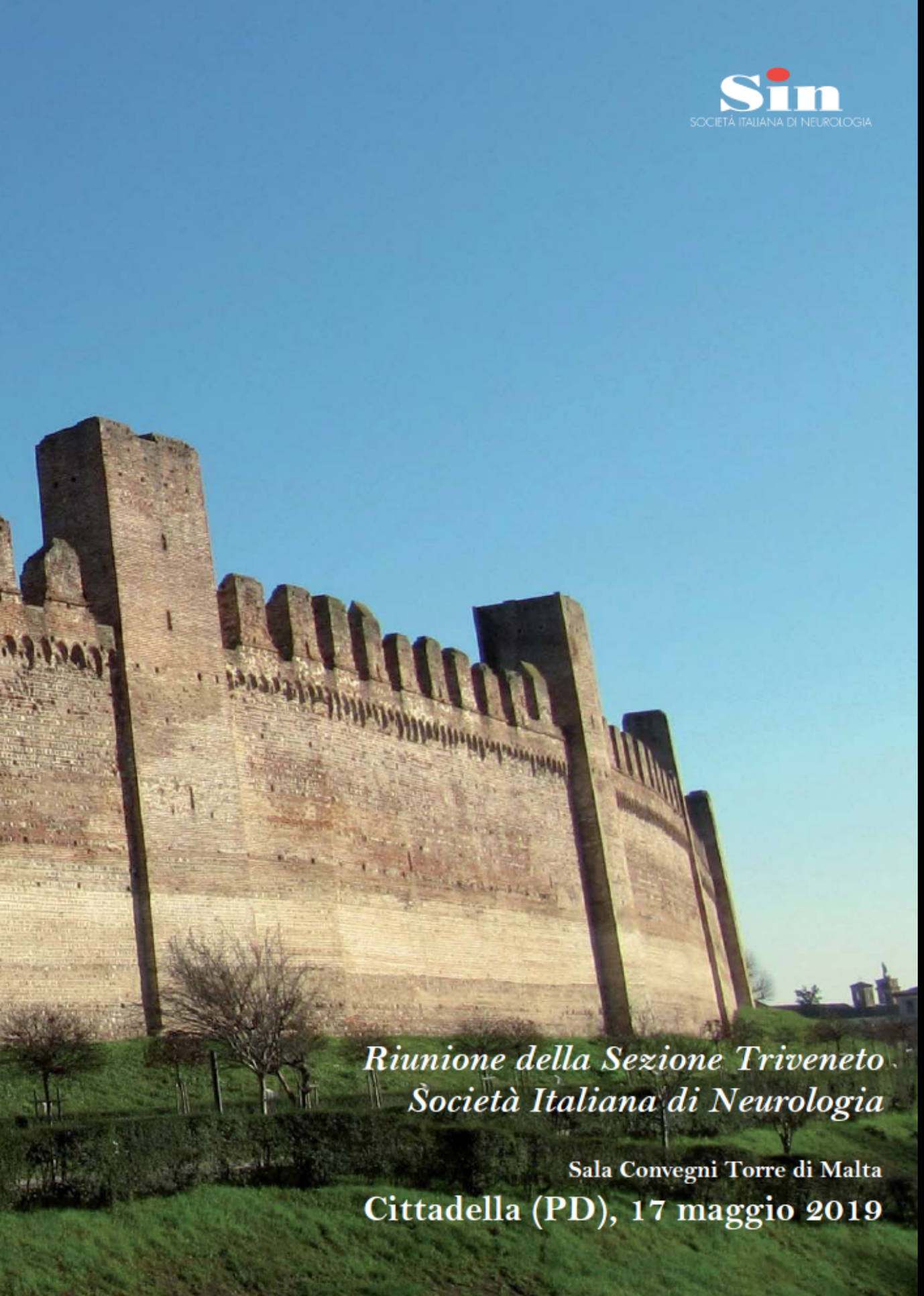
i nuovi farmaci per l'emicrania

REGIONE DEL VENETO

ULSS6 EUGANEA

edoardo mampreso

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

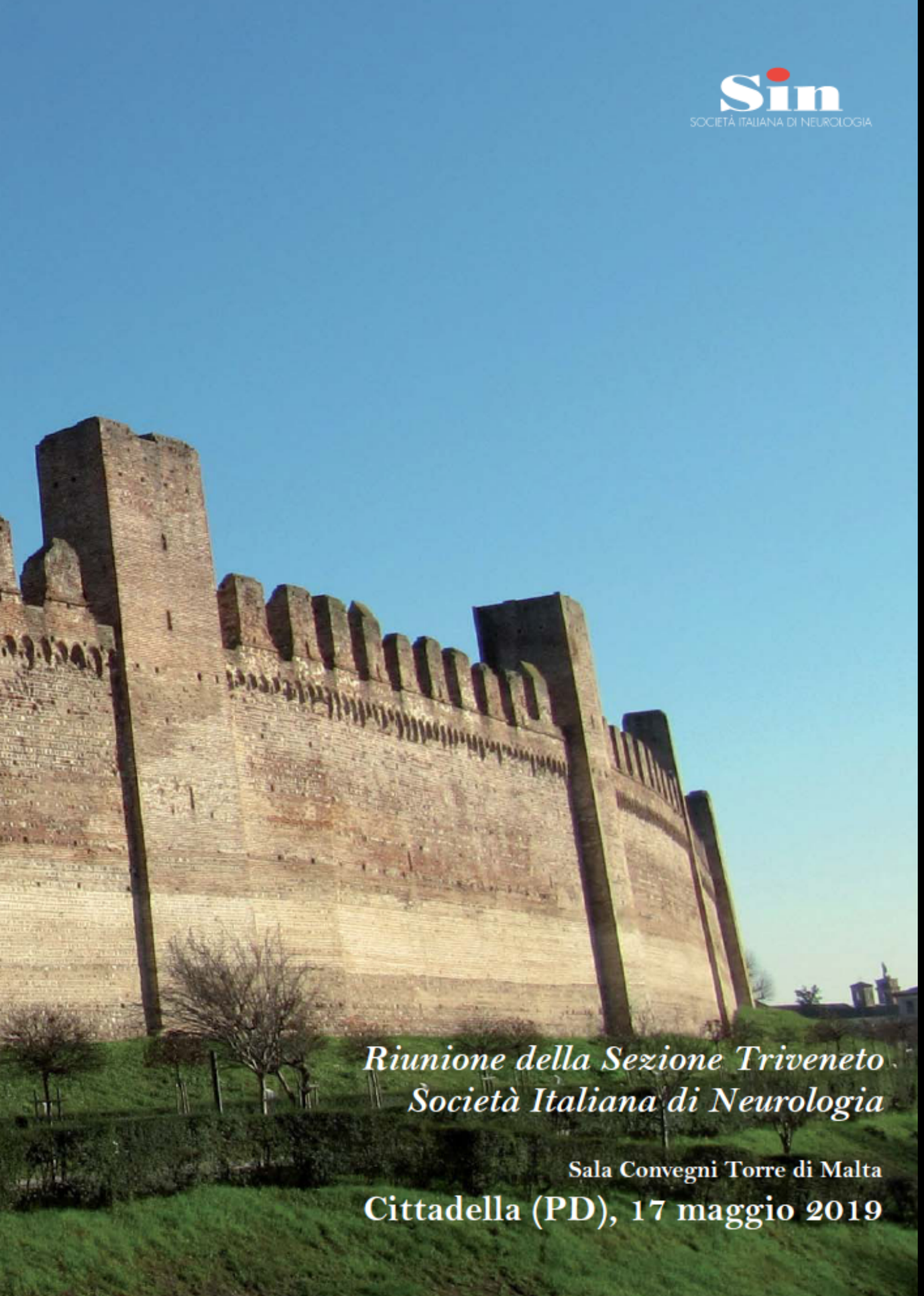


AGENDA

Riunione della Sezione Triveneto
Società Italiana di Neurologia

Sala Convegni Torre di Malta

Cittadella (PD), 17 maggio 2019



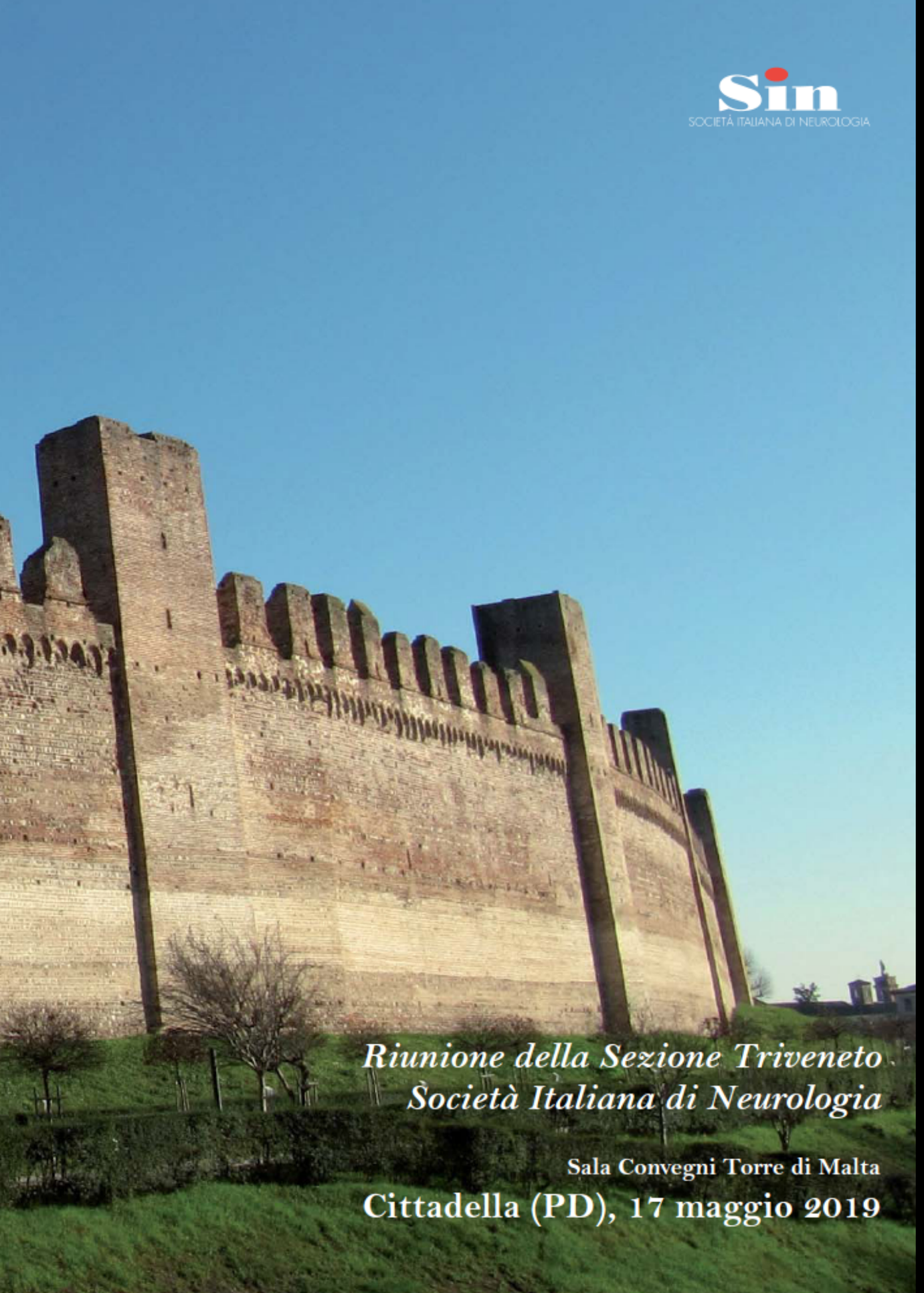
AGENDA

dalla parte del paziente

terapia d'attacco

terapia di profilassi

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA



Riunione della Sezione Triveneto
Società Italiana di Neurologia

Sala Convegni Torre di Malta

Cittadella (PD), 17 maggio 2019

AGENDA

dalla parte del paziente

terapia d'attacco

terapia di profilassi

ATLAS

OF HEADACHE DISORDERS AND RESOURCES IN THE WORLD 2011

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

World Health Organization

Lifting The Burden
The Global Campaign against Headache

% di pazienti che ha ricevuto diagnosi specialistica

RESULTS

THEMES - DIAGNOSIS AND ASSESSMENT

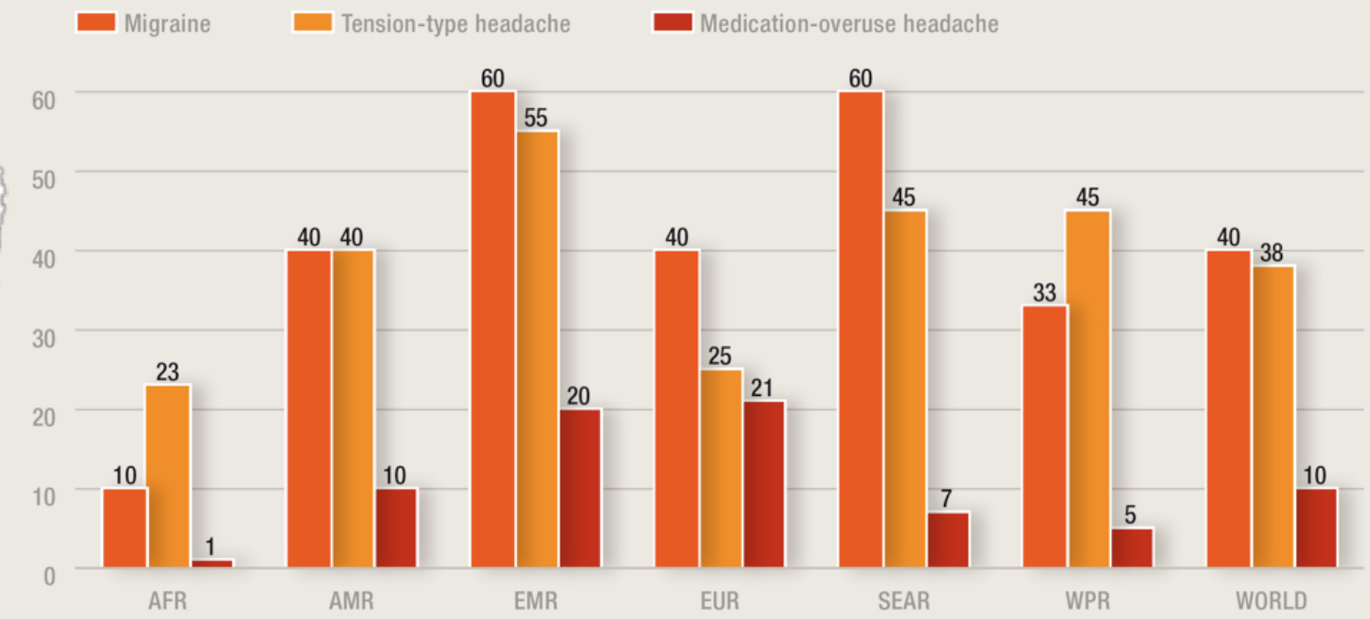


FIG. 5.1 Estimated percentages of people with specific headache disorders who have been professionally diagnosed, worldwide and by WHO region (medians of individual responses)

ATLAS

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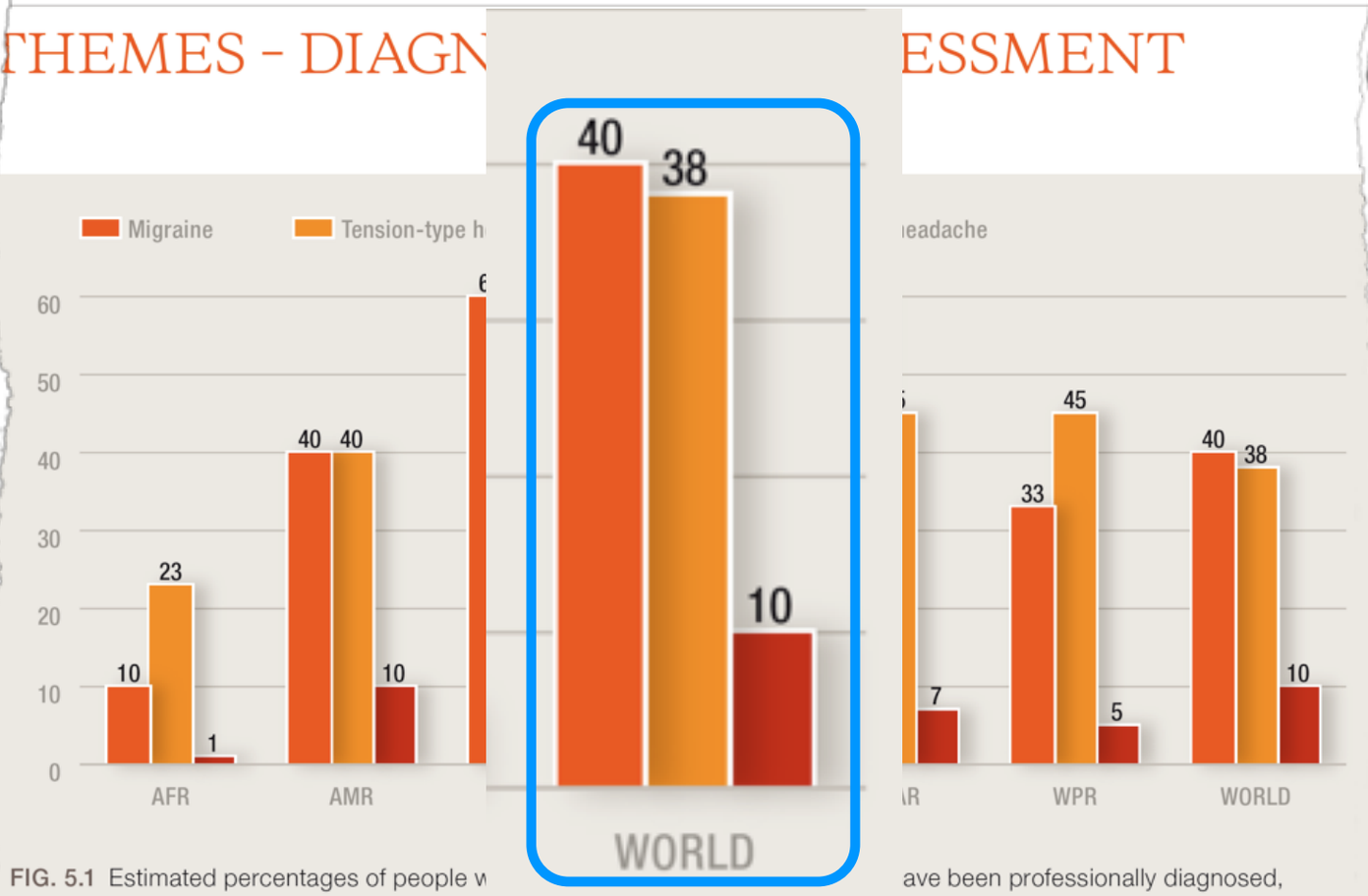

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elevata % di pazienti non diagnosticati

World Health Organization

Lifting The Burden
The Global Campaign against Headache

Migraine is the number one cause of disability among adults under 50; number two among all ages.

Steiner et al.
J Headache Pain 2018;19(1):17.

Steiner T et al. JHP 2018

Migraine is the top cause of disability among women under 50.* Will health politicians now take notice?

Steiner T et al. JHP 2018

Lifting The Burden
The Global Campaign against Headache

**Steiner et al. Journal of Headache and Pain (2018) 19:17*

emicrania: l’accesso alle cure

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

emicrania: l'accesso alle cure

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]

- Eurolight was a cross-sectional questionnaire-based survey in 10 European countries
- population-based in six (Germany, Italy, Lithuania, Luxembourg, Netherlands, Spain)
- from consecutive patients attending general practitioners (GPs) for any reason in three (Austria, France, UK)

Table 1 Summary of sampling and data collection methods in each country [adapted from reference [12]

Country	Denominator (n)	Responders (n)	Responder proportion (%)	Gender (% female)	Target population and mode of distribution of questionnaire
Studies with a general-population basis					
Germany	3000	338	11.3	57	Random general-population sample from urban and rural areas, contacted by regular post
Italy	3500	500	14.3	58	Stratified general-population sample from urban and rural areas, contacted by regular post

Katsarava *et al. The Journal of Headache and Pain* (2018) 19:10
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Table 3 Utilization of medical care by participants with migraine (N = 3466)

Country	N	Using triptans (of all with migraine) n (%)	Migraine on ≥5 days/ month n (%)	Using preventative medication (of those with migraine on ≥5 days/month) n (%)	Consulting health professionals n (%)			
					Specialist	General practitioner	Non-medical	None
Studies with a general-population basis								
Germany	109	12 (11.0)	42 (38.5)	1 (2.4)	7 (6.4)	14 (12.8)	5 (4.6)	83 (76.1)
Italy	221	14 (6.3)	61 (27.6)	1 (1.6)	14 (6.3)	21 (9.5)	15 (6.8)	171 (77.4)
Lithuania	149	5 (3.4)	62 (41.6)	2 (3.2)	16 (10.7)	23 (15.4)	2 (1.3)	108 (72.5)
Luxemburg	669	48 (7.2)	219 (32.7)	10 (4.6)	39 (5.8)	105 (15.7)	27 (4.0)	498 (74.4)
Netherlands-population	815	75 (9.2)	171 (20.8)	11 (6.4)	25 (3.1)	106 (13.0)	36 (4.4)	648 (79.5)
Spain-workplace	401	90 (22.4)	153 (38.2)	21 (13.7)	60 (15.0)	72 (18.0)	28 (7.0)	241 (60.1)

Katsarava *et al. The Journal of Headache and Pain* (2018) 19:10
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emicrania: il “fardello”

Vo P al., JHP 2018 19: 82

emicrania: il "fardello"

Vo et al. The Journal of Headache and Pain (2018) 19:82
https://doi.org/10.1186/s10194-018-0907-6

The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom

Pamela Vo[1], Juanzhi Fang[2], Aikaterini Bilitou[3], Annik K. Laflamme[1] and Shaloo Gupta[4*]

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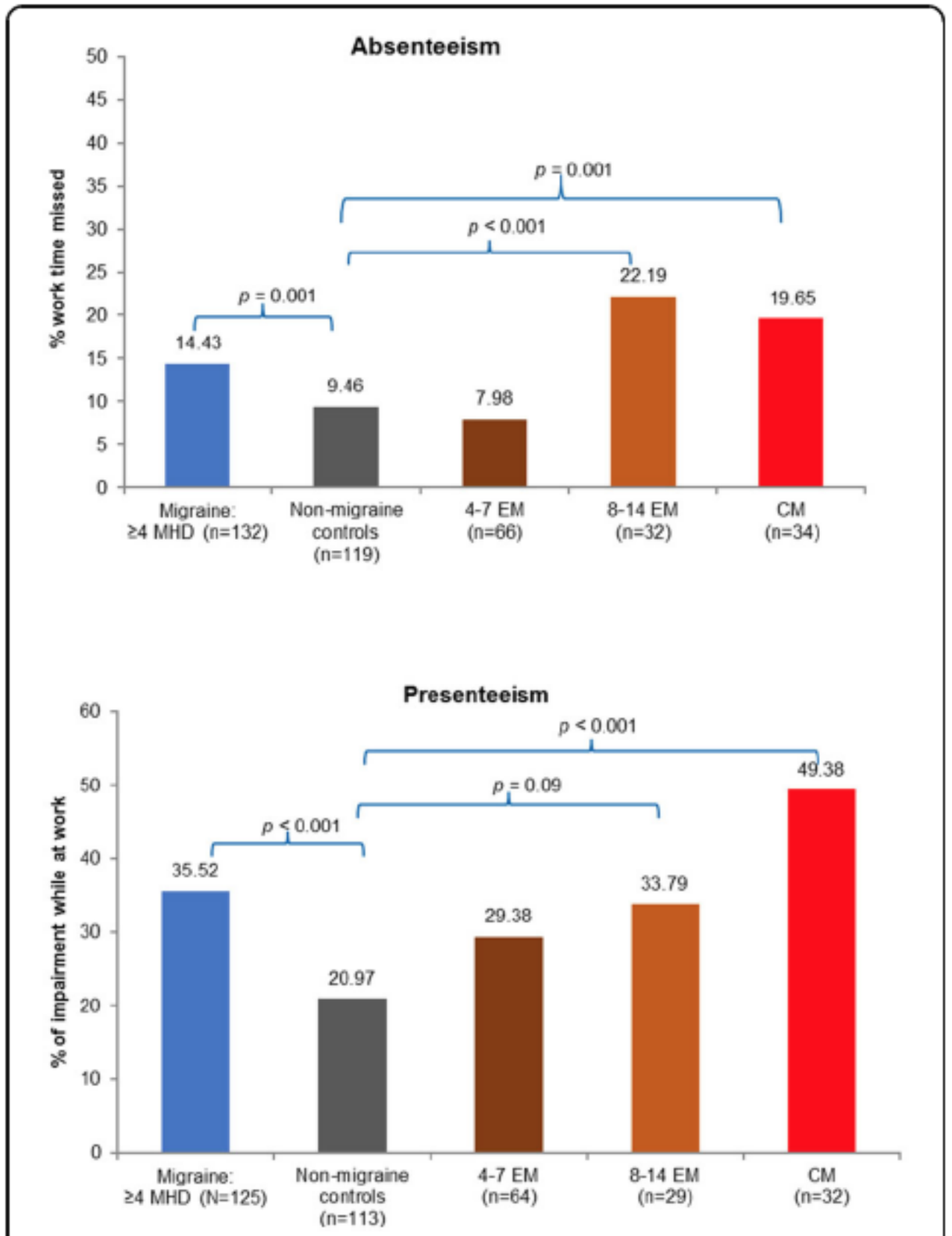

Fig. 4 Work productivity loss in migraine subgroups vs propensity score matched non-migraine controls by the WPAI metricsMann-Whitney tests were used for analysis.CM, chronic migraine; EM, episodic migraine; MHD, monthly headache day; WPAI, work productivity and activity impairment.

Vo P al., JHP 2018 19: 82

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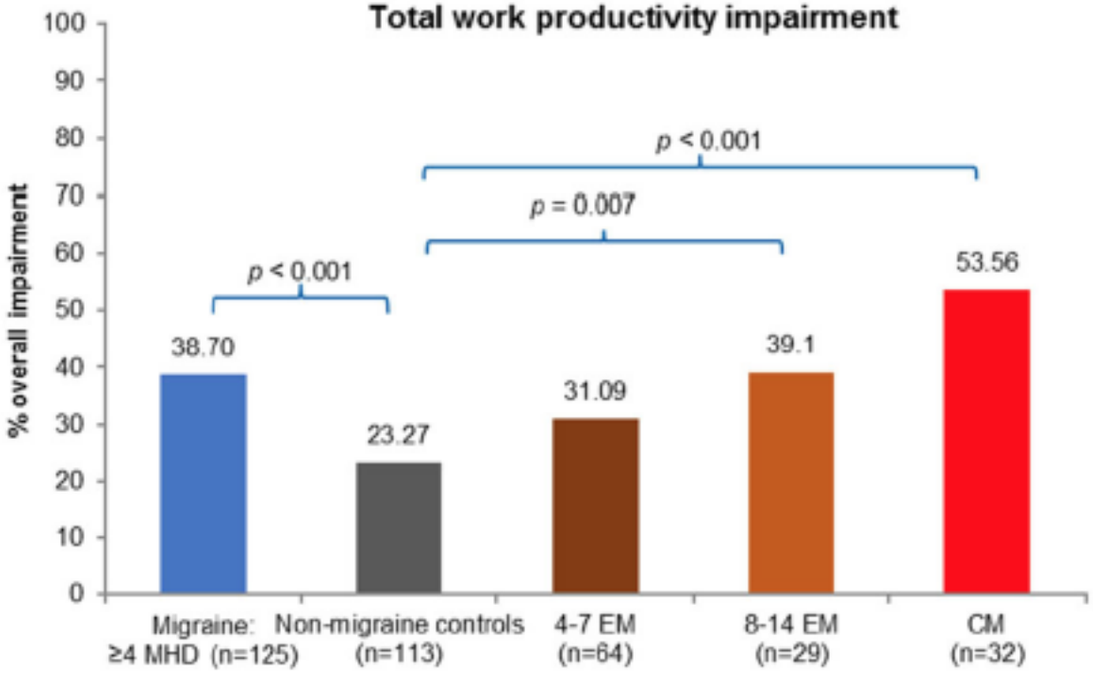

Fig. 5 Total work productivity and activity impairment in migraine subgroups vs propensity score matched non-migraine controls Mann-Whitney tests were used for analysis.CM, chronic migraine; EM, episodic migraine; MHD, monthly headache day.

Vo P al., JHP 2018 19: 82

emicrania: l’aderenza alla terapia

emicrania: l'aderenza alla terapia

1994

Cephalalgia. 1994 Dec;14(6):463-4.

If migraine prophylaxis does not work, think about compliance.

Steiner TJ1, Catarci T, Hering R, Whitmarsh T, Couturier EG.

Author information

Abstract

Data are presented on nine patients with migraine by IHS criteria, recruited from those presenting to the clinic for treatment and needing prophylaxis. Pizotifen 0.5 mg tds was prescribed for 8 weeks and dispensed in special containers with an electronic event recorded concealed in the lid. This responded to the pressure change with each opening of the container and recorded it in real time. The information was later downloaded to a PC for analysis. At trial end, two patients had been lost to follow-up, one had not started the treatment at all, two had dropped out because of alleged side effects (drowsiness), and four patients had completed the study. For these, the quantity of tablets used as a percentage of that prescribed (i.e., compliance assessed on the basis of returned-tablet count) ranged from 62.6% to 91.9%; the percentage of days in which three doses had been taken ranged from only 15.8% to 79%; the percentage of doses taken on schedule (8 h +/- 25% after the previous dose) ranged from 21.1% to 47.3%. It is possible that all evaluations of efficacy and tolerance of migraine prophylactics reported so far have been unsoundly based.

emicrania: l'aderenza alla terapia

1998

Cephalalgia. 1998 Jan;18(1):52-6.

Noncompliance may render migraine prophylaxis useless, but once-daily regimens are better.

Mulleners WM1, Whitmarsh TE, Steiner TJ.
Author information

Abstract
Medicines work better if taken, which must be true of migraine prophylaxis. There is evidence that compliance with regular medication can be badly deficient. To assess how serious the problem might be in routine migraine management, we undertook a covert observational 2-month survey in a specialist headache clinic using objective measures of compliance. Subjects were 38 patients needing prophylaxis with medication prescribed once (od), twice (bd), or three times daily (tds). Medication was dispensed, unknown to them, in Medication Event Monitoring Systems (MEMS) to record openings in real time. Number, timing, and pattern of actual openings were compared with what was expected. Compliance rates averaged 66%, although returned pill counts indicated 91%. A substantial and significant difference was shown between od and bd or tds regimens. Measures of dosing interval--used-on-schedule rate and therapeutic coverage--averaged between 44% and 71%. Once-daily treatment was associated with a used-on-schedule rate more than double those of multiple daily dosing, but still only 66%. We conclude that routine use of drug prophylaxis in migraine may be so seriously undermined by poor compliance that it has little chance of efficacy. Returned-pill counting is inadequate for compliance assessment.

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emicrania: patients’ preference

Mitsikostas *et al. The Journal of Headache and Pain* (2017) 18:102
DOI 10.1186/s10194-017-0813-3

emicrania: patients' preference

RESEARCH ARTICLE Open Access

Patients' preferences for headache acute and preventive treatment

Dimos D. Mitsikostas[1*], Ioanna Belesioti[1], Chryssa Arvaniti[2], Euthymia Mitropoulou[1], Christina Deligianni[1], Elina Kasioti[1], Theodoros Constantinidis[3], Manolis Dermitzakis[4], Michail Vikelis[5] and on behalf of the Hellenic Headache Society

Mitsikostas DD et al. The Journal of Headache and Pain (2017) 18:102

HELLENIC HEADACHE SOCIETY

terapia di prevenzione

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Mitsikostas DD et al. The Journal of Headache and Pain (2017) 18:102

Q8. What is more important for a pharmaceutical treatment you are taking daily to make your headaches become more rare/scarce and less severe (please mark only one answer)?

1. The safety of drug treatment, if there are adverse events and what impact they have in me.
2. The efficacy of the drug treatment, if my headaches will be cured or improved.
3. The route of drug administration, if the drug is a pill or injection or a suppository, etc.

Mitsikostas *et al. The Journal of Headache*
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terapia di prevenzione

The Journal of Headache and Pain

Table 2 Participants' preferences for headache treatment by primary headache disorder

Q No	Question	All	Migraine	Episodic Migraine	Chronic Migraine	Tension-Type Headache (TTH)	Episodic TTH	Chronic TTH	Cluster Headache (CH)	Episodic CH	Chronic CH
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Safety	124 (24.1)	86 (23.1)	53 (24.1)	33 (21.7)	30 (28.0)	8 (32.0)	22 (26.8)	8 (22.9)	6 (42.9)	2 (9.5)
	Efficacy	372 (72.4)	271 (72.8)	158 (71.8)	113 (74.3)	74 (69.2)	16 (64.0)	58 (70.7)	27 (77.1)	8 (57.1)	19 (90.5)
	Route of administration	18 (3.5)	15 (4.0)	9 (4.1)	6 (3.9)	3 (2.80	1 (4.0)	2 (2.4)	0	0	0

Mitsikostas DD et al. The Journal of Headache and Pain (2017) 18:102

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terapia di prevenzione

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The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

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terapia di prevenzione

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		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	1 pill/day	275 (53.8)	189 (51.1)	122 (55.5)	67 (44.7)	67 (63.2)	16 (64.0)	51 (63.0)	19 (54.3)	7 (50.0)	12 (57.1)
	2 pills/ day	39 (7.6)	27 (7.3)	18 (8.2)	9 (6.0)	9 (8.5)	4 (16.0)	5 (6.2)	3 (8.6)	2 (14.3)	1 (4.8)
	3 pills/day	10 (2.0)	8 (2.2)	6 (2.7)	2 (1.3)	0	0	0	2 (5.7)	0	2 (9.5)
	sc injection/ month	41 (8.0)	30 (8.1)	22 (10.0)	8 (5.3)	9 (8.5)	2 (8.0)	7 (8.6)	2 (5.7)	0	2 (9.5)
	iv injection/ month	16 (3.1)	14 (3.8)	9 (4.1)	5 (3.3)	1 (0.9)	0	1 (1.2)	1 (2.9)	1 (7.1)	0
	sc injection/ 3 month	68 (13.3)	55 (14.9)	27 (12.3)	28 (18.7)	9 (8.5)	0	9 (11.1)	4 (11.4)	2 (14.3)	2 (9.5)
	iv injection/ 3 month	62 (12.1)	47 (12.7)	16 (7.3)	31 (20.7)	11 (10.4)	3 (12.0)	8 (9.9)	4 (11.4)	2 (14.3)	2 (9.5)

Mitsikostas DD et al. The Journal of Headache and Pain (2017) 18:102

Q9. Which route of drug administration do you prefer most, independently to safety and efficacy? (Consider that all drugs share the same efficacy and safety and please mark only one answer)

Mitsikostas *et al. The Journal of Headache*
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terapia di prevenzione

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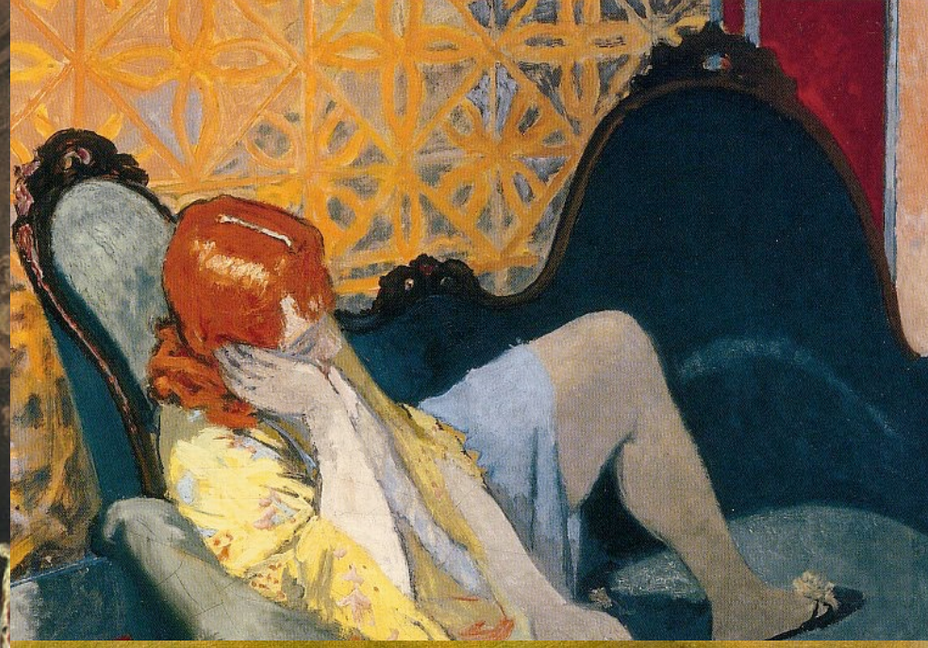
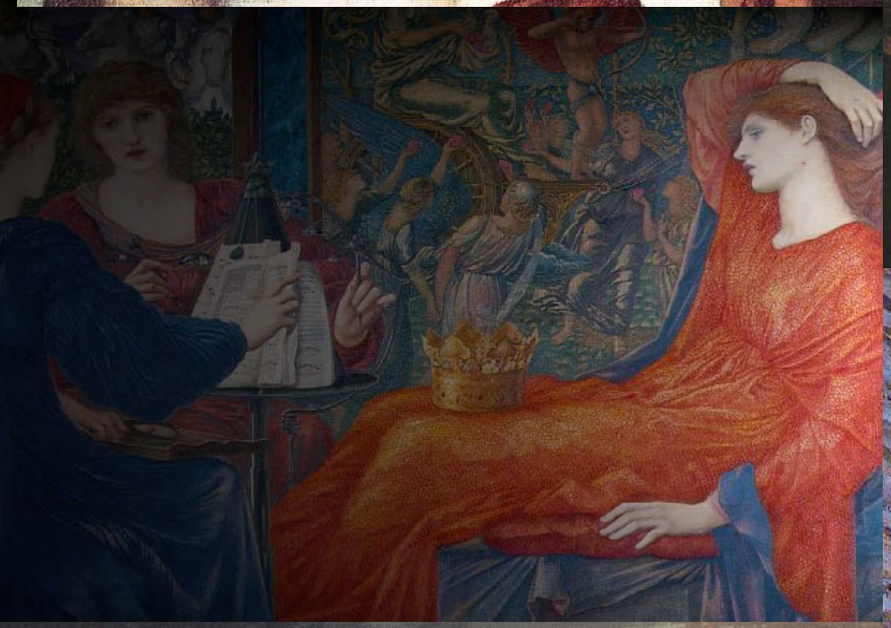
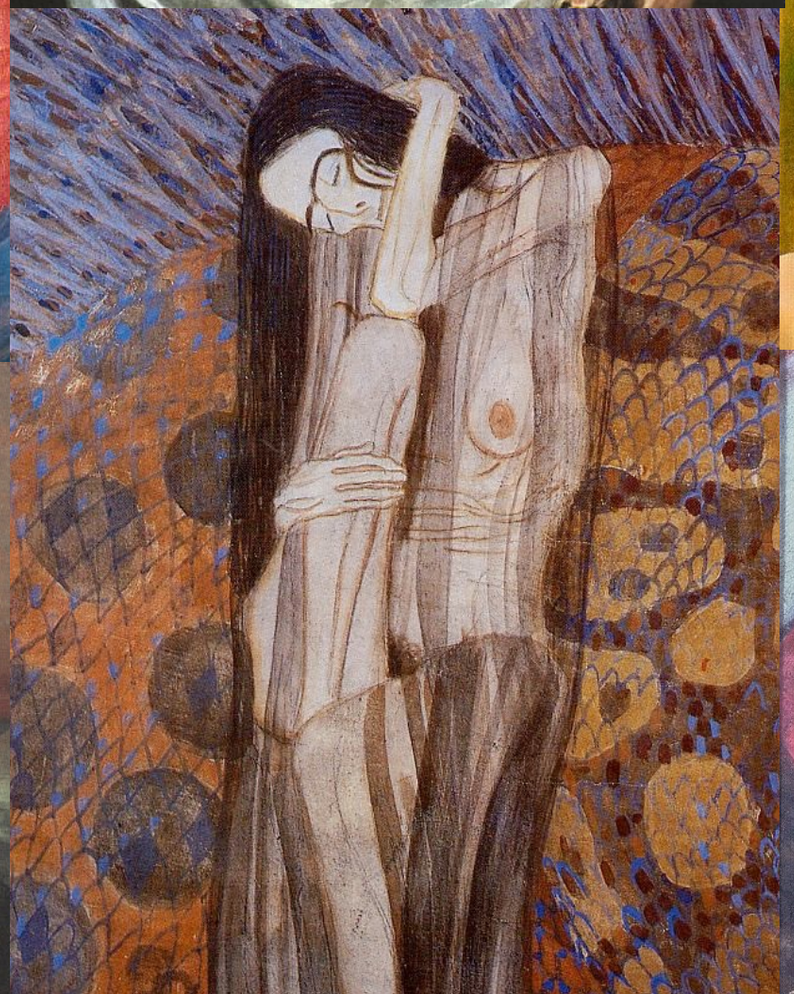
	1 pill/day	275 (53.8)	189 (51.1)	122 (55.5)	67 (44.7)	67 (63.2)	16 (64.0)	51 (63.0)	19 (54.3)	7 (50.0)	12 (57.1)
	2 pills/ day	39 (7.6)	27 (7.3)	18 (8.2)	9 (6.0)	9 (8.5)	4 (16.0)	5 (6.2)	3 (8.6)	2 (14.3)	1 (4.8)
	3 pills/day	10 (2.0)	8 (2.2)	6 (2.7)	2 (1.3)	0	0	0	2 (5.7)	0	2 (9.5)
	sc injection/ month	41 (8.0)	30 (8.1)	22 (10.0)	8 (5.3)	9 (8.5)	2 (8.0)	7 (8.6)	2 (5.7)	0	2 (9.5)
	iv injection/ month	16 (3.1)	14 (3.8)	9 (4.1)	5 (3.3)	1 (0.9)	0	1 (1.2)	1 (2.9)	1 (7.1)	0
	sc injection/ 3 month	68 (13.3)	55 (14.9)	27 (12.3)	28 (18.7)	9 (8.5)	0	9 (11.1)	4 (11.4)	2 (14.3)	2 (9.5)
	iv injection/ 3 month	62 (12.1)	47 (12.7)	16 (7.3)	31 (20.7)	11 (10.4)	3 (12.0)	8 (9.9)	4 (11.4)	2 (14.3)	2 (9.5)

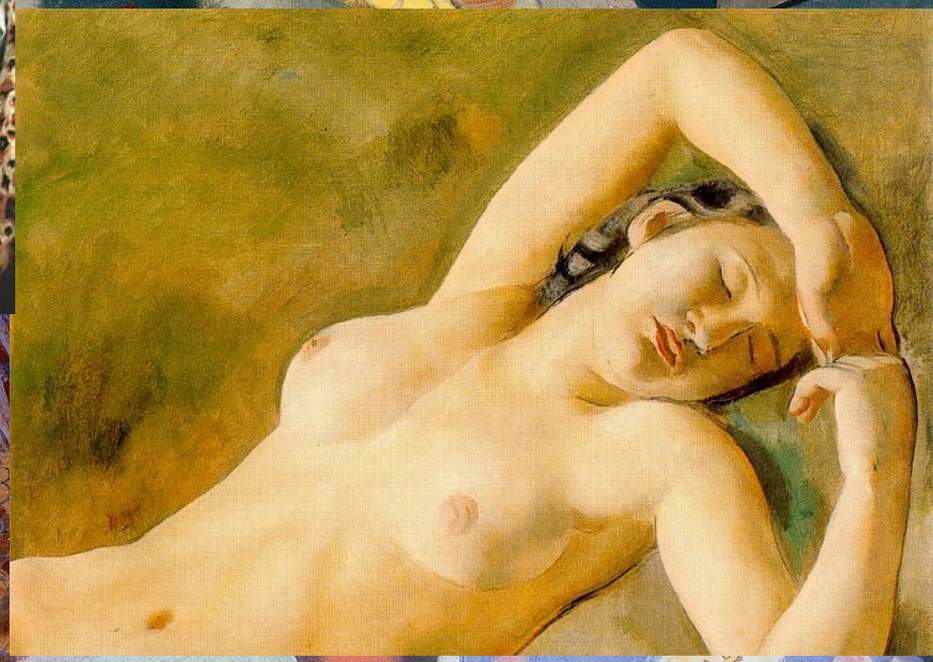
Mitsikostas DD et al. The Journal of Headache and Pain (2017) 18:102

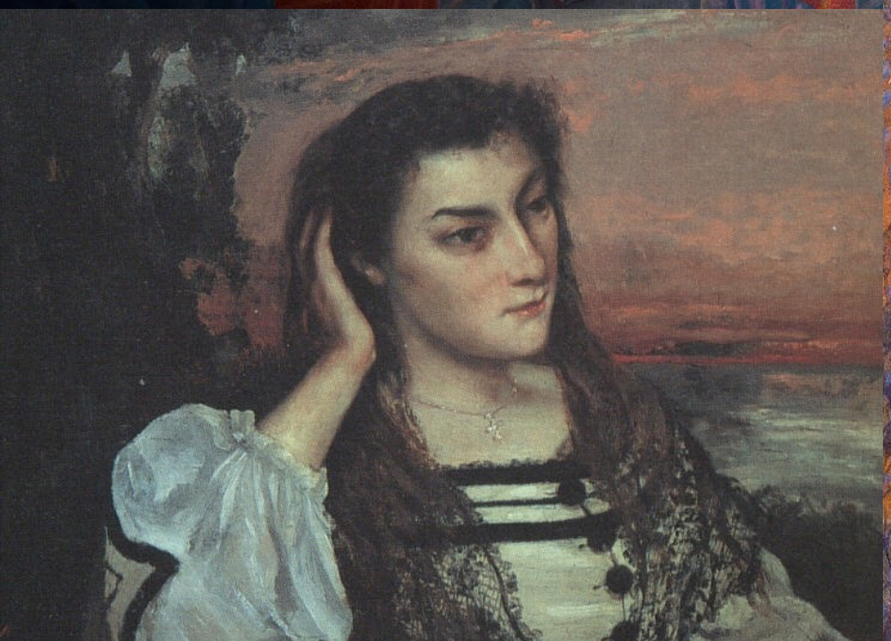
Q9. Which route of drug administration do you prefer most, independently to safety and efficacy? (Consider that all drugs share the same efficacy and safety and please mark only one answer)

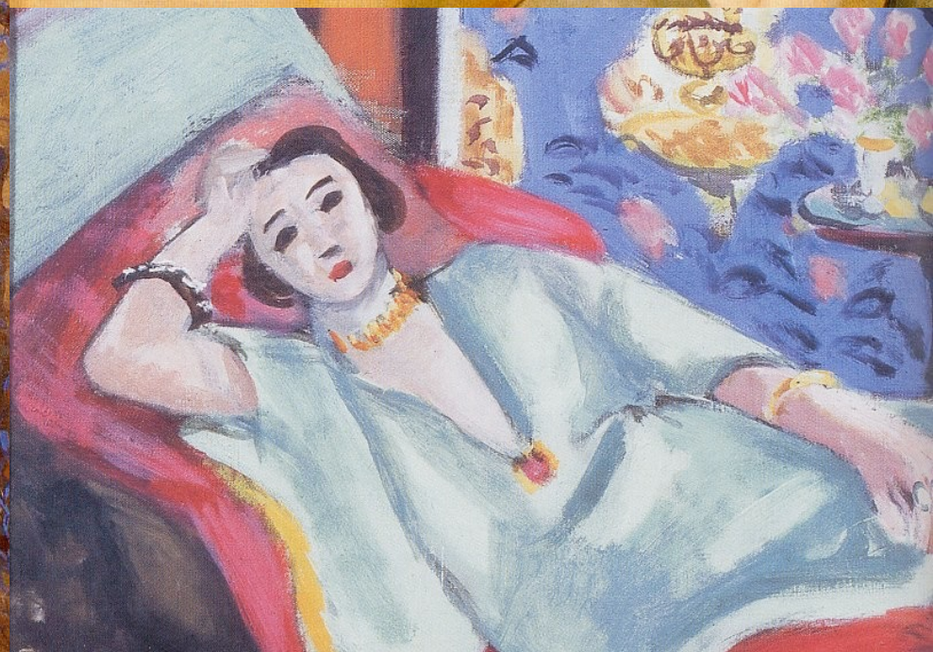




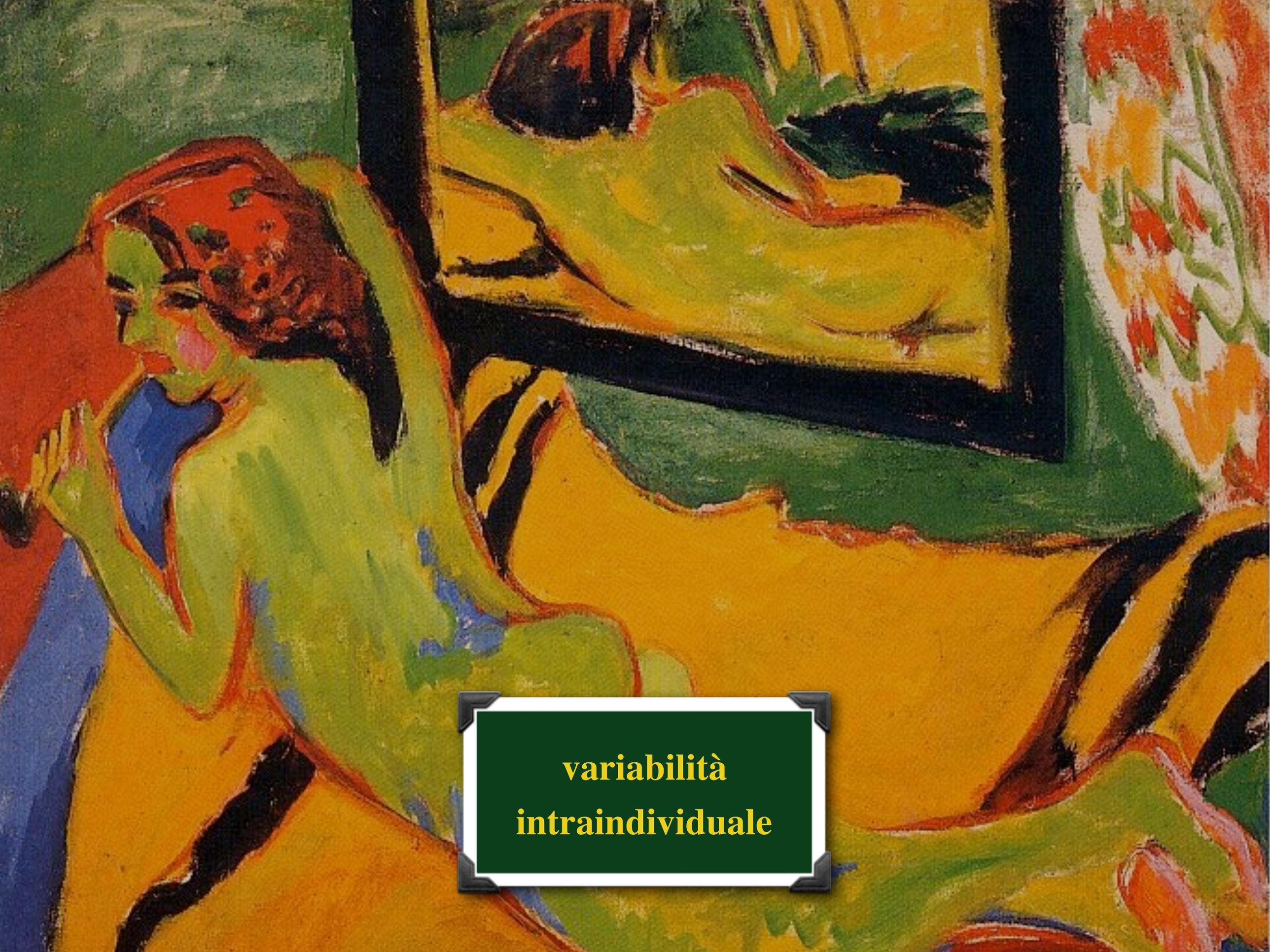








variabilità interindividuale


variabilità
intraindividuale

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

Riunione della Sezione Triveneto
Società Italiana di Neurologia

Sala Convegni Torre di Malta

Cittadella (PD), 17 maggio 2019

AGENDA

dalla parte del paziente

terapia d'attacco

terapia di profilassi


121
122
123
ISLE DE CEILAN
I. Grande
Jafanapatan
I Manar
Trinquimale
Das Settecorolas
Candea
Bois de Canselle
Chilao
Negombo
Ceitauaca
Baticala
Colombo
Cotan
Pico de Adam
Iala
Galle
Pointe de Galle

Sri Lanka - Ceylon - Serendib

Sri Lanka - Ceylon - Serendib

LA SERENDIPITA'
termine coniato nel 1754 da Horace Walpole dopo la lettura di i

"Tre principi di Serendippo" di Cristoforo Armeno (XVI sec)

Sri Lanka - Ceylon - Serendib

LA SERENDIPITA'
termine coniato nel 1754 da Horace Walpole dopo la lettura di i

"Tre principi di Serendippo" di Cristoforo Armeno (XVI sec)

...scoprire una cosa non cercata e imprevista mentre se ne sta cercando un'altra...

Alexander Fleming (1881-1955)

Alexander Fleming (1881-1955)

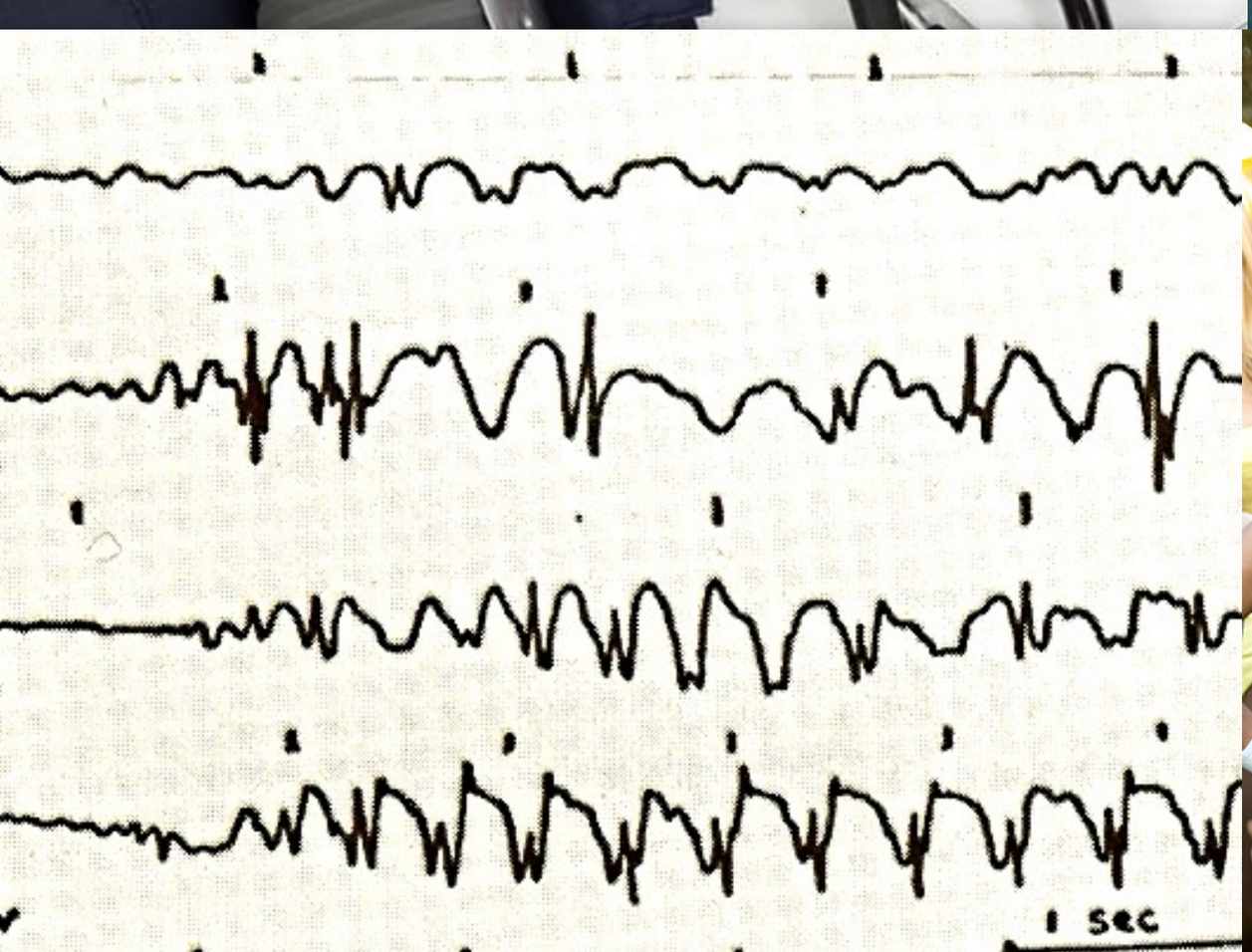
1928. scoperta della penicillina


SPHYGMOMANOMETER
0483
mmHg


SPHYGMOMANOMETER
CE 0483
mmHg


SPHYGMOMANOMETER
CE 0483
mmHg
1 sec


SPHYGMOMANOMETER
CE 0483
mmHg


1 sec

osservazione

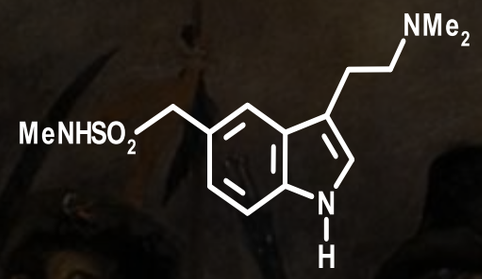
ipotesi

deduzione

esperimento

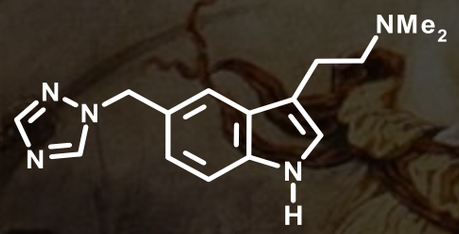
14 luglio 1789

14 luglio 1789



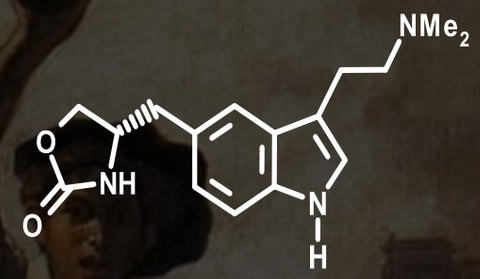
SUMATRIPTAN

50-100 MG CPR *(300)*
6 MG FIALE S.C. *(12)*
20 MG SPRAY *(40)*
10 MG SPRAY PED (20)
25 MG SUPP *(50)*



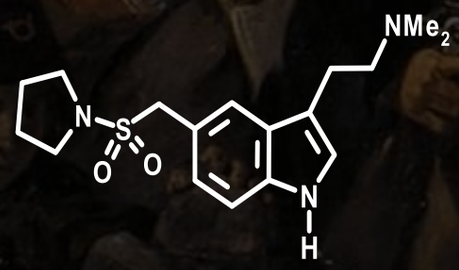
ZOLMITRIPTAN

2,5 MG CPR *(5,0)*
2.5 MG CPR ORODISP *(5,0)*



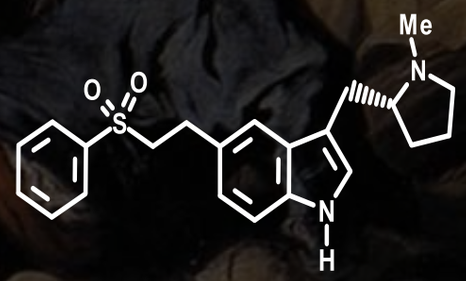
RIZATRIPTAN

5-10 MG CPR *(20)*
10 MG LIOF *(20)*



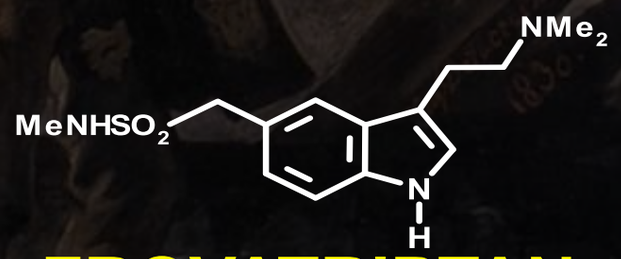
ALMOTRIPTAN

12,5 MG CPR *(25,0)*



ELETRIPTAN

20-40 MG CPR *(80)*



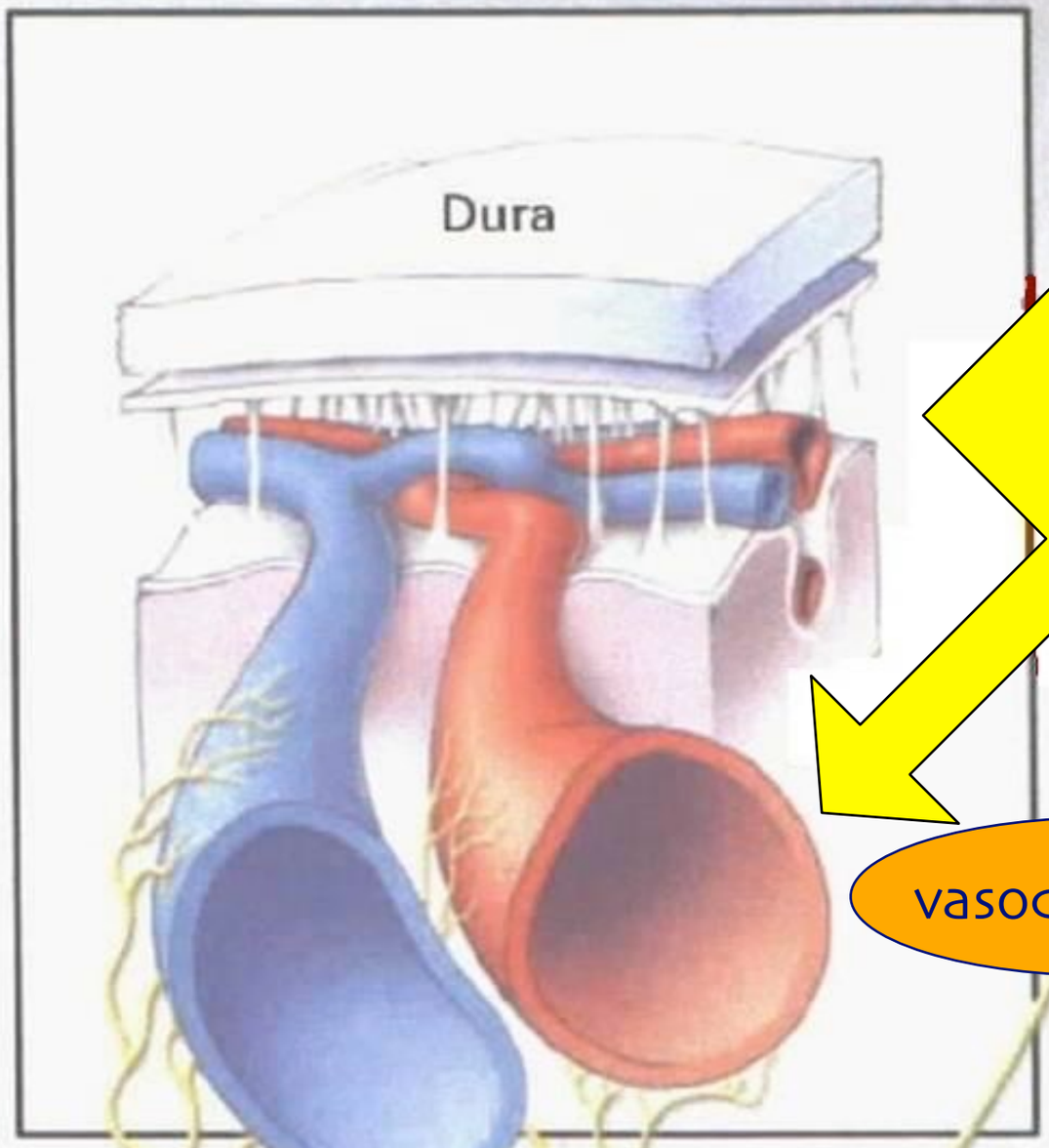
FROVATRIPTAN

2,5 MG CPR (5,0)

recettori		ergotaminici	triptani
serotoninergici	1A	++++	+
	1B	+++	++
	1D	+++	+++
	1E	+	+
	1F	+	+
	2A	+++	-
	2C	+++	-
adrenergici	α1	+++	-
	α2	+++	-
dopaminergici	D1	-	-
	D2	+++	-

recettori		ergotaminici	triptani
serotoninergici	1A	++++	+
	1B	+++	++
	1D	+++	+++
	1E	+	+
	1F	+	+
	2A	+++	-
	2C	+++	-
adrenergici	α1	+++	-
	α2	+++	-
dopaminergici	D1	-	-
	D2	+++	-

Presynaptic receptors located on trigeminal neurons regulate CGRP release.
The presynaptic serotonin (5-hydroxytryptamine) receptors 5-HT1B and 5-HT1D inhibit CGRP release



vasi
5-HT$_{1B}$

vasocostrizione

Trigeminal ganglion

Trigeminal nucleus

C1

C2

Brain stem

5-HT$_{1D}$
neuroni
centrali

modulazione del dolore

5-HT$_{1D}$
fibre
periferiche

inibizione
dell'infiammazione
neurogenica

Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: https://www.tandfonline.com/loi/iemt20

Pharmacokinetics and pharmacodynamics of new acute treatments for migraine

Chiari Lupi, Silvia Benemei, Simona Guerzoni, Lanfranco Pellesi & Andrea Negro

To cite this article: Chiari Lupi, Silvia Benemei, Simona Guerzoni, Lanfranco Pellesi & Andrea Negro (2019): Pharmacokinetics and pharmacodynamics of new acute treatments for migraine, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1080/17425255.2019.1578749

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Accepted author version posted online: 04 Feb 2019.

Lupi C et al. Exp opinion on Drug Metabolism & Toxicology, 2019

ditani

osservazione

- i recettori 5-HT1F sono poco espressi nei vasi cerebrali e coronarici, mentre sono espressi nei neuroni sensoriali trigeminali periferici e centrali;
- sono recettori presinaptici la cui attivazione sopprime il rilascio trigeminale di CGRP

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ipotesi

- l'agonismo selettivo dei recettori 5-HT1F potrebbe avere azione antiemicranica in acuto

deduzione ed esperimento

- agonisti selettivi, ad alta affinità, dei recettori 5-HT1F sono stati creati, tra di essi il lasmiditan (COL-144 o LY573144) ed altri: LY334370, LY344864, and LY349950
- lasmiditan agisce sul sistema trigeminale senza causare vasocostrizione (causa bassa affinità per recettori 5-HT1B)

Lupi C et al. Exp opinion on Drug Metabolism & Toxicology, 2019

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Lasmiditan is an effective acute treatment for migraine

A phase 3 randomized study

Bernice Kuca, BA, MS, Stephen D. Silberstein, MD, Linda Wietecha, BSN, MS, Paul H. Berg, MS, Gregory Dozier, MPH, and Richard B. Lipton, MD, on behalf of the COL MIG-301 Study Group

Neurology® 2018;91:e2222-e2232. doi:10.1212/WNL.0000000000006641

Correspondence
Ms. Wietecha
wietecha_linda_a@lilly.com

Abstract

Objective

To assess the efficacy and safety of lasmiditan in the acute treatment of migraine.

Methods

Adult patients with migraine were randomized (1:1:1) to a double-blind dose of oral lasmiditan 200 mg, lasmiditan 100 mg, or placebo and were asked to treat their next migraine attack within 4 hours of onset. Over 48 hours after dosing, patients used an electronic diary to record headache pain and the presence of nausea, phonophobia, and photophobia, one of which was designated their most bothersome symptom (MBS).

Results

Of the 1,856 patients who treated an attack, 77.9% had ≥1 cardiovascular risk factors in addition to migraine. Compared with placebo, more patients dosed with lasmiditan 200 mg were free of headache pain at 2 hours after dosing (32.2% vs 15.3%; odds ratio [OR] 2.6, 95% confidence interval [CI] 2.0–3.6, $p < 0.001$), similar to those dosed with lasmiditan 100 mg (28.2%; OR 2.2, 95% CI 1.6–3.0, $p < 0.001$). Furthermore, compared with those dosed with placebo, more patients dosed with lasmiditan 200 mg (40.7% vs 29.5%; OR 1.6, 95% CI 1.3–2.1, $p < 0.001$) and lasmiditan 100 mg (40.9%; OR 1.7, 95% CI, 1.3–2.2, $p < 0.001$) were free of their MBS at 2 hours after dosing. Adverse events were mostly mild or moderate in intensity.

Conclusions

Lasmiditan dosed at 200 and 100 mg was efficacious and well tolerated in the treatment of acute migraine among patients with a high level of cardiovascular risk factors.

ClinicalTrials.gov identifier

NCT02439320.

RELATED ARTICLE

Article
Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study
Page 1082

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Page 1082

MORE ONLINE

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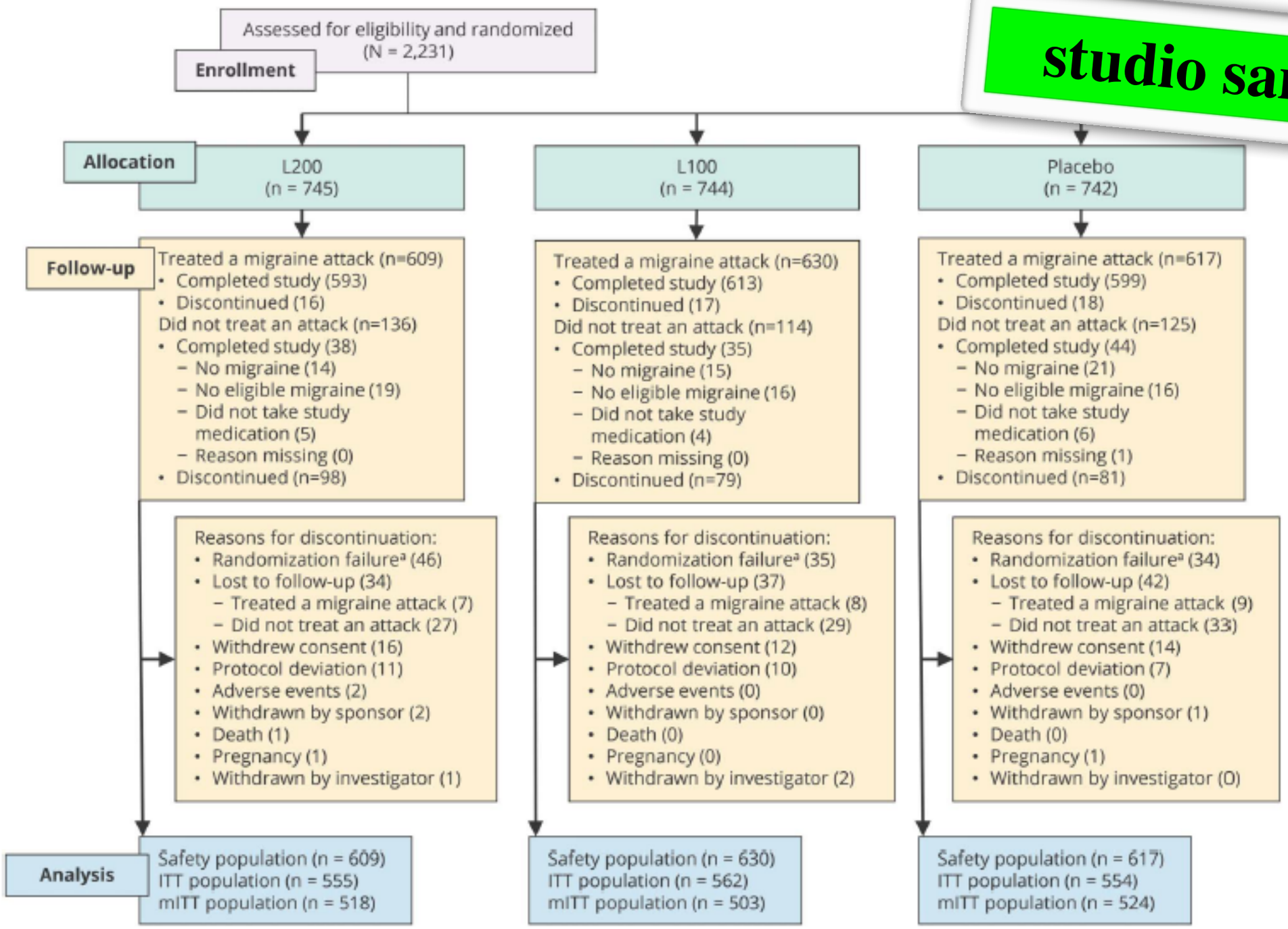
Figure 1 Study flow (first dose)

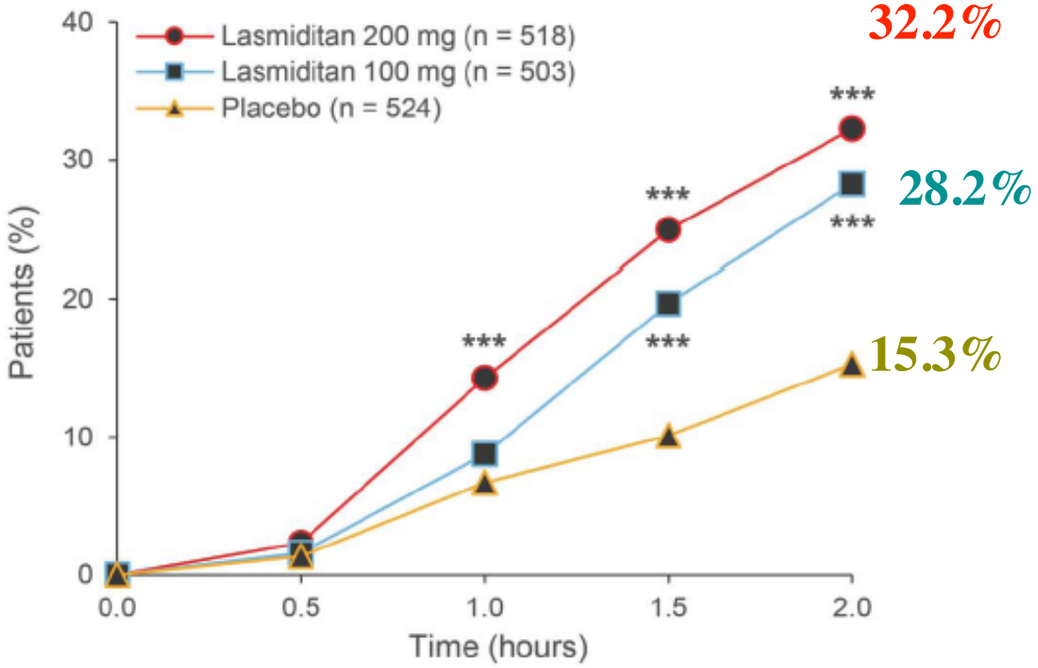


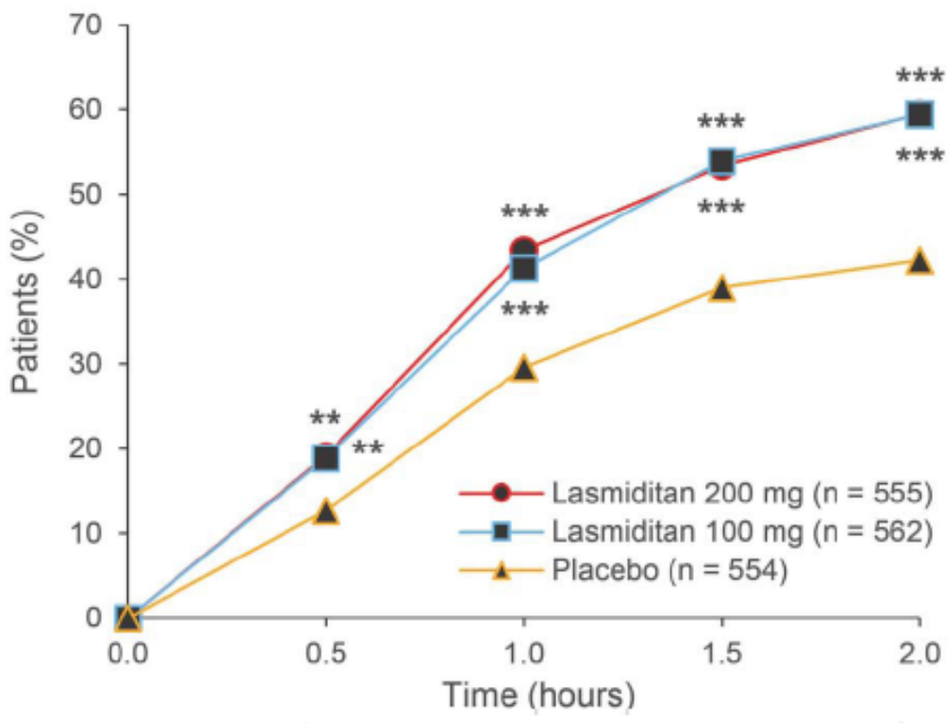
ITT = intent-to-treat; L100 = lasmiditan 100 mg; L200 = lasmiditan 200 mg; mITT = modified intent-to-treat. [a]Patients who were randomized but then deemed ineligible at the telephone confirmation (after completion of all screening evaluations).

One patient died of an accidental overdose of methadone and oxycodone before taking the study drug.

studio samurai

Figure 2 Headache pain free, MBS free, and headache relief after the first dose





studio samurai

headache pain free at 2 hours

- lasmiditan 200 mg 32.2%
- lasmitidan 100 mg 28.2%
- placebo 15.3%

- dati simili nello studio SPARTAN

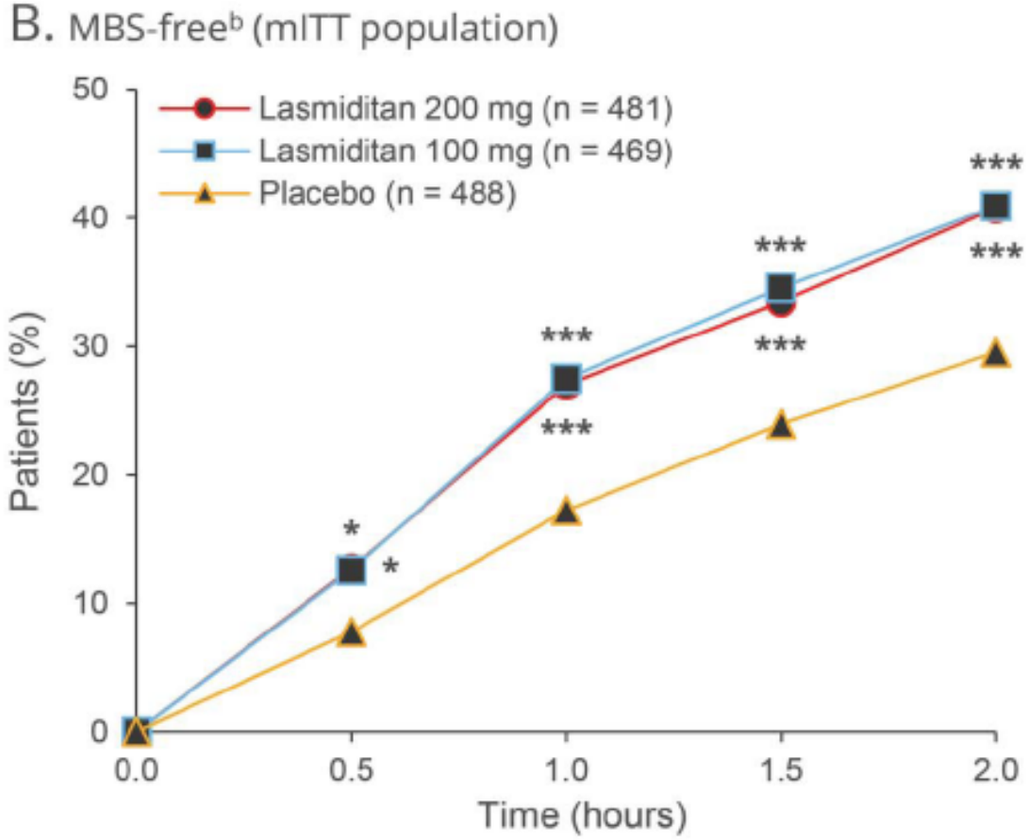


Table 3 Patient global impression of change and disability level by treatment group

ITT population	Lasmiditan 200 mg (n = 555)	Lasmiditan 100 mg (n = 562)	Placebo (n = 554)
	Global impression of change at 2 h, n (%)		
Very much better	57 (10.3)	54 (9.6)	34 (6.1)
Much better	153 (27.6)	155 (27.6)	87 (15.7)
A little better	143 (25.8)	153 (27.2)	159 (28.7)
No change	60 (10.8)	83 (14.8)	146 (26.4)
A little worse	31 (5.6)	16 (2.8)	28 (5.1)
Much worse	13 (2.3)	8 (1.4)	14 (2.5)
Very much worse	5 (0.9)	8 (1.4)	3 (0.5)
***p* Value vs placebo**	<0.001	<0.001	
	Disability level at 2 h, n (%)		
Not at all (0)	180 (32.4)	181 (32.2)	119 (21.5)
Mild interference (1)	115 (20.7)	137 (24.4)	156 (28.2)
Marked interference (2)	92 (16.6)	95 (16.9)	122 (22.0)
Completely, needs bed rest (3)	75 (13.5)	64 (11.4)	74 (13.4)
***p* Value vs placebo**	<0.001	<0.001	

Abbreviation: ITT = intent-to-treat.

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Completely, needs bed rest (3)	75 (13.5)	64 (11.4)	74 (13.4)
***p* Value vs placebo**	<0.001	<0.001	

Abbreviation: ITT = intent-to-treat.

Table 3 Patient global impression of change and disability level by treatment group

ITT population	Lasmiditan 200 mg (n = 555)	Lasmiditan 100 mg (n = 562)	Placebo (n = 554)
	Global impression of change at 2 h, n (%)		
Very much better	57 (10.3)	54 (9.6)	34 (6.1)
Much better	153 (27.6)	155 (27.6)	87 (15.7)
A little better	143 (25.8)	153 (27.2)	159 (28.7)
No change	60 (10.8)	83 (14.8)	146 (26.4)
A little worse	31 (5.6)	16 (2.8)	28 (5.1)
Much worse	13 (2.3)	8 (1.4)	14 (2.5)
Very much worse	5 (0.9)	8 (1.4)	3 (0.5)
***p* Value vs placebo**	<0.001	<0.001	
	Disability level at 2 h, n (%)		
Not at all (0)	180 (32.4)	181 (32.2)	119 (21.5)
Mild interference (1)	115 (20.7)	137 (24.4)	156 (28.2)
Marked interference (2)	92 (16.6)	95 (16.9)	122 (22.0)
Completely, needs bed rest (3)	75 (13.5)	64 (11.4)	74 (13.4)
***p* Value vs placebo**	<0.001	<0.001	

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Table 4 Treatment-emergent adverse events (TEAEs) after the first dose

Safety population	Lasmiditan 200 mg (n = 609), n (%)	Lasmiditan 100 mg (n = 630), n (%)	Placebo (n = 617), n (%)
At least 1 TEAE	260 (42.7)	229 (36.3)	101 (16.4)
At least 1 TEAE related to study medication	237 (38.9)	205 (32.5)	78 (12.6)
At least 1 serious TEAE	2 (0.3)	0 (0.0)	1 (0.2)
TEAEs with incidence ≥2% in any lasmiditan group and greater than placebo			
Dizziness	99 (16.3)	79 (12.5)	21 (3.4)
Paresthesia	48 (7.9)	36 (5.7)	13 (2.1)
Somnolence	33 (5.4)	36 (5.7)	14 (2.3)
Nausea	32 (5.3)	19 (3.0)	12 (1.9)
Fatigue	19 (3.1)	26 (4.1)	2 (0.3)
Lethargy	15 (2.5)	12 (1.9)	2 (0.3)
Incidence of cardiovascular TEAEs			
Palpitations	4 (0.7)	2 (0.3)	0 (0.0)
Sinus bradycardia	1 (0.2)	0 (0.0)	0 (0.0)
Bradycardia	0 (0.0)	1 (0.2)	1 (0.2)
Tachycardia	0 (0.0)	1 (0.2)	0 (0.0)
Left ventricular hypertrophy	0 (0.0)	0 (0.0)	1 (0.2)

Abbreviation: TEAE = treatment-emergent adverse event (an event that started or worsened after the first dose of study medication [i.e., it did not present with the migraine] and occurred within 48 hours of dosing).

studio samurai

adverse events

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- è in corso una fase open-label sui pazienti che hanno completato studi SAMURAI e SPARTAN
- un nuovo trial inizierà a Maggio 2019
- 14 novembre 2018 Lilly ha inviato la richiesta FDA

osservazione

ipotesi

deduzione

esperimento

il CGRP…una storia dal 1982

il CGRP…una storia dal 1982

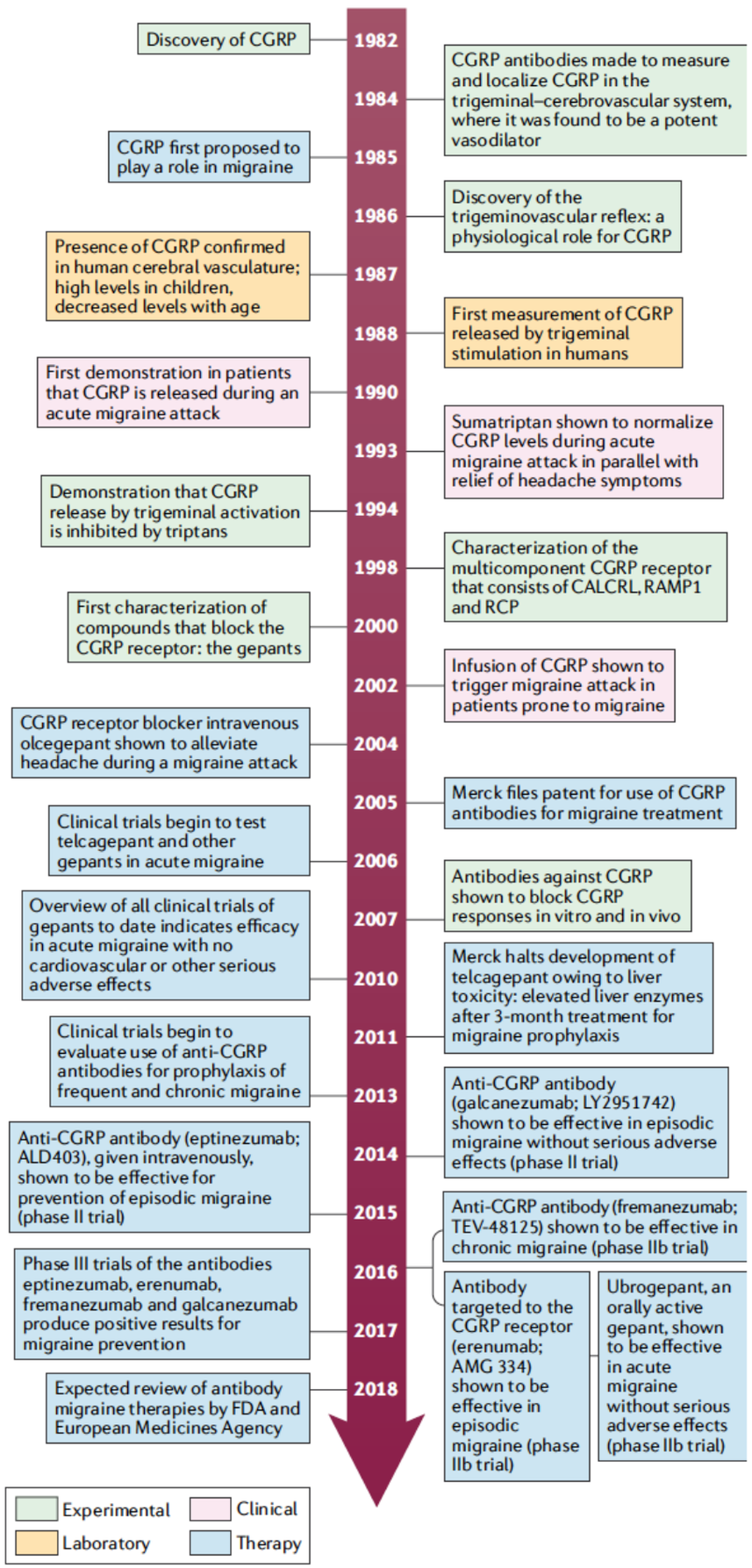


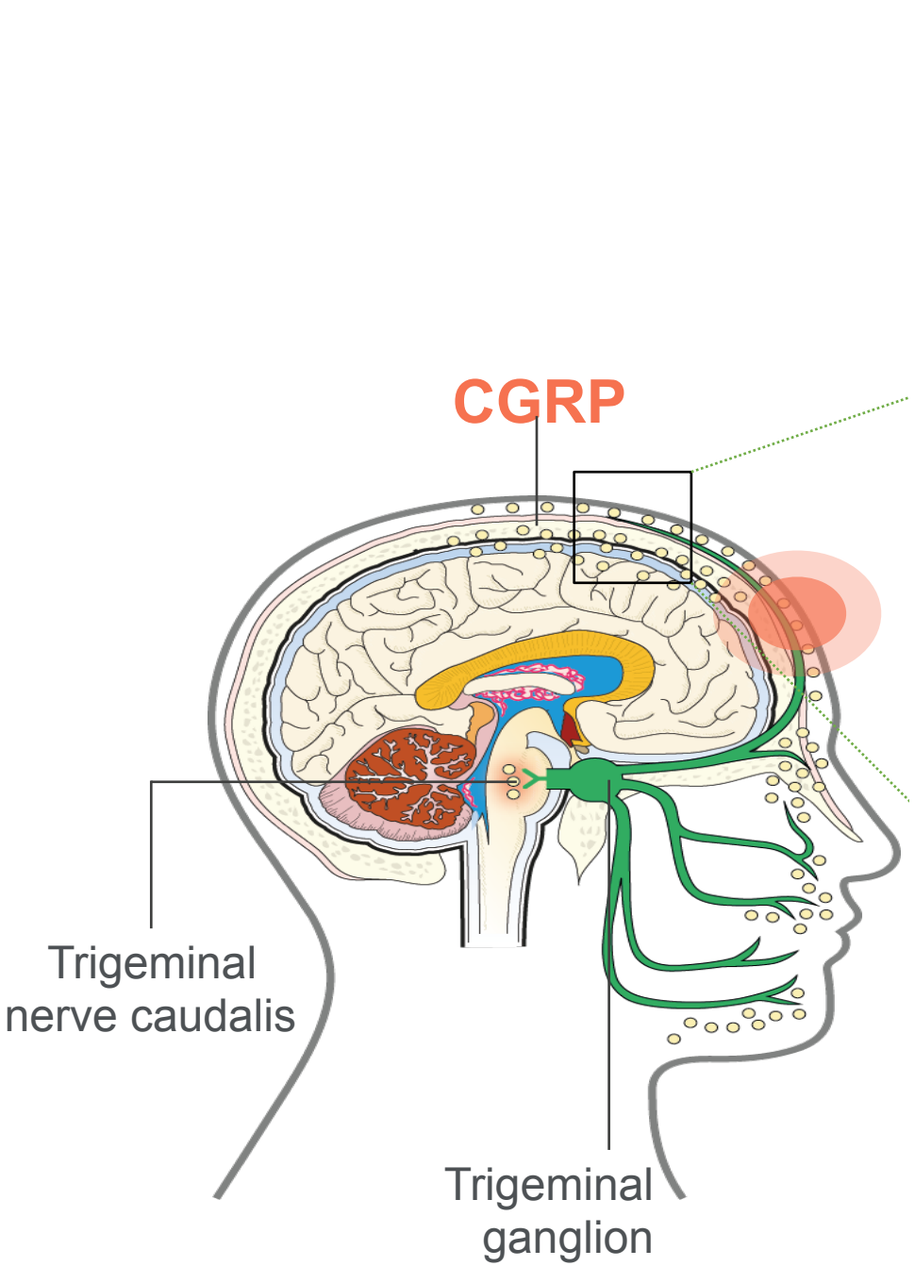
Fig. 1 | **Timeline of the key events in the development of drugs that target CGRP for migraine therapy.** CALCRL, calcitonin receptor-like receptor; CGRP, calcitonin gene-related peptide; RAMP1, receptor activity-modifying protein 1; RCP, receptor coupling protein.

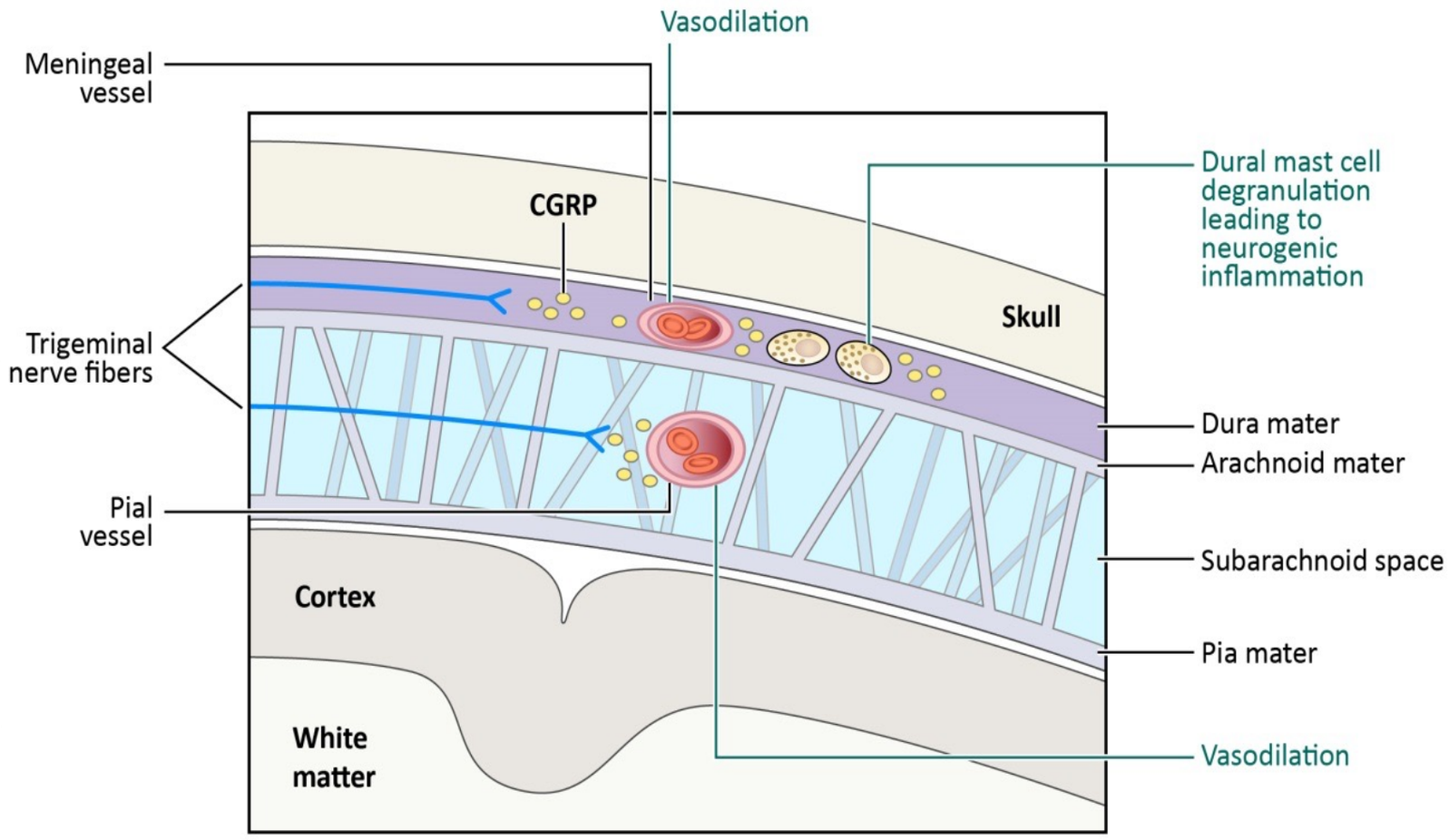
L. Edvinsson et al. Nature Review, 2018

osservazione

il CGRP

- appartiene ad una famiglia di peptidi regolatori
- durante la crisi emicranica il CGRP viene rilasciato dalle fibre del nervo trigemino, comportando vasodilatazione e infiammazione neurogenica
- è il principale, ma forse non l'unico, mediatore implicato nel dolore emicranico
- per produrre il dolore emicranico agisce a livello periferico, al di fuori della barriera emato-encefalica
- poichè media azioni pro-infiammatorie, ma non omeostatiche, il blocco della sua azione non produce reazioni avverse severe





L. Edvinsson et al. Nature Review, 2018
Bigal ME, et al. Headache 2013
Russell FA, et al. Physiol Rev 2014

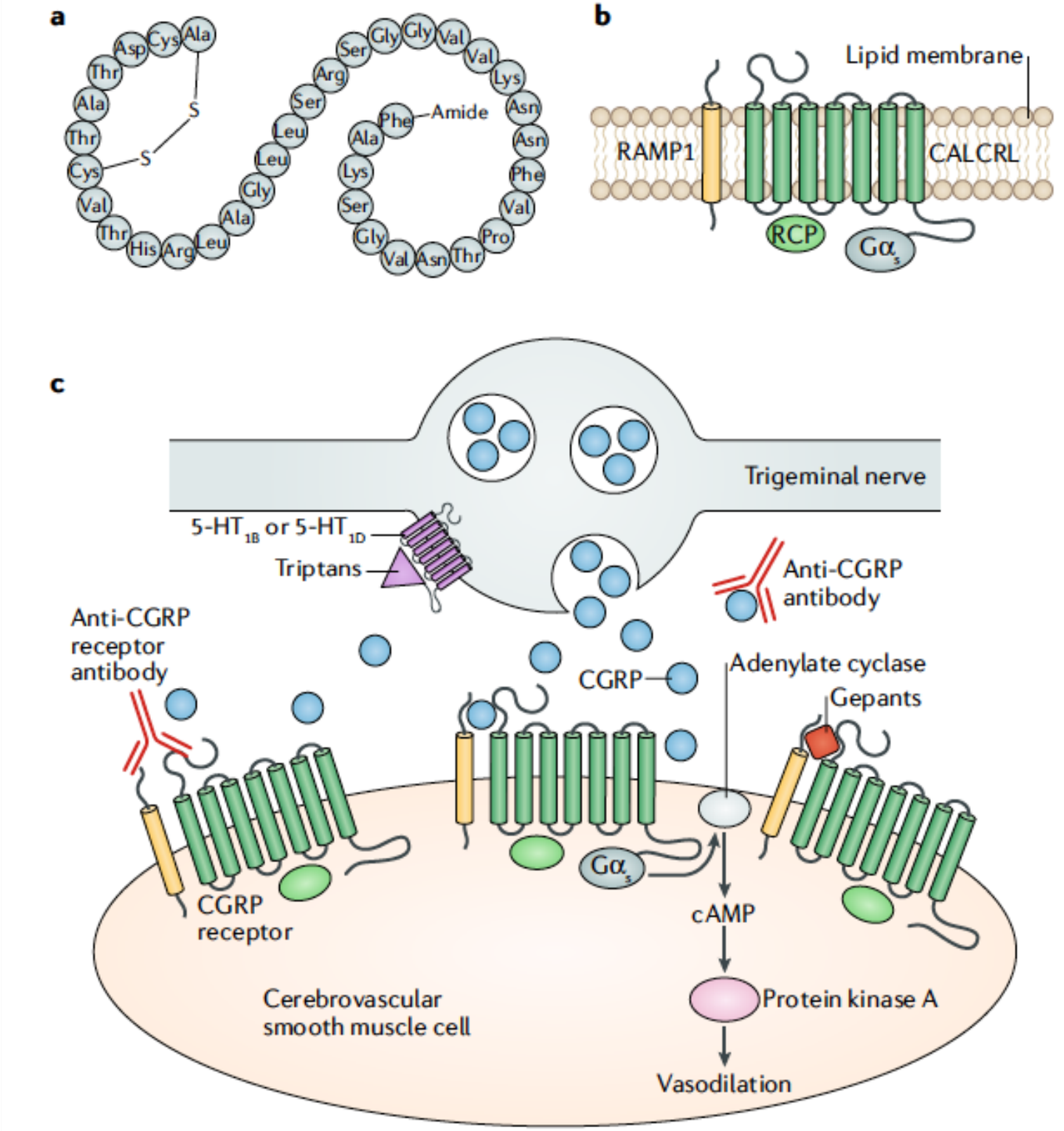
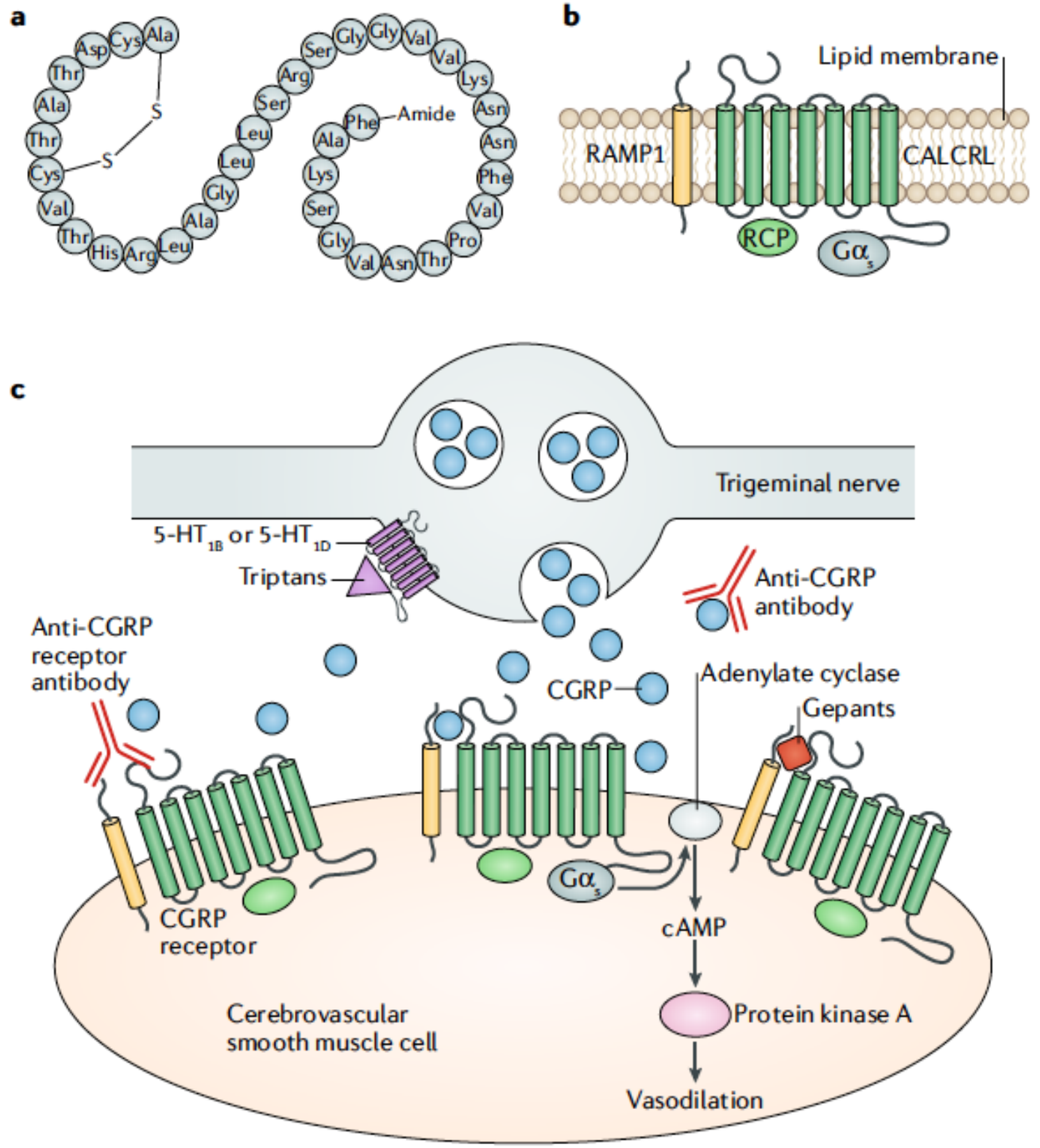


Fig. 2 | **Components of CGRP transmission and sites of action for CGRP-related migraine therapies. a** | Amino acid structure of human α-type calcitonin gene-related peptide (CGRP). **b** | The CGRP receptor complex, which consists of the two integral membrane proteins calcitonin receptor-like receptor (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.

gepanti



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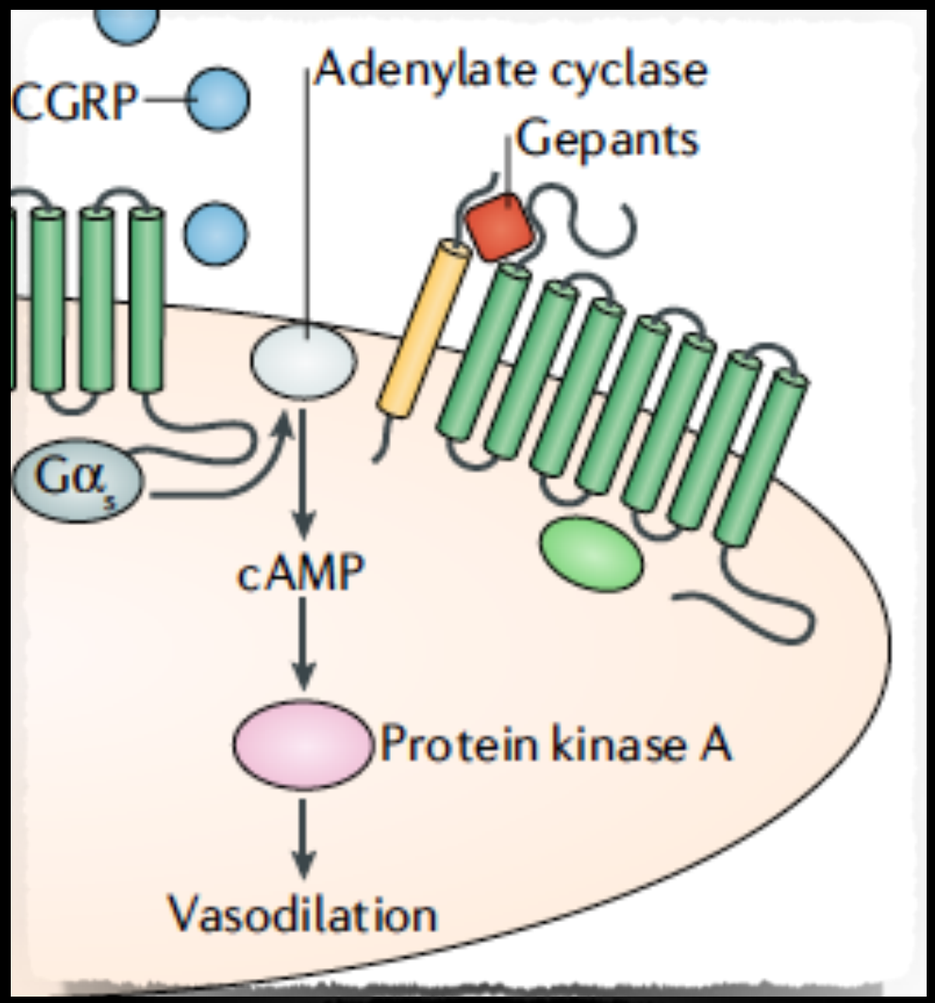
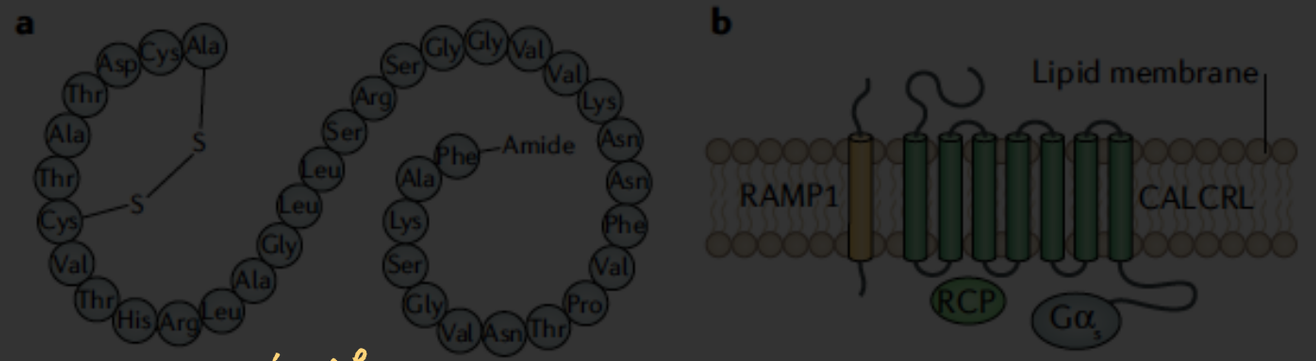
L. Edvinsson et al. Nature Review, 2018

gepanti

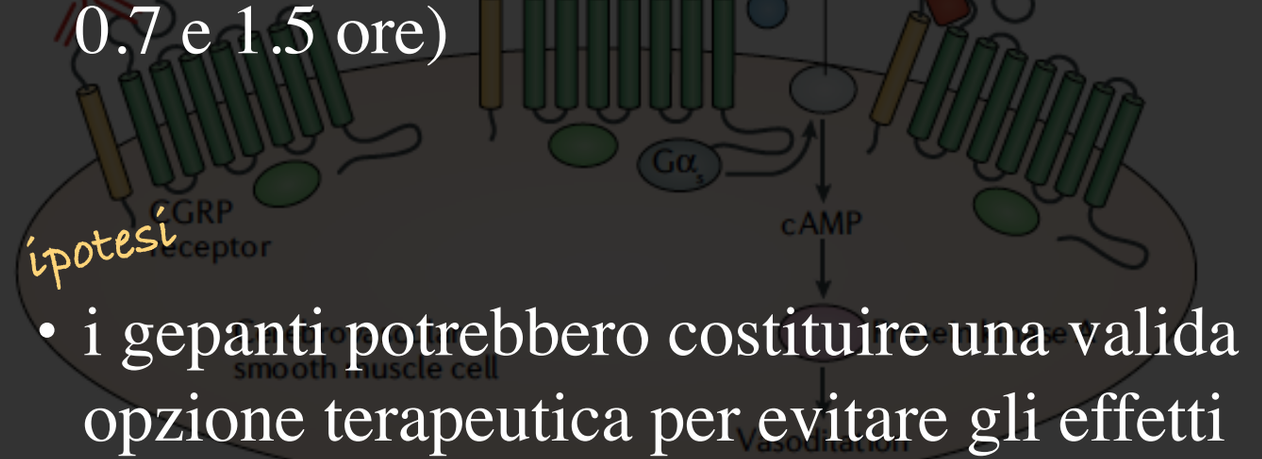


L. Edvinsson et al. Nature Review, 2018



osservazione

- gepanti sono piccole molecole agoniste per recettore CGRP
- sono dotate di alta affinità, bloccando gli effetti neurovascolari del CGRP
- non hanno azione vasocostrittrice diretta
- gepanti hanno emivita breve (Tmax tra 0.7 e 1.5 ore)



ipotesi

- i gepanti potrebbero costituire una valida opzione terapeutica per evitare gli effetti indesiderati dei triptani

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gepanti

gepanti

olcegepant (BIBN4096BS) → formulazione ev, buona efficacia Vs placebo → scarsa maneggevolezza

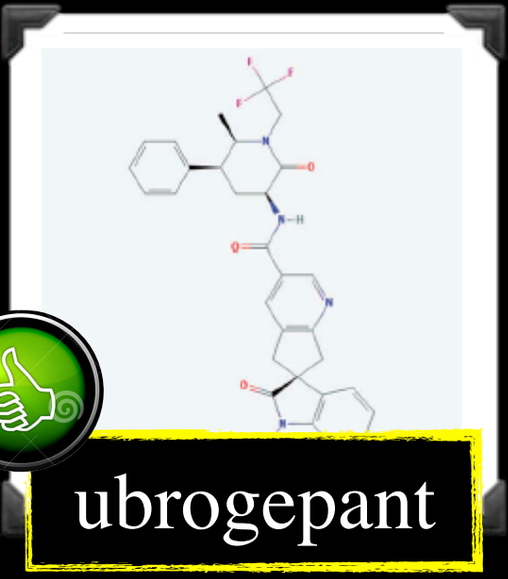
telcagepant (MK-0974) → orale, efficacia in fase II superiore a placebo e comparabile a zolmitriptan → testato in profilassi ha dato epatotossicità

MK-3207 → orale, efficacia in fase II superiore a placebo → epatotossicità

BI 44370 TA → orale, 400 mg, efficacia in fase II superiore a placebo e comparabile a eletriptan 40 → ?

Sicurezza ed efficacia di Ubrogepant (1 mg, 10 mg, 25 mg, 50 mg, 100 mg) testata in studio fase IIb (multicenter, randomized, double-blind, placebo-controlled trial)

Due studi di fase III hanno dato conferma di sicurezza ed efficacia (multicenter randomised, double-blind, placebo-controlled trials)
ubrogepant 50 mg e 100 mg Vs placebo (Achieve 1)
ubrogepant 25 mg and 50 mg Vs placebo (Achieve 2)



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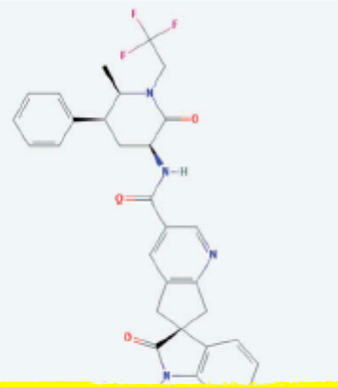
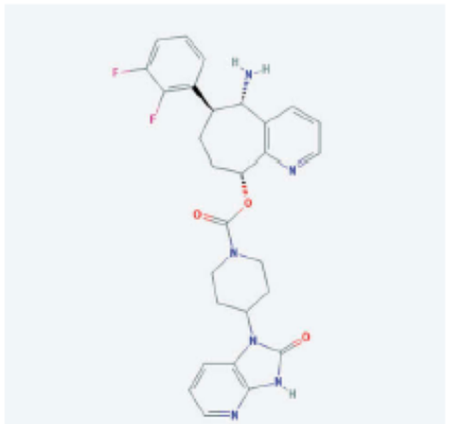


ubrogepant



rimegepant

sicurezza ed efficacia di Rimegepant testata in studio di fase II (double-blind, randomized, placebo-controlled, dose-ranging trial) - 885 partecipanti

endpoint primario: libertà dal dolore a 2 ore più elevato nel braccio Rimegepant 150 mg (32.9%) Vs altre dosi e placebo ($p < 0.001$) - 15.3% nel placebo.
Sumatriptan 100 mg di poco superiore a tutte le dosi di Rimegepant (35%)

Rimegepant non da “triptan syndrome”

E’ in corso uno studio prospettico (multicentre open-label long-term safety study) (dati previsti a fine 2019)

Sicurezza ed efficacia di Ubrogepant (1 mg, 10 mg, 25 mg, 50 mg, 100 mg) testata in studio fase IIb (multicenter, randomized, double-blind, placebo-controlled trial)

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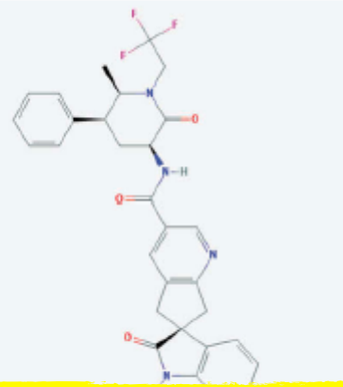
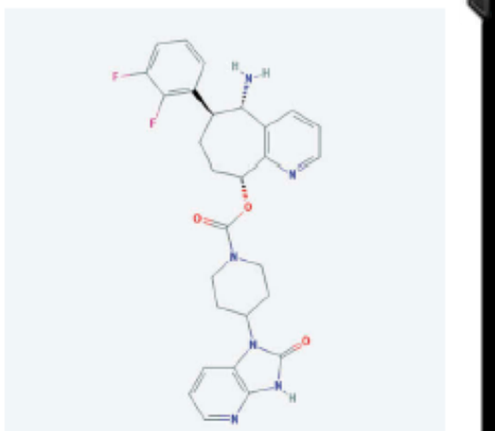


ubrogepant



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E’ in corso uno studio prospettico (multicentre open-label long-term safety study) (dati previsti a fine 2019)

BHV 3500

E’ in corso un trial per valutare efficacia e sicurezza della sommistrazione intranasale di questo piccolo antagonista CGRP

nuove “ricette” con vecchi “ingredienti”

- autoiniettore di 3 mg di sumatriptan (DFN-11)
- efficacia e tollerabilità simile a 6 mg
- < triptan syndrome

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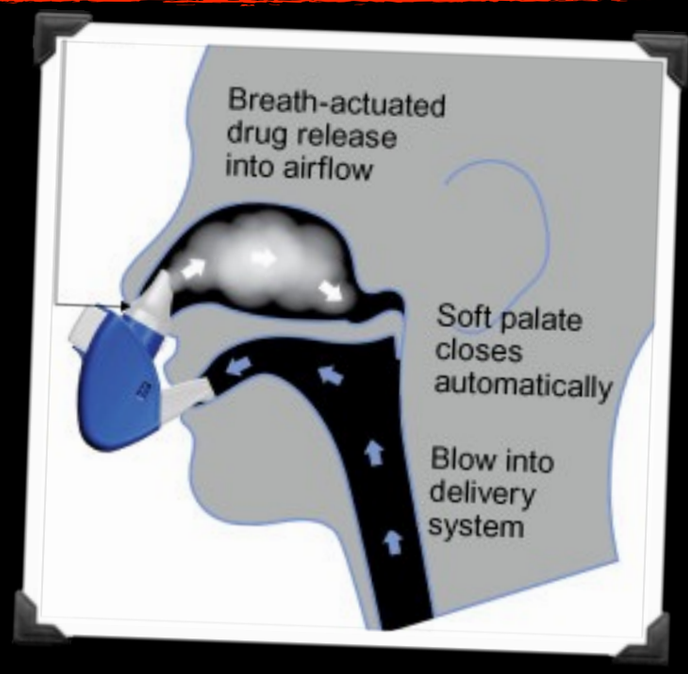
- autoiniettore di 3 mg di sumatriptan (DFN-11)
- efficacia e tollerabilità simile a 6 mg
- < triptan syndrome

- sumatriptan intranasale con sistema AVP-825
- più efficiente dei normali spray
- risposta a 30’ migliore della maggior parte dei triptani
- dati migliori rispetto a suma 100 mg per pain relief e pain free a 2 ore
- approvato in gennaio 2016 da FDA



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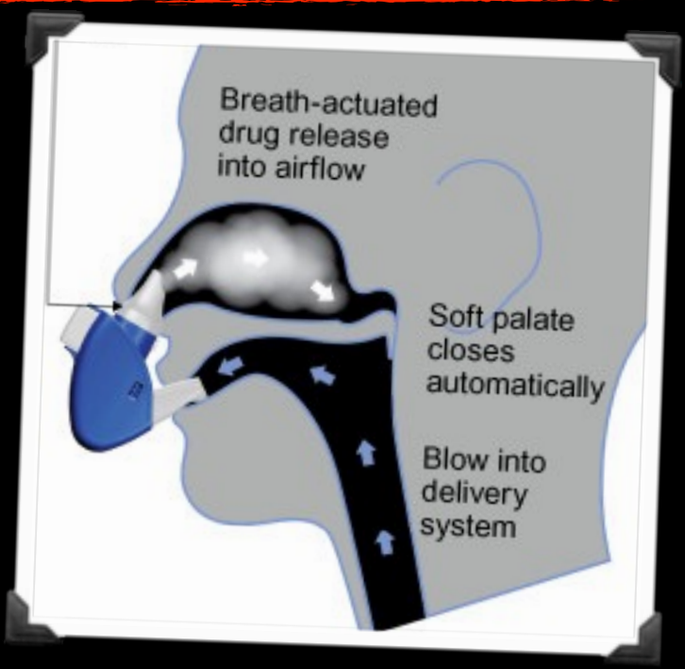
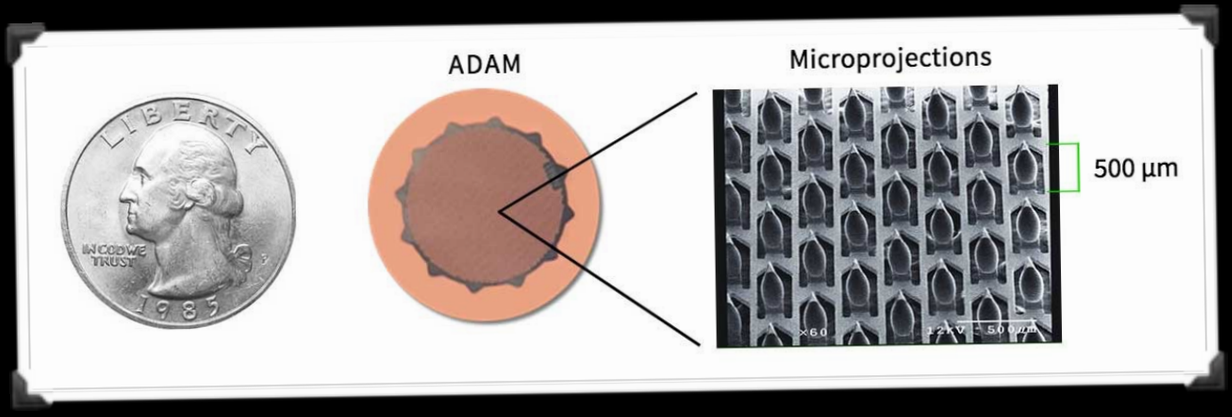


- zolmitriptan 3.8 mg somministrato tramite cerotto
- Adhesive Dermally-Applied Microarray (ADAM)
- circa 42% dei pazienti pain free a 2 ore e circa 70% liberi da sintomi associati



la gestione della crisi

approccio graduale

fans

associazione con antiemetici

triptani

a partire dalla somministrazione di fans e analgesici, tappe successive in crescendo, se inefficace il precedente trattamento

dolore lieve

fans o analgesici

approccio stratificato

sintomi vegetativi disabilitanti

associare antiemetico

dolore moderato - forte

triptano

prevede una preliminare valutazione dell'intensità degli attacchi e quindi "ab initio" la prescrizione terapeutica più adeguata

la gestione della crisi

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(lasmitidan - gepanti)

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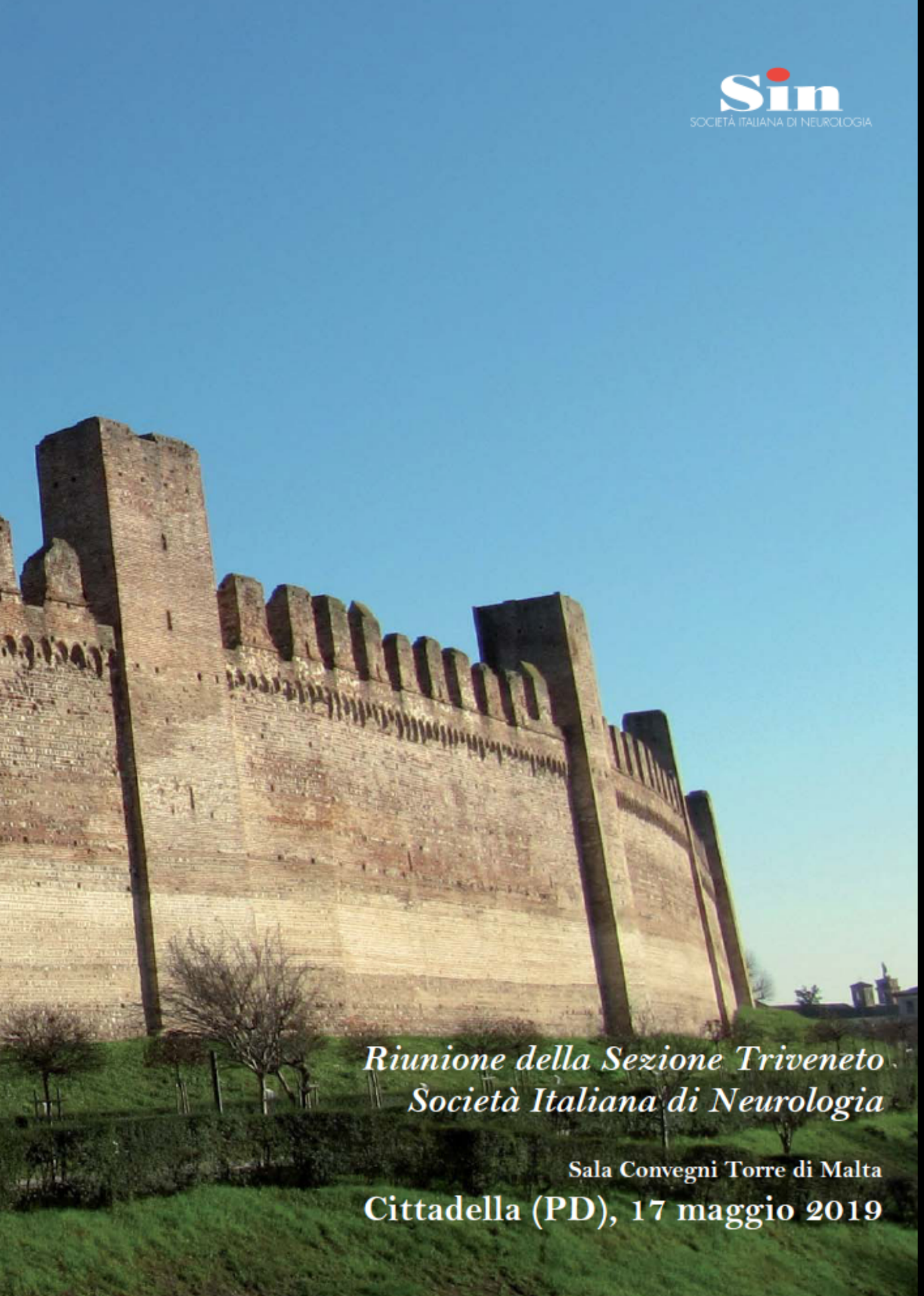
Sin
SOCIETÀ ITALIANA DI NEUROLOGIA



Riunione della Sezione Triveneto
Società Italiana di Neurologia

Sala Convegni Torre di Malta

Cittadella (PD), 17 maggio 2019

AGENDA

dalla parte del paziente

terapia d'attacco

terapia di profilassi

l'emicrania è per gran parte autogestita

Bigal et al. Neurology 2008,71:559–66
D'Amico et al., Neuropsichyatric Disease and Treatment 2008:4(6)1155-1167
Cevoli et al., Cephalagia 2009, 29:1285-93
Dodick et al. Headache 2016

l'emicrania è per gran parte autogestita

solo dal 3% al 13% dei pazienti con emicrania assume un trattamento preventivo

In Italia solo il *4.8%* dei pazienti con emicrania ha usato un trattamento preventivo

Negli Stati Uniti solo il *4.5%* pazienti con diagnosi di emicrania cronica ha ricevuto una prescrizione per trattamento preventivo

Bigal et al. Neurology 2008,71:559–66
D'Amico et al., Neuropsichyatric Disease and Treatment 2008:4(6)1155-1167
Cevoli et al., Cephalagia 2009, 29:1285-93
Dodick et al. Headache 2016

emicrania: ruolo della PROFILASSI

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

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

emicrania: i fallimenti

emicrania: i fallimenti

Cephalalgia
An International Journal of Headache
International Headache Society

Cephalalgia
2017, Vol. 37(5) 470–485

DOI: 10.1177/0333102416678382
journals.sagepub.com/home/cep
SAGE

Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis

Zsolt Hepp[1], David W Dodick[2], Sepideh F Varon[1], Jenny Chia[1], Nitya Matthew[1], Patrick Gillard[1], Ryan N Hansen[3] and Emily Beth Devine[3]

"Persistence to commonly prescribed oral migraine-preventive medications is poor, with higher discontinuation rates in patients who cycle through various medications"

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

emicrania: i fallimenti

Cephalalgia
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International Headache Society

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SAGE

Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: [illegible] claims analysis

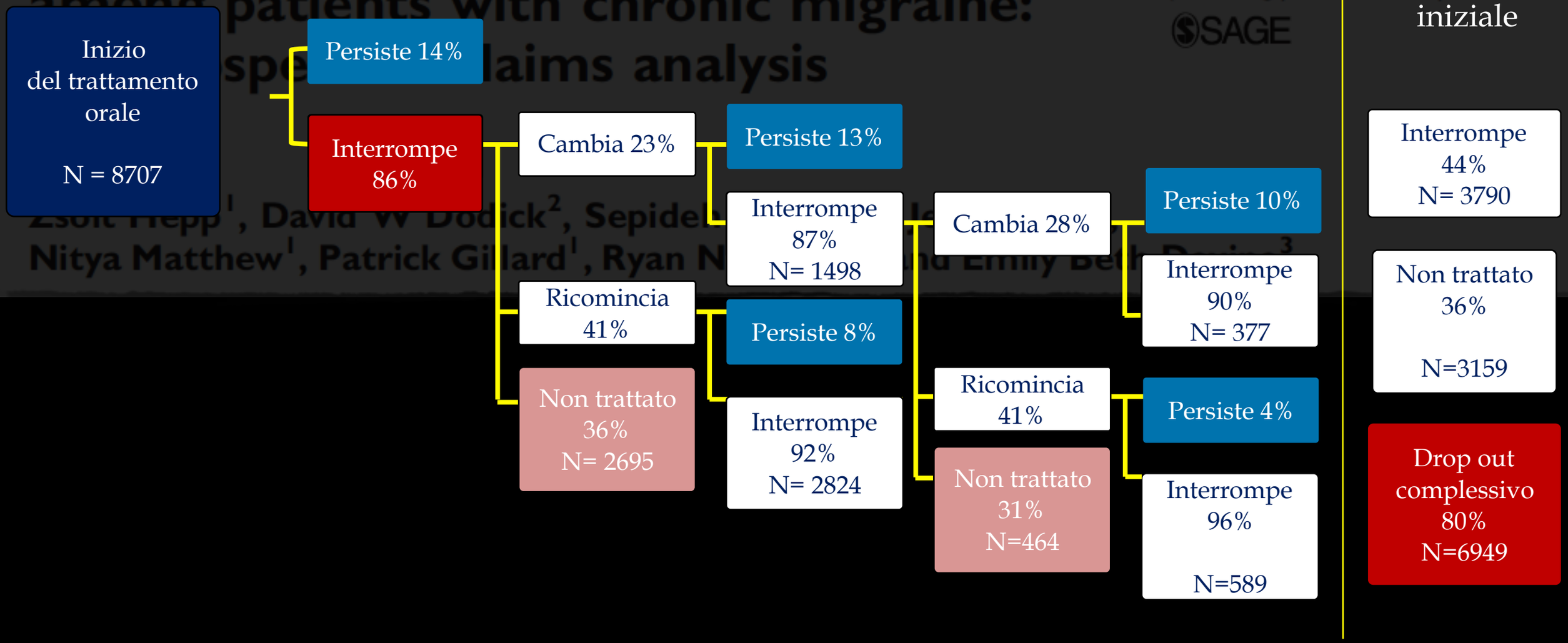
Zsolt Hepp[1], David W Dodick[2], Sepideh [illegible], Nitya Matthew[1], Patrick Gillard[1], Ryan N[illegible] and Emily Bech [illegible][3]

Primo trattamento orale

Secondo trattamento orale

Terzo trattamento orale

Dopo 3 trattamenti orali rispetto alla popolazione iniziale



Adattata da Hepp et al., Cephalalgia 2017 Apr;37(5):470-485.

emicrania: ruolo del DIARIO

emicrania: ruolo del DIARIO

PER LA TERAPIA DELLE CEFALEE PRIMARIE

2011

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PER LA TERAPIA DELLE

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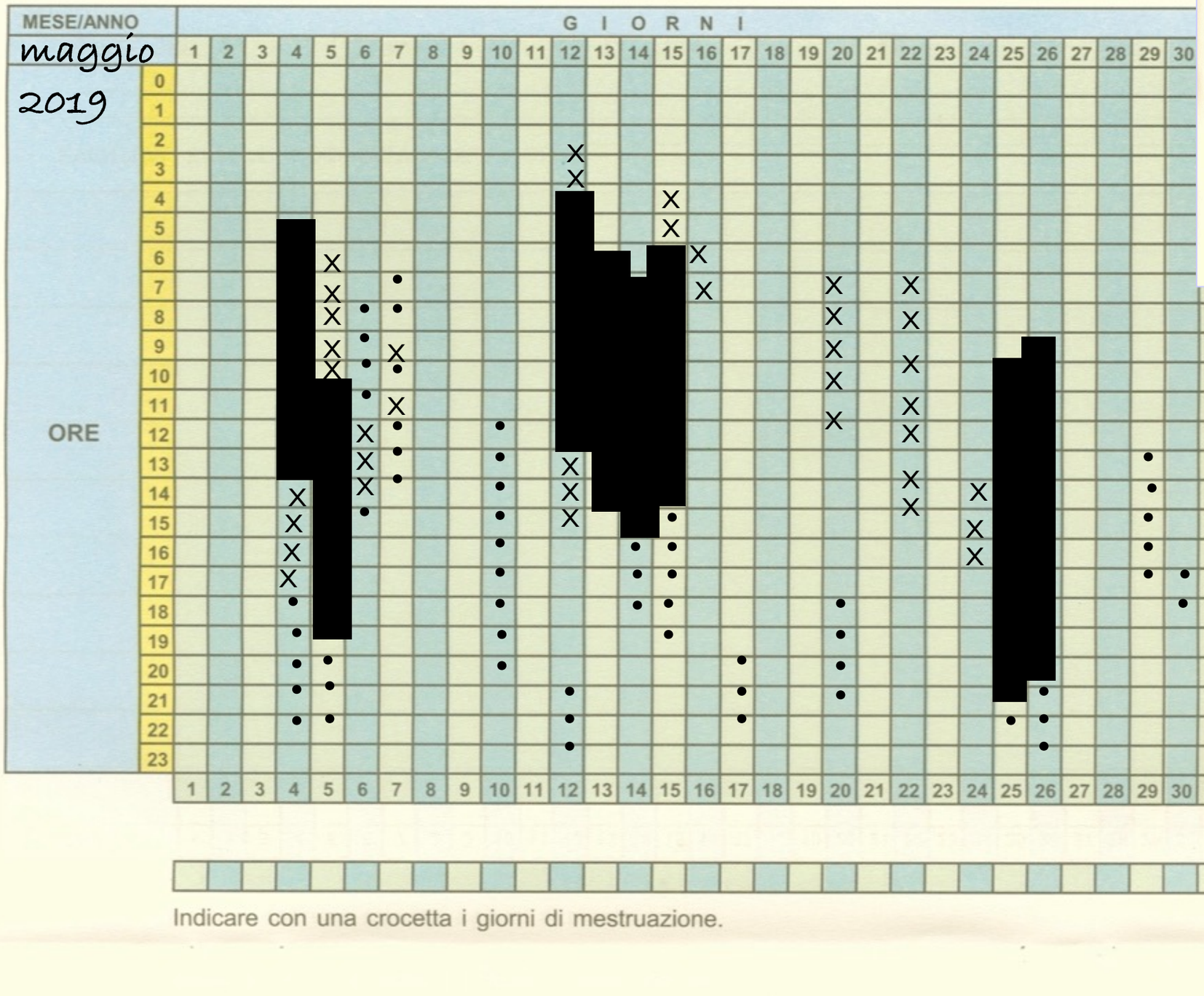

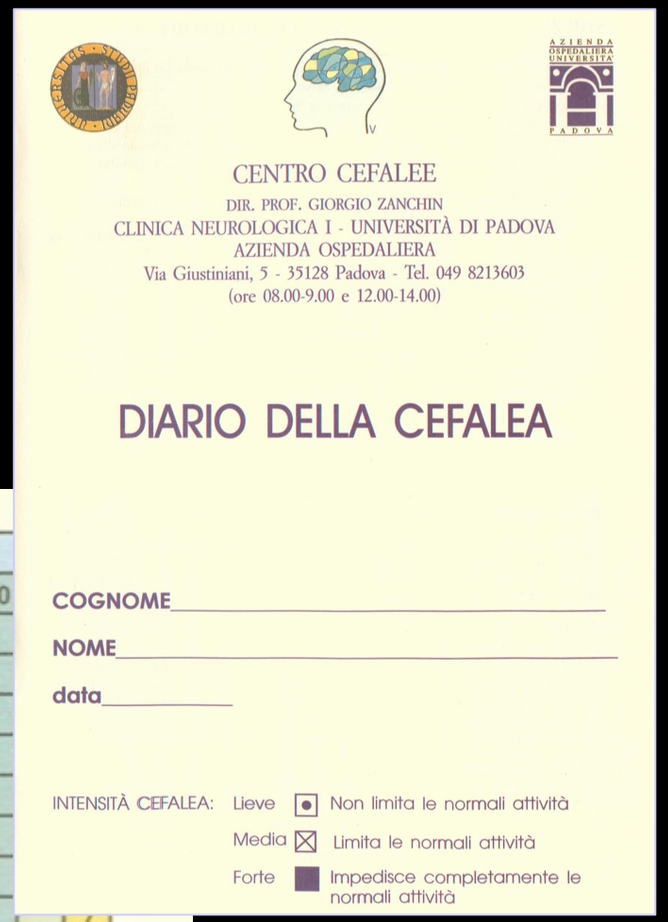

CENTRO CEFALEE

DIR. PROF. GIORGIO ZANCHIN
CLINICA NEUROLOGICA I - UNIVERSITÀ DI PADOVA
AZIENDA OSPEDALIERA
Via Giustiniani, 5 - 35128 Padova - Tel. 049 8213603
(ore 08.00-9.00 e 12.00-14.00)

DIARIO DELLA CEFALEA

COGNOME_____

NOME_____

data_____

INTENSITÀ CEFALEA:
- Lieve — Non limita le normali attività
- Media — Limita le normali attività
- Forte — Impedisce completamente le normali attività

linee guida sisc

LINEE GUIDA PER LA TERAPIA DELLE CEFALEE PRIMARIE

2011

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SOCIETÀ ITALIANA PER LO STUDIO DELLE CEFALEE

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Approccio terapeutico

- **La sola terapia sintomatica è indicata:**

  Quando una cefalea disabilitante sia presente per meno di 4 giorni al mese (16).

- **La terapia di profilassi deve essere instaurata:**

  accanto alla terapia sintomatica, se sono presenti almeno 4 giorni al mese di cefalea disabilitante. Si può impostare una terapia di profilassi anche quando gli attacchi disabilitanti siano presenti per meno di 4 giorni al mese ma non siano responsivi alla terapia sintomatica.

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TRATTAMENTO FARMACOLOGICO DI PROFILASSI DELL'EMICRANIA

Principi generali:

Prima di intraprendere un trattamento di profilassi è buona norma cercare di identificare tutti i fattori scatenanti ed aggravanti (vedi Tabella 4) attraverso l'uso del diario e provvedere, quando è possibile, alla loro eliminazione, che può di per sé contribuire a ridurre la frequenza e/o l'intensità degli attacchi (648).
Gli obiettivi principali di una terapia di profilassi sono quelli di ridurre la frequenza degli attacchi e la disabilità del paziente emicranico, migliorando la sua qualità di vita e riportandolo ad una efficienza fisica accettabile. Un trattamento si considera efficace quando riduce di almeno il 50% la frequenza degli attacchi (649).
I benefici clinici possono comparire a distanza di 1-3 mesi dall'inizio della terapia (650).
In caso di resistenza ad un trattamento di profilassi, può essere intrapreso un nuovo trattamento farmacologico (648, 650).

osservazione

ipotesi

deduzione

esperimento

L. Edvinsson et al. Nature Review, 2018

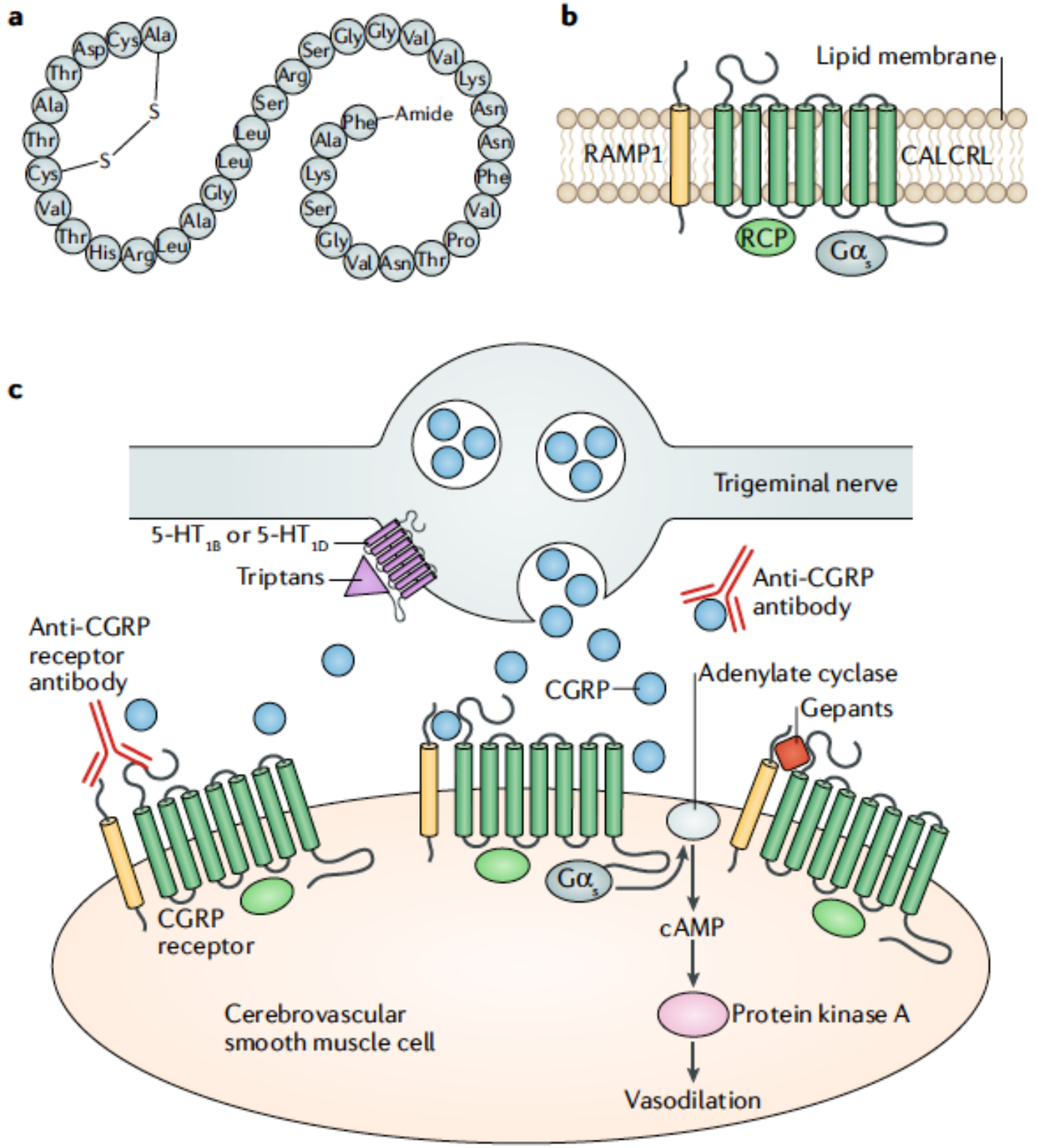
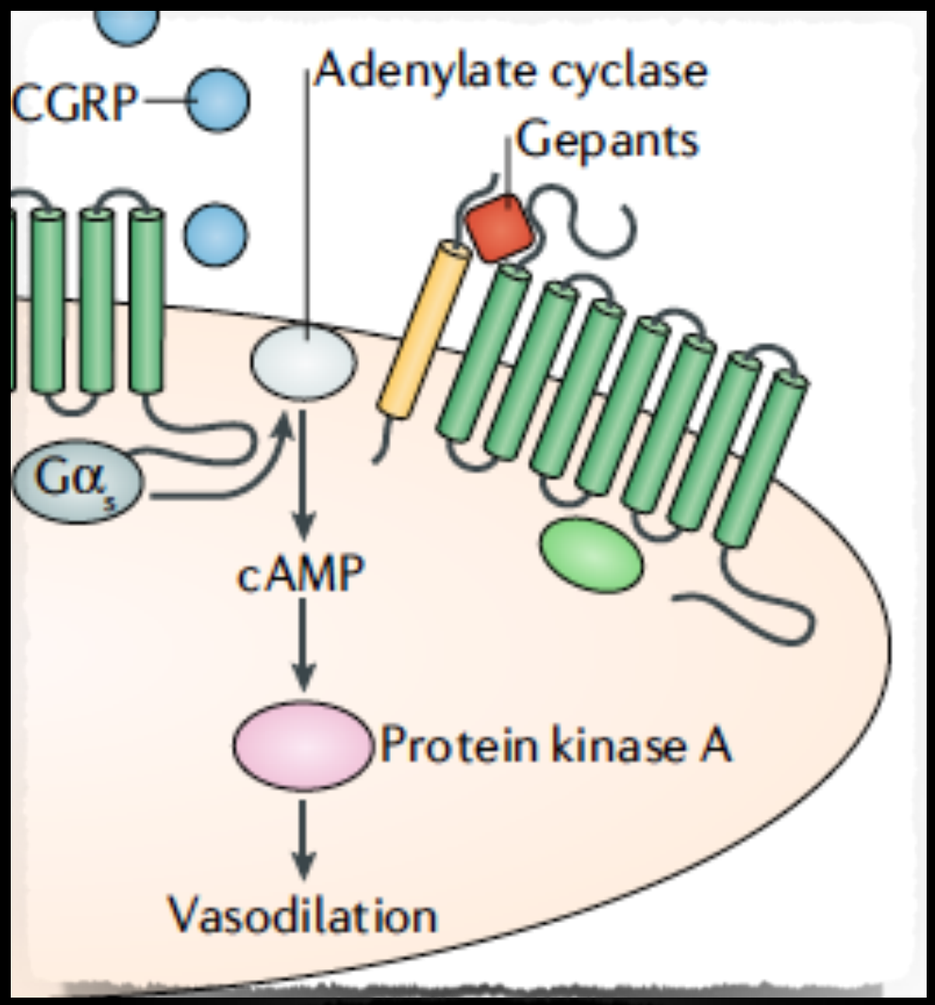
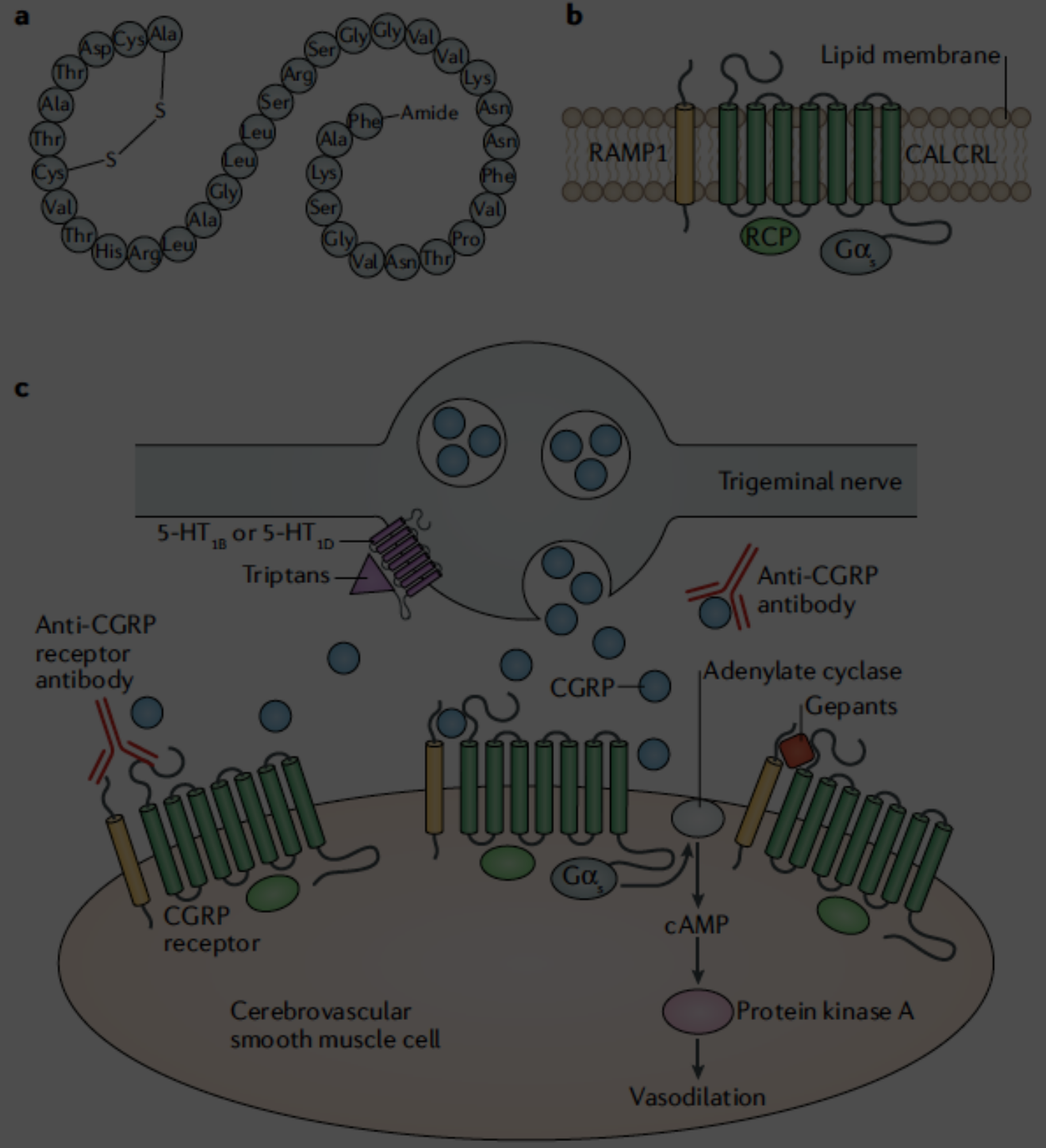


Fig. 2 | **Components of CGRP transmission and sites of action for CGRP-related migraine therapies. a** | Amino acid structure of human α-type calcitonin gene-related peptide (CGRP). **b** | The CGRP receptor complex, which consists of the two integral membrane proteins calcitonin receptor-like receptor (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.

gepanti



L. Edvinsson et al. Nature Review, 2018



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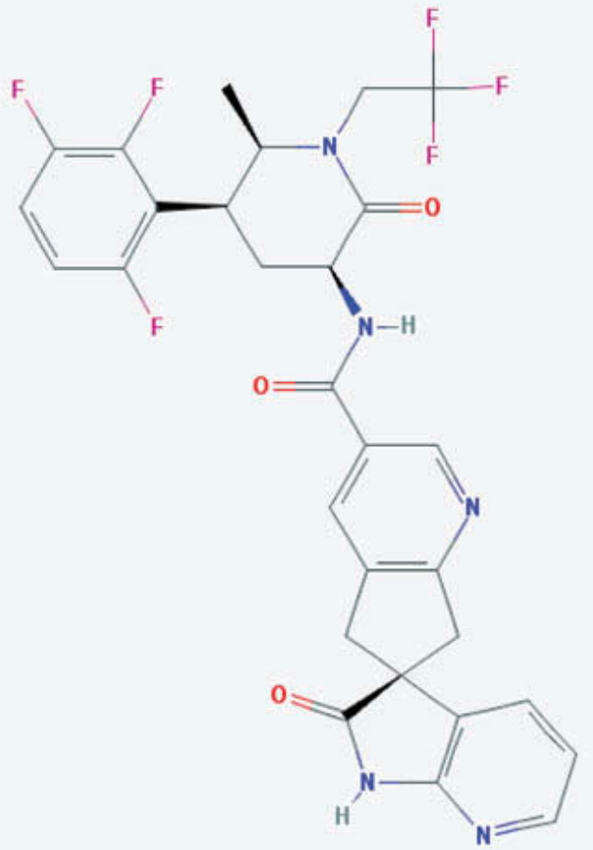
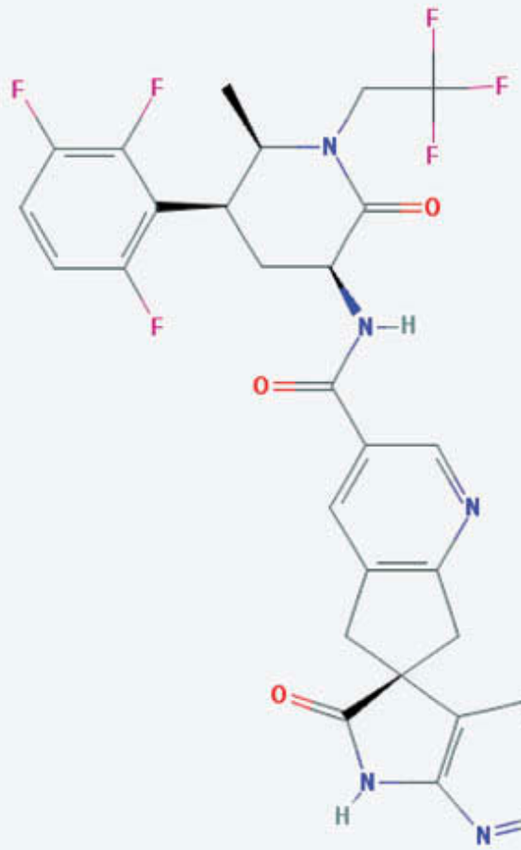
atogepant

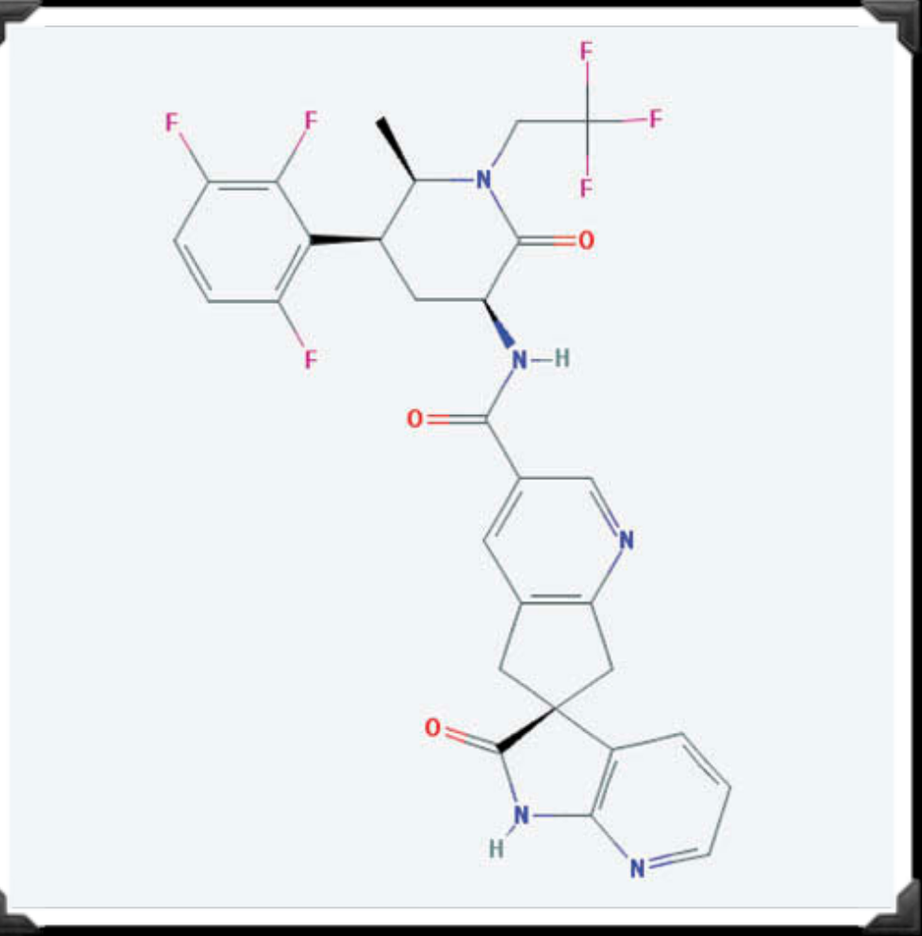


atogepant



- unico gepante utilizzato in studi di prevenzione, causa maggiore emivita degli altri

atogepant



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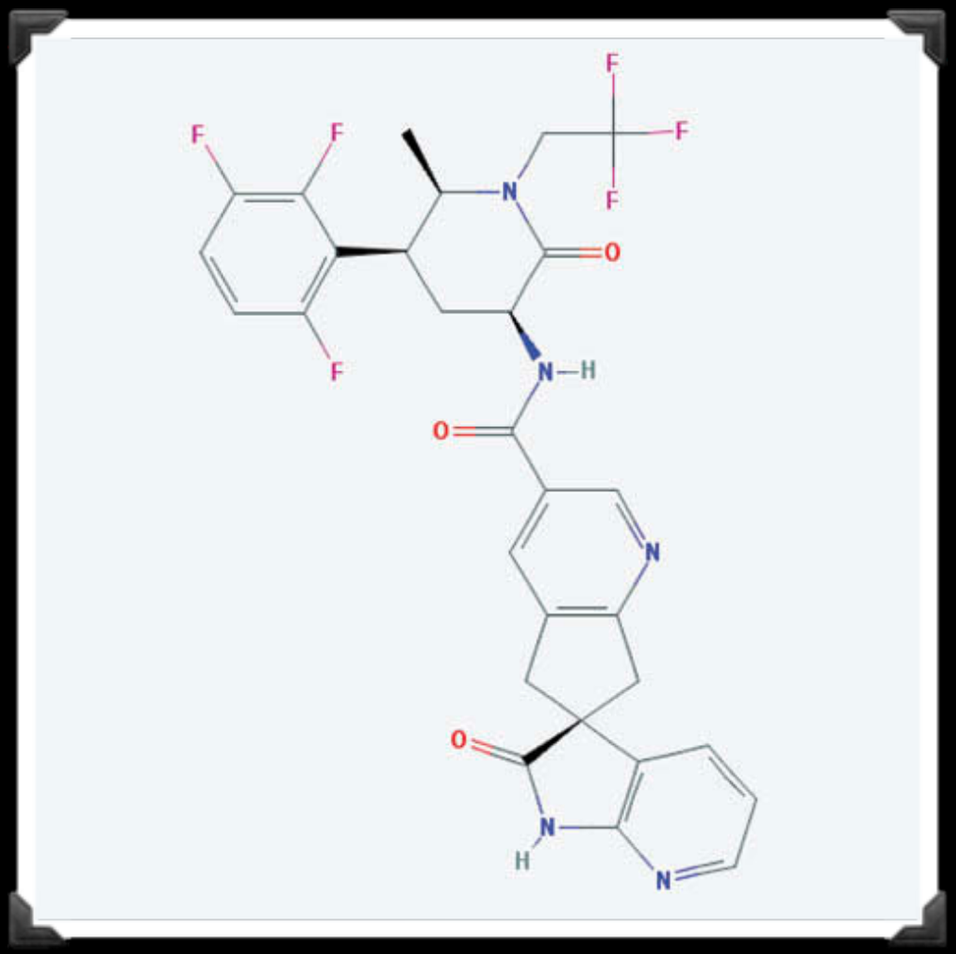
- studio di fase II/III ha valutato efficacia e sicurezza di atogepant a differenti dosaggi Vs placebo (multicentre randomized, double-blind, placebo controlled, parallel-group) in prevenzione di emicrania episodica (NCT02848326)

atogepant



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- end point primario raggiunto per tutti i bracci attivi (riduzione dal basale dei giorni di emicrania in 12-settimane di trattamento)

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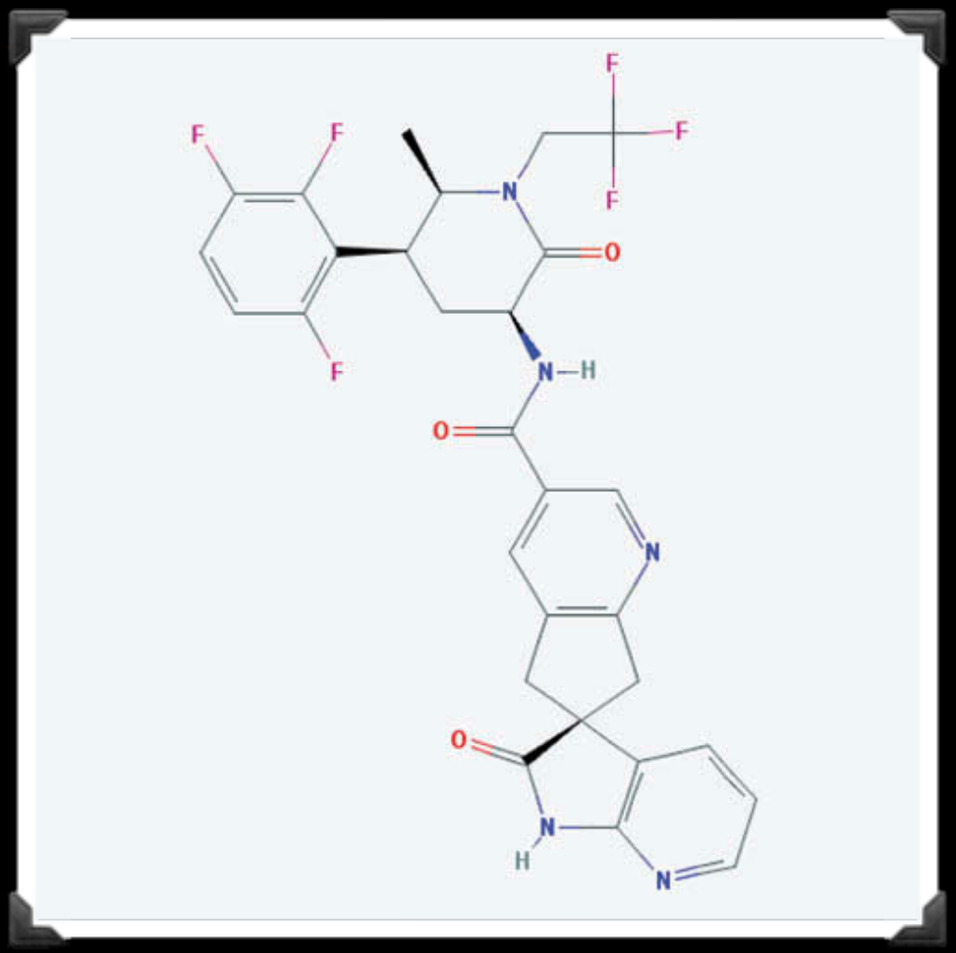

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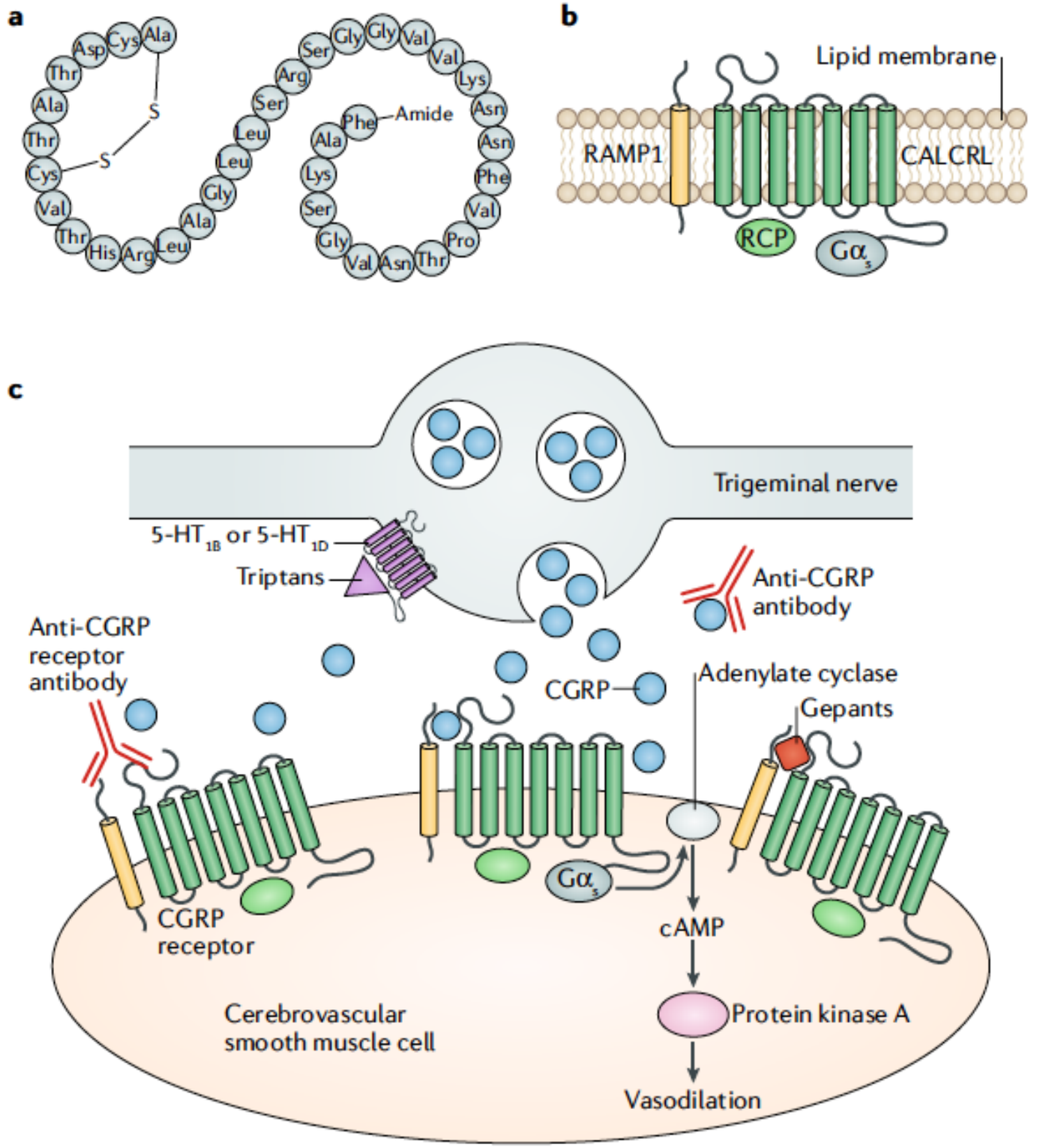
- end point primario raggiunto per tutti i bracci attivi (riduzione dal basale dei giorni di emicrania in 12-settimane di trattamento)

- atogepant appare ben tollerato, i più comuni eventi avversi sono stati: nausea, astenia, stipsi, nasofaringite, infezioni del tratto urinario;
- profilo di sicurezza epatico sovrapponibile a placebo

L. Edvinsson et al. Nature Review, 2018



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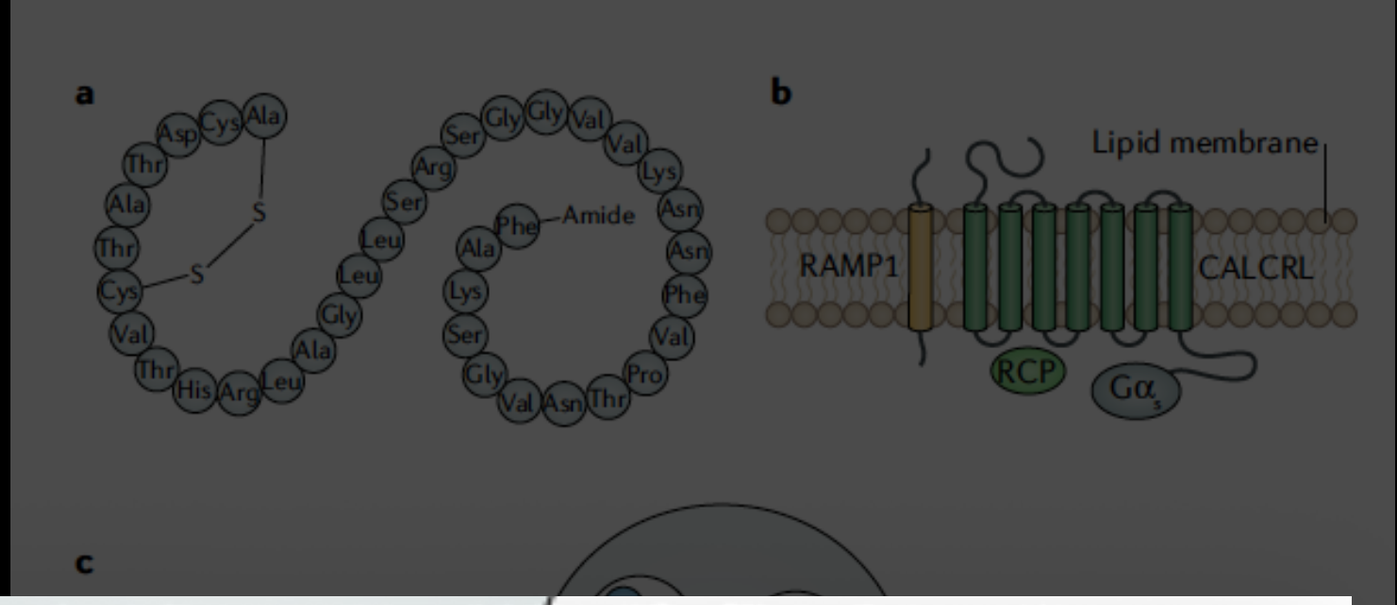
anticorpi monoclonali



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L. Edvinsson et al. Nature Review, 2018

anticorpi monoclonali

anticorpi monoclonali

Erenumab	Galcanezumab	Fremanezumab	Eptinezumab

anticorpi monoclonali

	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
target	CGRP receptor	CGRP ligand	CGRP ligand	CGRP ligand

anticorpi monoclonali

	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
target	**CGRP receptor**	**CGRP ligand**	**CGRP ligand**	**CGRP ligand**
dosing	Monthly	Monthly	Monthly, Quarterly	Quarterly

anticorpi monoclonali

	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
target	**CGRP receptor**	**CGRP ligand**	**CGRP ligand**	**CGRP ligand**
dosing	Monthly	Monthly	Monthly, Quarterly	Quarterly
ROA	s.c. injection	s.c. injection	s.c. injection	i.v. infusion

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dosing	Monthly	Monthly	Monthly, Quarterly	Quarterly
ROA	s.c. injection	s.c. injection	s.c. injection	i.v. infusion
auto injector	Yes	Yes	No (Delayed)	N/A

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	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
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dosing	Monthly	Monthly	Monthly, Quarterly	Quarterly
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$t_{½}$	21 days	~25–30 days	32 days	~32 days

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IgG Subtype	IgG2	IgG4	IgG2Δa	IgG1

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dosing	Monthly	Monthly	Monthly, Quarterly	Quarterly
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IgG Subtype	IgG2	IgG4	IgG2Δa	IgG1
Human sequences	human (100% human)	fully humanized (>95% human)	fully humanized (>95% human)	Humanized (>90% human)

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target	**CGRP receptor**	**CGRP ligand**	**CGRP ligand**	**CGRP ligand**
dosing	Monthly	Monthly	Monthly, Quarterly	Quarterly
ROA	s.c. injection	s.c. injection	s.c. injection	i.v. infusion
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Human sequences	human (100% human)	fully humanized (>95% human)	fully humanized (>95% human)	Humanized (>90% human)
Expression system	Chinese hamster ovary (CHO)	Murine	Murine	Yeast (*Pichia pastoris*)

percorso trial clinici

percorso trial clinici

		Phase II
Erenumab AMGEN NOVARTIS	EM	NCT02630459 NCT01952574
	CM	NCT02066415 NCT02174861

percorso trial clinici

		Phase II
Erenumab AMGEN NOVARTIS	EM	NCT02630459 NCT01952574
	CM	NCT02066415 NCT02174861
Galcanezumab Lilly	EM	NCT02163993 NCT01625988

percorso trial clinici

		Phase II
Erenumab (AMGEN, NOVARTIS)	EM	NCT02630459 NCT01952574
	CM	NCT02066415 NCT02174861
Galcanezumab (Lilly)	EM	NCT02163993 NCT01625988
Fremanezumab (teva)	EM	NCT02025556
	CM	NCT02021773

percorso trial clinici

		Phase II
Erenumab (AMGEN, NOVARTIS)	EM	NCT02630459 NCT01952574
	CM	NCT02066415 NCT02174861
Galcanezumab (Lilly)	EM	NCT02163993 NCT01625988
Fremanezumab (teva)	EM	NCT02025556
	CM	NCT02021773
Eptinezumab (ALDER BIOPHARMACEUTICALS)	EM	NCT01772524
	CM	NCT02275117

percorso trial clinici

		Phase II		Phase III		Received Study Drug Phase III
Erenumab AMGEN NOVARTIS	EM	NCT02630459 NCT01952574	EM	STRIVE: NCT02456740 ARISE: NCT02483585	2194*
	CM	NCT02066415 NCT02174861			
Galcanezumab Lilly	EM	NCT02163993 NCT01625988	EM	EVOLVE-1: NCT02614183 EVOLVE-2: NCT02614196	2028
			CM	REGAIN: NCT02614261	
Fremanezumab teva	EM	NCT02025556	EM	HALO EM: NCT02629861	2004
	CM	NCT02021773	CM	HALO CM: NCT02621931	
Eptinezumab ALDER BIOPHARMACEUTICALS	EM	NCT01772524	EM	PROMISE-1: NCT02559895	1960
	CM	NCT02275117	CM	PROMISE-2: NCT02974153	

*Numbers phase 2 CM included

emicrania episodica

emicrania episodica

riduzione giorni di emicrania

emicrania episodica

				riduzione giorni di emicrania			
		fase		attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	STRIVE	III	70 mg/mese	- 3.2	- 1.8	- 1.4	43%

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						(< 0.0001)	placebo 26.6%

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	ARISE	III	70 mg/mese	- 2.9	- 1.8	-1.0	40%
						(< 0.0001)	placebo 29.5%

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GALCANEZUMAB	EVOLVE 1	III	120 mg/mese (+240 ld)	- 4.7	-2.8	- 1.9	62%

emicrania episodica

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			240 mg/mese	- 4.6		- 1.8	61%
						(< 0.0001)	placebo 38.6%

emicrania episodica

		fase		riduzione giorni di emicrania attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	STRIVE	III	70 mg/mese	- 3.2	- 1.8	- 1.4	43%
			140 mg/mese	- 3.7		- 1.9	50%
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			240 mg/mese	- 4.6		- 1.8	61%
						(< 0.0001)	placebo 38.6%
	EVOLVE 2	III	120 mg/mese	- 4.3	- 2.3	- 2.0	59%

emicrania episodica

		fase		riduzione giorni di emicrania attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	STRIVE	III	70 mg/mese	- 3.2	- 1.8	- 1.4	43%
			140 mg/mese	- 3.7		- 1.9	50%
						(< 0.0001)	placebo 26.6%
	ARISE	III	70 mg/mese	- 2.9	- 1.8	-1.0	40%
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			240 mg/mese	- 4.6		- 1.8	61%
						(< 0.0001)	placebo 38.6%
	EVOLVE 2	III	120 mg/mese	- 4.3	- 2.3	- 2.0	59%
			240 mg/mese	- 4.2		- 1.9	57%
							placebo 36%

emicrania episodica

		fase		riduzione giorni di emicrania attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	STRIVE	III	70 mg/mese	- 3.2	- 1.8	- 1.4	43%
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	ARISE	III	70 mg/mese	- 2.9	- 1.8	-1.0	40%
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			240 mg/mese	- 4.6		- 1.8	61%
						(< 0.0001)	placebo 38.6%
	EVOLVE 2	III	120 mg/mese	- 4.3	- 2.3	- 2.0	59%
			240 mg/mese	- 4.2		- 1.9	57%
							placebo 36%
FREMANEZUMAB	Bigal, 2015	IIb	225 mg/mese	- 6.2	- 3.4	- 2.8	53%

emicrania episodica

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			240 mg/mese	- 4.2		- 1.9	57%
							placebo 36%
FREMANEZUMAB	Bigal, 2015	IIb	225 mg/mese	- 6.2	- 3.4	- 2.8	53%
			675 mg/mese	- 6.0		- 2.6	59%
						(< 0.00001)	placebo 28%

emicrania episodica

		fase		riduzione giorni di emicrania attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	STRIVE	III	70 mg/mese	- 3.2	- 1.8	- 1.4	43%
			140 mg/mese	- 3.7		- 1.9	50%
						(< 0.0001)	placebo 26.6%
	ARISE	III	70 mg/mese	- 2.9	- 1.8	-1.0	40%
						(< 0.0001)	placebo 29.5%
GALCANEZUMAB	EVOLVE 1	III	120 mg/mese (+240 ld)	- 4.7	-2.8	- 1.9	62%
			240 mg/mese	- 4.6		- 1.8	61%
						(< 0.0001)	placebo 38.6%
	EVOLVE 2	III	120 mg/mese	- 4.3	- 2.3	- 2.0	59%
			240 mg/mese	- 4.2		- 1.9	57%
							placebo 36%
FREMANEZUMAB	Bigal, 2015	IIb	225 mg/mese	- 6.2	- 3.4	- 2.8	53%
			675 mg/mese	- 6.0		- 2.6	59%
						(< 0.00001)	placebo 28%
	HALO EM	III	225 mg/mese	- 4.0	- 2.6	- 1.5	48%

emicrania episodica

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			675 mg/mese	- 6.0		- 2.6	59%
						(< 0.00001)	placebo 28%
	HALO EM	III	225 mg/mese	- 4.0	- 2.6	- 1.5	48%
			675 mg / 3 mesi	- 3.9		- 1.3	44%
						(< 0.0001)	placebo 27.9%

emicrania episodica

		fase		riduzione giorni di emicrania attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	STRIVE	III	70 mg/mese	- 3.2	- 1.8	- 1.4	43%
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	HALO EM	III	225 mg/mese	- 4.0	- 2.6	- 1.5	48%
			675 mg / 3 mesi	- 3.9		- 1.3	44%
						(< 0.0001)	placebo 27.9%
EPTINEZUMAB	PROMISE 1	III	30 mg ev /3 mesi	- 4.0	- 3.2	-1	50%

emicrania episodica

		fase		riduzione giorni di emicrania attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	STRIVE	III	70 mg/mese	- 3.2	- 1.8	- 1.4	43%
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	HALO EM	III	225 mg/mese	- 4.0	- 2.6	- 1.5	48%
			675 mg / 3 mesi	- 3.9		- 1.3	44%
						(< 0.0001)	placebo 27.9%
EPTINEZUMAB	PROMISE 1	III	30 mg ev /3 mesi	- 4.0	- 3.2	-1	50%
			100 mg ev /3 mesi	- 3.9		p=0.030	50%

emicrania episodica

		fase		riduzione giorni di emicrania attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	STRIVE	III	70 mg/mese	- 3.2	- 1.8	- 1.4	43%
			140 mg/mese	- 3.7		- 1.9	50%
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			675 mg / 3 mesi	- 3.9		- 1.3	44%
						(< 0.0001)	placebo 27.9%
EPTINEZUMAB	PROMISE 1	III	30 mg ev /3 mesi	- 4.0	- 3.2	-1	50%
			100 mg ev /3 mesi	- 3.9		p=0.030	50%
			300 mg ev /3 mesi	- 4.3			56%
							placebo 37.4%

emicrania cronica

emicrania cronica

riduzione giorni di emicrania

emicrania cronica

fase	riduzione giorni di emicrania			> 50% MIGRAINE RESPONDERS
	attivo	placebo	Delta	

emicrania cronica

				riduzione giorni di emicrania			
		fase		attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	Tepper, 2017	II	70 mg/mese	- 6.6	- 4.2	- 2.5	40%

emicrania cronica

		fase		riduzione giorni di emicrania			
				attivo	placebo	Delta	> 50% MIGRAINE RESPONDERS
ERENUMAB	Tepper, 2017	II	70 mg/mese	- 6.6	- 4.2	- 2.5	40%
			140 mg/mese	- 6.6		- 2.5	41%

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			240 mg/mese	- 4.6		- 1.9	OR 2.1
						(< 0.001)	
FREMANEZUMAB	Bigal, 2015	IIb	225 mg/mese (+675 ld)	- 6.04	- 4.2	- 1.8	53%

emicrania cronica

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			240 mg/mese	- 4.6		- 1.9	OR 2.1
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FREMANEZUMAB	Bigal, 2015	IIb	225 mg/mese (+675 ld)	- 6.04	- 4.2	- 1.8	53%
			900 mg/mese	- 6.16		- 1.96	55%

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			240 mg/mese	- 4.6		- 1.9	OR 2.1
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			900 mg/mese	- 6.16		- 1.96	55%
						(0.0023)	placebo 31%

emicrania cronica

		fase		riduzione giorni di emicrania			
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	HALO CM	III	225 mg/mese (+675 ld)	- 4.6	- 2.5	- 2.1	41%

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			900 mg/mese	- 6.16		- 1.96	55%
						(0.0023)	placebo 31%
	HALO CM	III	225 mg/mese (+675 ld)	- 4.6	- 2.5	- 2.1	41%
			675 mg / 3 mesi	- 4.3		- 1.8	38%

emicrania cronica

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GALCANEZUMAB	REGAIN	III	120 mg/mese (+240 ld)	- 4.8	-2.7	- 2.1	OR 2.1
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						(0.0023)	placebo 31%
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			675 mg / 3 mesi	- 4.3		- 1.8	38%
						(< 0.0001)	placebo 18%

emicrania cronica

		fase		riduzione giorni di emicrania			> 50% MIGRAINE RESPONDERS
				attivo	placebo	Delta	
ERENUMAB	Tepper, 2017	II	70 mg/mese	- 6.6	- 4.2	- 2.5	40%
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EPTINEZUMAB	PROMISE 2	III	100 mg/mese	- 7.7	- 5.6	- 2.1	58%

emicrania cronica

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						(0.0023)	placebo 31%
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						(< 0.0001)	placebo 18%
EPTINEZUMAB	PROMISE 2	III	100 mg/mese	- 7.7	- 5.6	- 2.1	58%
			300 mg/mese	- 8.2		- 2.6	61%

emicrania cronica

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			300 mg/mese	- 8.2		- 2.6	61%
						(< 0.0001)	placebo 39.3%

alcune precisazioni

- negli studi popolazione per gran parte femminile (>80%)
- in alcuni studi consentito uso contemporaneo di terapie di profilassi
- generalmente esclusi pazienti che avevano > 2 fallimenti terapeutici
- effetti collaterali sovrapponibili a placebo *(dolore nel sito di iniezione, indurimento nel sito di iniezione, eritema locale, lombalgia, nasofaringite, stipsi, infezione delle vie respiratorie superiori, etc…)*

fonte: Expert’s opinion

con cautela in…

- under 18, per gli ignoti effetti ormonali: ipofisi e ipotalamo sono strutture non “protette” dalla barriera emato-encefalica
- under 25 per gli ignoti effetti a lungo termine
- coloro ad elevato rischio cardio e cerebro-vascolare (diabete, dislipidemie, ipertensione non controllata)
- artrite reumatoide od altre malattie immunologiche
- condizioni cliniche associate a stipsi, in particolare malattia infiammatoria cronica intestinale
- recente chirurgia e/o ferite in guarigione
- fratture recenti od ossa in formazione, osteoporosi/osteopenia
- gravidanza
- disturbi della coagulazione

fonte: Expert’s opinion

Published Ahead of Print on August 23, 2017 as 10.1212/WNL.0000000000004391

Erenumab (AMG 334) in episodic migraine

Interim analysis of an ongoing open-label study

real life

Messoud Ashina, MD, PhD
David Dodick, MD
Peter J. Goadsby, MD, PhD
Uwe Reuter, MD
Stephen Silberstein, MD
Feng Zhang, MS

ABSTRACT

Objective: To assess long-term safety and efficacy of anti–calcitonin gene-related peptide receptor erenumab in patients with episodic migraine (EM).

Methods: Patients enrolled in a 12-week, double-blind, placebo-controlled clinical trial (NCT01952574) who continued in an open-label extension (OLE) study will receive erenumab 70 mg every 4 weeks for up to 5 years. This preplanned interim analysis, conducted after all participants had completed the 1-year open-label follow-up, evaluated changes in monthly migraine

n = 307 hanno continuato 1 anno open label extension
erenumab 70 mg
settimana numero 64 -> drop out del 28%
valutabili n 273

Ashina M et al. Neurology, 2017

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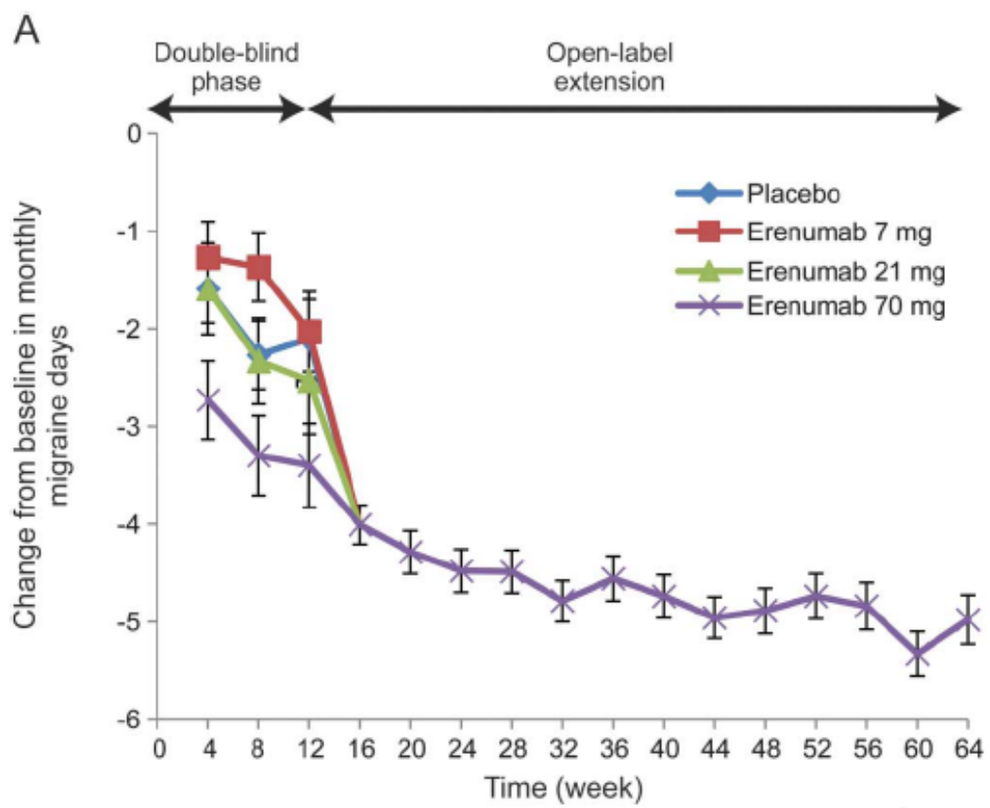
riduzione giorni di cefalea

≥50%	≥75%	100%

Figure 1 Changes in monthly migraine days and migraine-specific medication use



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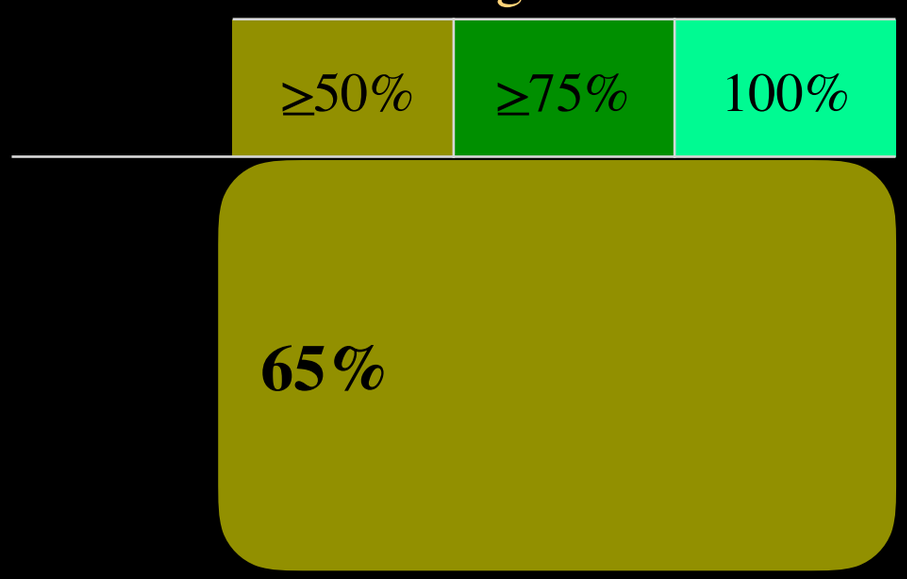
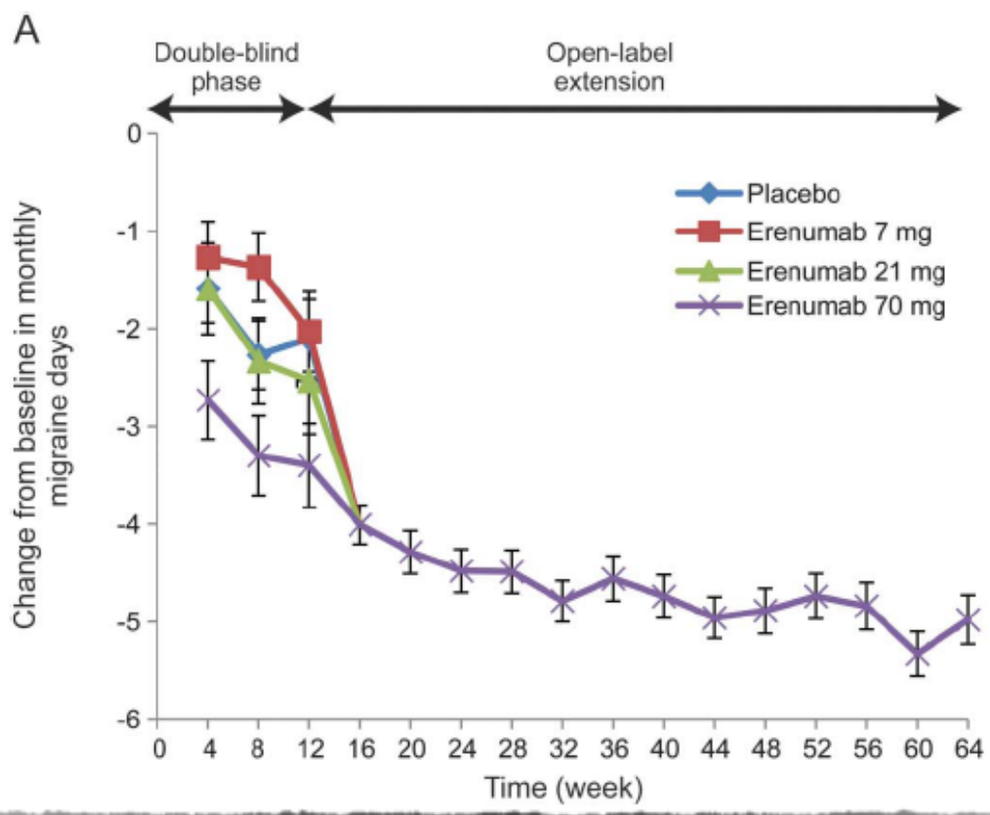


Figure 1 Changes in monthly migraine days and migraine-specific medication use



Ashina M et al. Neurology, 2017

Published Ahead of Print on August 23, 2017 as 10.1212/WNL.0000000000004391

Erenumab (AMG 334) in episodic migraine

Interim analysis of an ongoing open-label study

real life

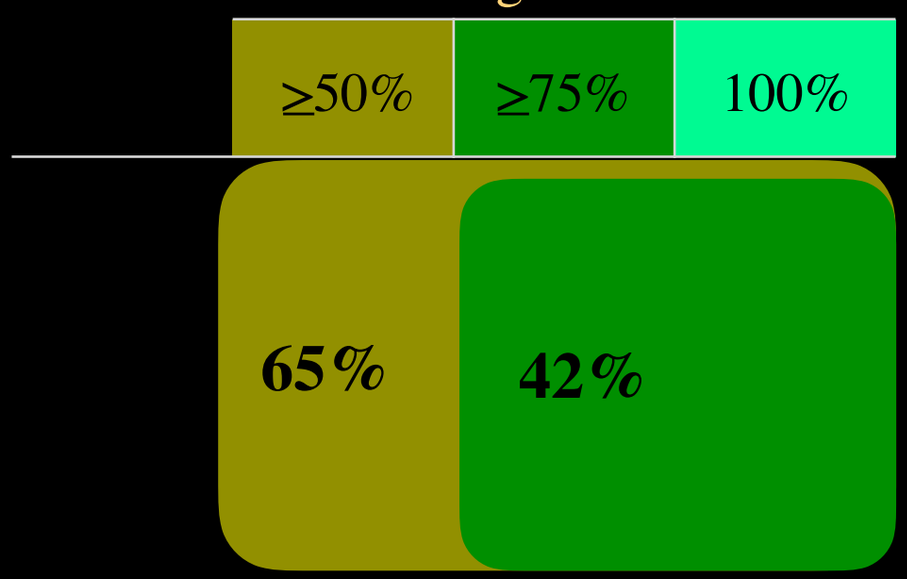
Messoud Ashina, MD, PhD
David Dodick, MD
Peter J. Goadsby, MD, PhD
Uwe Reuter, MD
Stephen Silberstein, MD
Feng Zhang, MS

ABSTRACT

Objective: To assess long-term safety and efficacy of anti–calcitonin gene-related peptide receptor erenumab in patients with episodic migraine (EM).

Methods: Patients enrolled in a 12-week, double-blind, placebo-controlled clinical trial (NCT01952574) who continued in an open-label extension (OLE) study will receive erenumab 70 mg every 4 weeks for up to 5 years. This preplanned interim analysis, conducted after all participants had completed the 1-year open-label fo

n = 307 hanno continuato 1 anno open label extension
erenumab 70 mg
settimana numero 64 -> drop out del 28%
valutabili n 273



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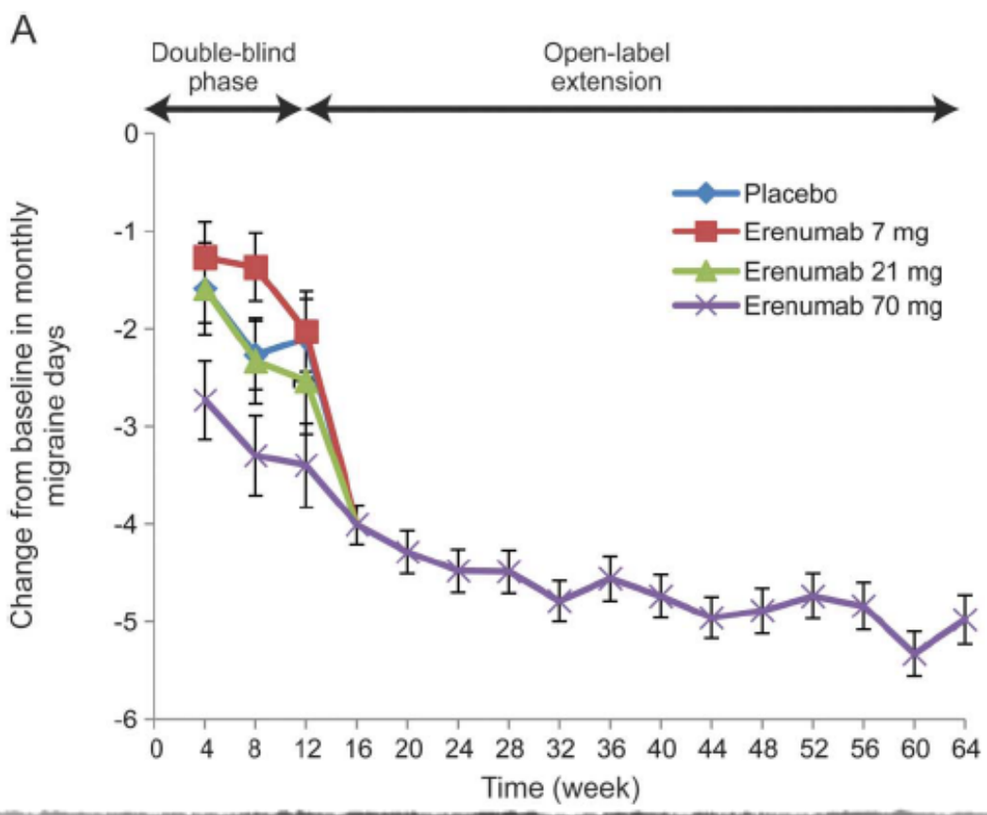

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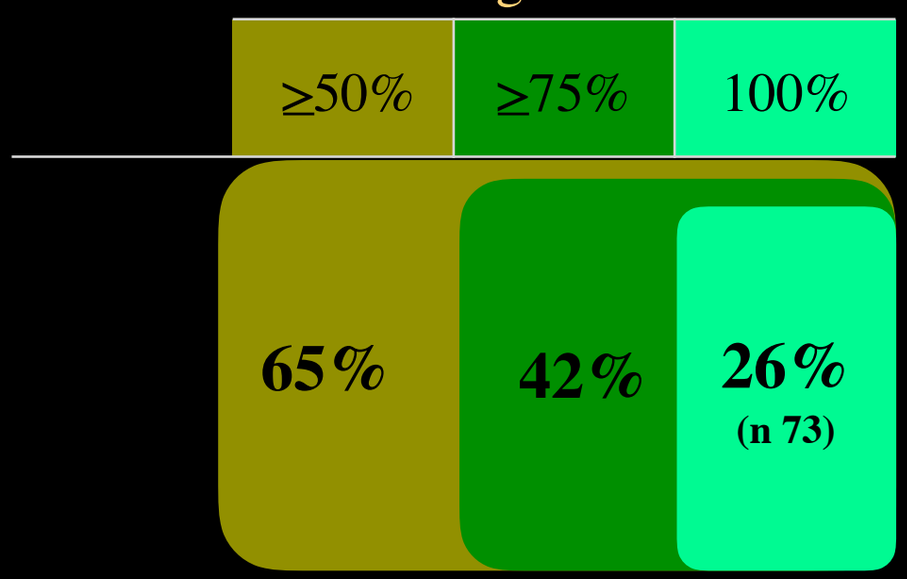

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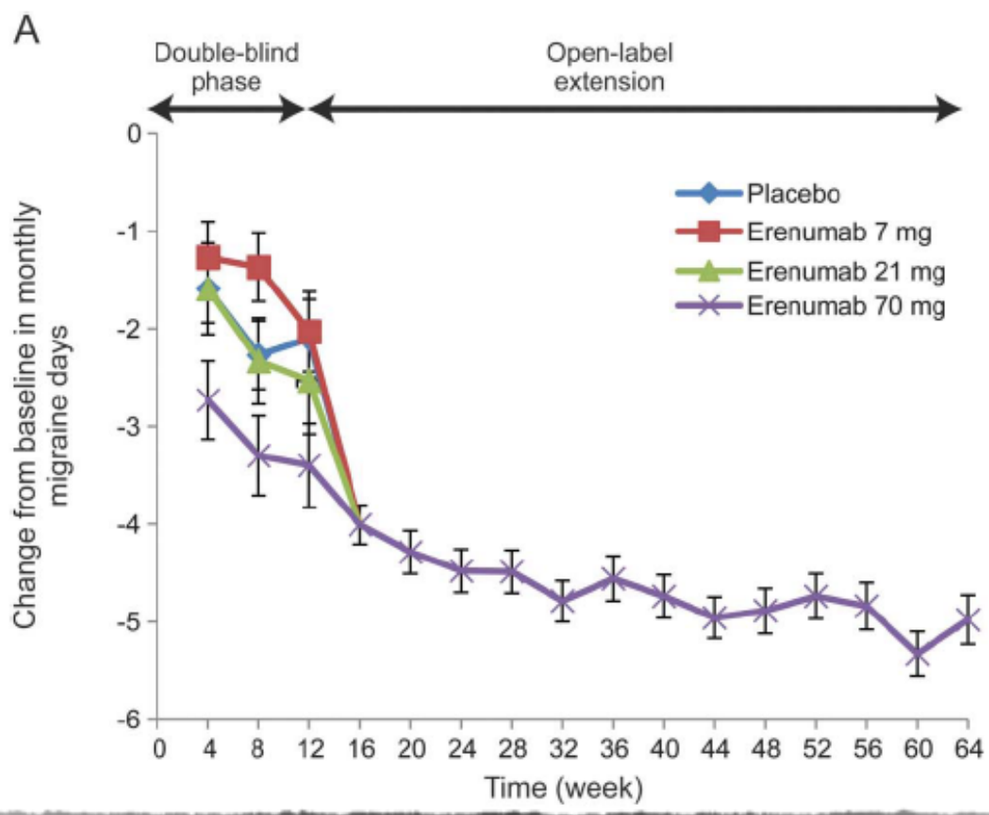

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ERENUMAB

GALCANEZUMAB

FREMANEZUMAB

EPTINEZUMAB

ERENUMAB

GALCANEZUMAB

27 settembre 2018

FREMANEZUMAB

14 settembre 2018

EPTINEZUMAB

not approved

	FDA	EMA
ERENUMAB	17 maggio 2018	31 luglio 2018
GALCANEZUMAB	27 settembre 2018	14 novembre 2018
FREMANEZUMAB	14 settembre 2018	1 aprile 2019
EPTINEZUMAB	not approved	

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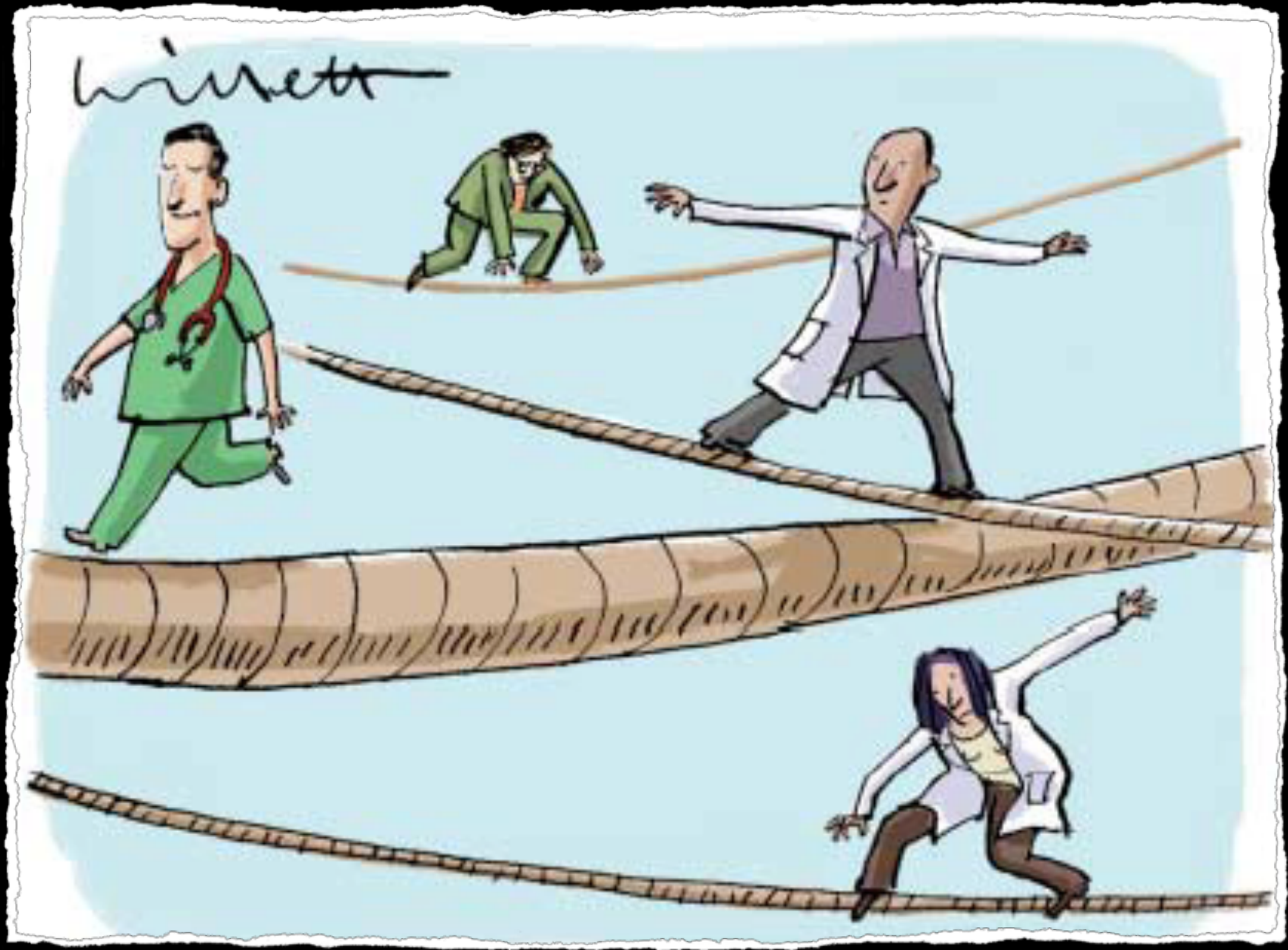

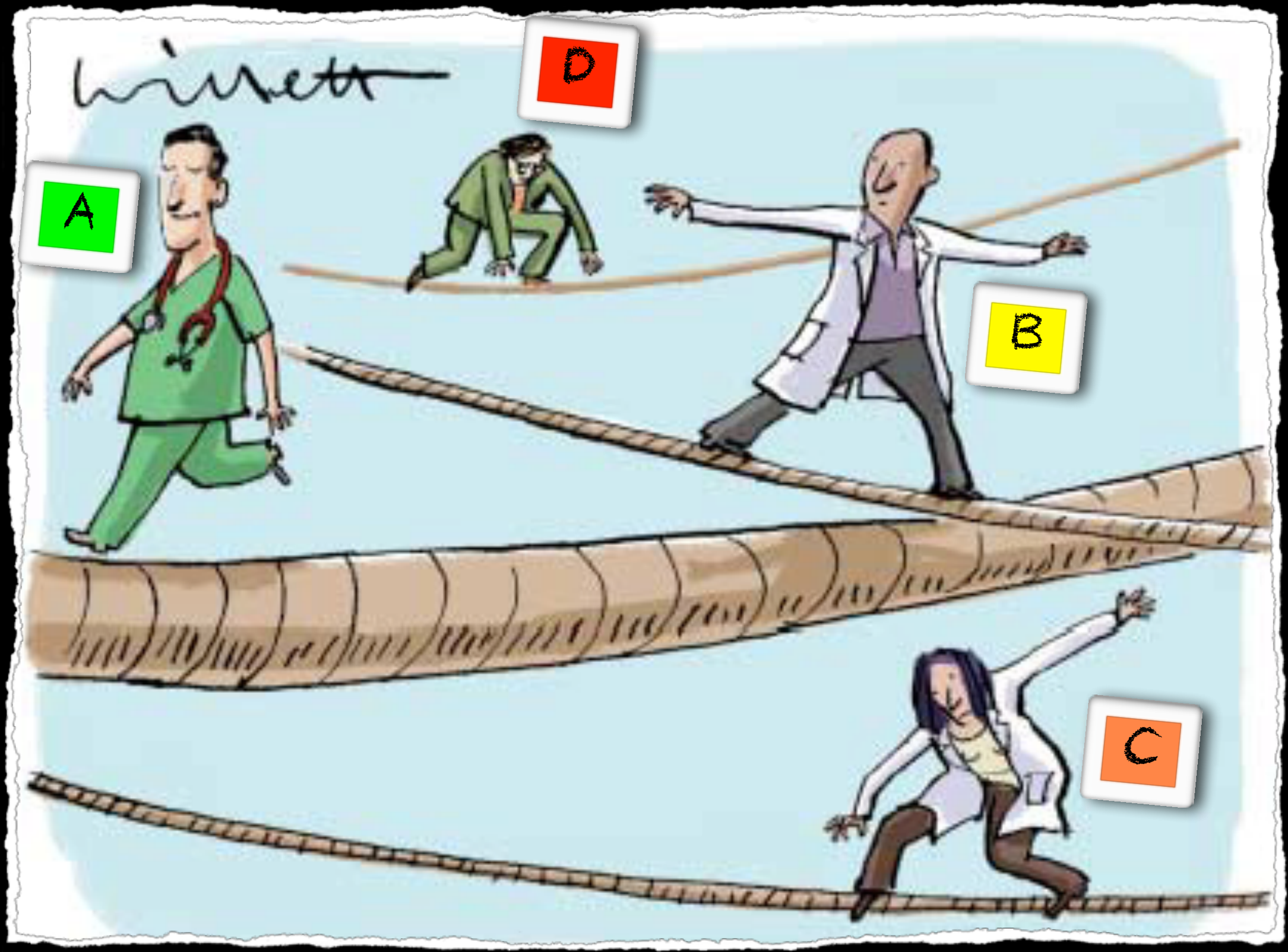
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Table 5 Recommendations on the use of calcitonin gene-related peptide monoclonal antibodies for the prevention of episodic and chronic migraine

Setting	Drug	Recommendation	Quality of evidence	Strength of the recommendation
Migraine prevention in patients with episodic migraine				
	Eptinezumab 1000 mg quarterly	Suggested	⊕⊕○○ LOW	↑? Weak
	Erenumab 70 mg monthly	Recommended	⊕⊕⊕⊕ HIGH	↑↑ Strong
	Erenumab 140 mg monthly	Recommended	⊕⊕⊕○ MEDIUM	↑↑Strong
	Fremanezumab 225 mg monthly	Recommended	⊕⊕⊕⊕ HIGH	↑↑ Strong
	Fremanezumab 675 mg quarterly	Recommended	⊕⊕⊕○ MEDIUM	↑↑Strong
	Galcanezumab 240 mg loading dose + 120 mg monthly	Recommended	⊕⊕⊕○ MEDIUM	↑↑ Strong
	Galcanezumab 240 mg monthly	Recommended	⊕⊕⊕○ MEDIUM	↑↑ Strong

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- Tutti gli studi includono pazienti con una lunga storia di malattia e pazienti che avevano precedentemente fallito due o più trattamenti preventivi.

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Fremanezumab 675 mg loading dose + 225 mg monthly	Recommended	⊕⊕⊕⊕ HIGH	↑↑ Strong
Galcanezumab 240 mg loading dose + 120 mg monthly	Recommended	⊕⊕⊕○ MEDIUM	↑↑Strong
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Symbols depict the strength of the recommendation according to the GRADE system

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…per chi?

Table 19 Recommendations about the use of anti-calcitonin gene-related peptide monoclonal an

Clinical question	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	Experts' opinion
	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	

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almeno 2 fallimenti

o impossibilità ad usare altre terapie

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emicrania episodica → **almeno 2 fallimenti**
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CONSENSUS ARTICLE

European headache federation guideli

…con altre profilassi?

2. How should other preventive treatments be managed when using anti-CGRP monoclonal antibodies in patients

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	Experts' opinion
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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	

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emicrania episodica → **STOP precedente terapia**

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emicrania episodica → **STOP precedente terapia**

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emicrania cronica in BoNT-A →

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emicrania cronica	**ADD on e poi STOP precedente terapia**
emicrania cronica in BoNT-A	**STOP BoNT-A e poi ADD on**
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emicrania cronica in BoNT-A	**STOP BoNT-A e poi ADD on**
emicrania cronica in mAbs	**eventuale ADD on terapia orale**

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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

Simona Sacco[1*], Lars Bendtsen[2], Messoud Ashina[2], Uwe Reuter[3], Gisela Terwindt[4], Dimos-Dimitrios Mitsikostas[5†] and Paolo Martelletti[6†]

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CONSENSUS ARTICLE

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…per quanto tempo?

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emicrania episodica

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emicrania episodica

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….e la MOH?

4. Should medication overuse be treated before offering treatment anti-CGRP monoclonal antibodies to patients with chronic migraine?

In patients with chronic migraine and medication overuse, we suggest to use erenumab, fremanezumab, and galcanezumab before or after withdrawal of acute medications	Experts' opinion

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emicrania cronica + MOH

SI ma prima o dopo disassuefazione

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AHS Consensus Statement

The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice

American Headache Society

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Table 5.—Indications for Initiating Treatment With Monoclonal Antibodies to Calcitonin Gene-Related Peptide or Its Receptor

Use is approved when ALL of the following are met:
A. Prescribed by a licensed medical provider[†]
B. Patient is at least 18 years of age
C. Diagnosis of ICHD-3 migraine with or without aura[‡] (4–7 monthly headache days) and both of the following:
a. Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:
1. Topiramate
2. Divalproex sodium/valproate sodium[§]
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Tricyclic antidepressant: amitriptyline, nortriptyline
5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
6. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline
b. At least moderate disability (MIDAS>11, HIT-6>50)
D. Diagnosis of ICHD-3 migraine with or without aura[‡] (8–14 monthly headache days) and inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:
a. Topiramate
b. Divalproex sodium/valproate sodium[§]
c. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
d. Tricyclic antidepressant: amitriptyline, nortriptyline
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emicrania episodica

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f. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline

E. Diagnosis of ICHD-3 chronic migraine[‡] and EITHER a or b:

a. Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following:

1. Topiramate
2. Divalproex sodium/valproate sodium[§]
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
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6. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline

b. Inability to tolerate or inadequate response to a minimum of 2 quarterly injection (6 months) of onabotulinumtoxinA

AAN-AHS, American Academy of Neurology-American Headache Society; HIT, Headache Impact Test; ICHD, International Classification of Headache Disorders; MHDs, monthly headache days; MIDAS, Migraine Disability Assessment.

[†]Doctor of medicine, doctor of osteopathy, advanced practice provider (DDS [Doctor of Dental Surgery] or DMD [Doctor of Medicine in Dentistry or Doctor of Dental Medicine]).

[‡]Patient can only meet criteria for C, D, or E.

[§]Not for use in women of childbearing potential who lack an appropriate method of birth control.[34,35]

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