LEE JUN JUN

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Kaohsiung City, Taiwan 83301

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EDUCATION

National Sun Yat-sen University 2018-
Department of Information Management
Doctor of Philosophy

Taipei Medical University 2011
College of Medicine
Bachelor of Medical

National Taiwan University 2004
Bachelor of Animal science

Juntendo University Hospital for Internship Training, Tokyo, Japan 2011
- The program modules were in cardiovascular and gastrointestinal medicine.

Utrecht University for ExploreDTI workshop, Utrecht, Netherland 2018
- The major component of the program was analysis of neuroimaging by ExploreDTI.

Honors and Distinctions
- Dean's list Award 2004
- Dean's list Award; Academic Excellence Award for pathology 2009
- Taiwan Neurology Society Best Poster Award 2017

WORK EXPERIENCE

Kaohsiung Chang Gung Memorial Hospital, Department of Neurology
Attending physician 2018-
Resident doctor 2011-18
- Perform clinical medical practice on general neurology, including neurology examinations, neuroemergency, hospitalized patient care, and outpatient department
- Data collection, analysis, and grant and manuscript writing on neurologic infection disease and neurodegenerative diseases
- Attend clinical trials in neurodegenerative diseases

National Taiwan University Veterinary Hospital
Assistant 2002-04
- Worked extensively on clinical practice of veterinary

TEACHING EXPERIENCE

Taiwan Dementia Society
Speaker 2018-
- Continue education for physicians

SKILLS AND ACTIVITIES

Headache management

Dementia research

Neuroimaging 2016 - present
- Analysis of multimodality of neuroimaging by DKE, ExploreDTI, TBSS, SPM, and CAT

RELEVANT PUBLICATIONS AND PRESENTATIONS

Publications

- **Jun-Jun Lee**, Wen-Neng Chang, Jung-Lung Hsu, Chi-Wei Huang, Ya-Ting Chang, Shih-Wei Hsu, Shu-Hua Huang, Chen-Chang Lee, Chia-Yi Lien, Chiung-Chih Chang. "Diffusion Kurtosis Imaging as a Neuroimaging Biomarker in Patients with Carbon Monoxide Intoxication." *Neurotoxicology* (2018) Sep 68:38-46

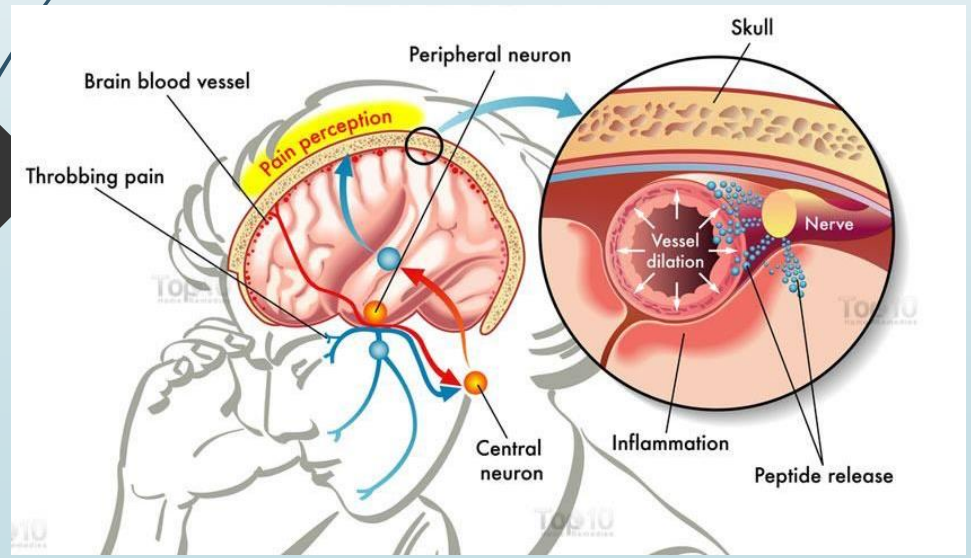
- **Jun-Jun Lee**, Tsai Meng-Han, Lien Chia-Yi, Huang Yu-Ju, Wen-Neng Chang. "Intra-family phenotype variations in familial neuromyelitis optica spectrum disorders." Multiple sclerosis and related disorder (2019) Feb 4;30:57-62
- **Jun-Jun Lee(co-first author)**, Chia-Yi Lien, Chun-Chih Chien, Chi-Ren Huang, Nai-Wen Tsai, Chiung-Chih Chang, Cheng-Hsien Lu, and Wen-Neng Chang. "Anaerobic Bacterial Meningitis in Adults." *Journal of Clinical Neuroscience* 50 (2018): 45-50.
- Chia-Yi Lien, **Jun-Jun Lee (co-first author)**, Chun-Chih Chien, Chi-Ren Huang, Cheng-Hsien Lu, and Wen-Neng Chang. "Clinical Characteristics of Citrobacter Meningitis in Adults: High Incidence in Patients with a Postneurosurgical State and Strains Not Susceptible to Third-Generation Cephalosporins." *Journal of Clinical Neuroscience* (2018):83-87
- **Jun-Jun Lee**, Chia-Yi Lien, Chi-Ren Huang, Nai-Wen Tsai, Chiung-Chih Chang, Cheng-Hsien Lu, Wen-Neng Chang. "Clinical Characteristics and Therapeutic Outcomes of Postneurosurgical Bacterial Meningitis in Elderly Patients over 65: A Hospital-based Study." *Acta Neurol Taiwan* (2017); 26:144-153
- Hua-Tsen Hsiao, **Jun-Jun Lee**, Hsiu-Hui Chen, Ming-Kung Wu, Chi-Wei Huang, Ya-Ting Chang, Chia-Yi Lien, Jing-Jy Wang, Hsin-I Chang, Chiung-Chih Chang. "Adequacy of nutrition and body weight in patients with early stage dementia: The cognition and aging study."*Clinical Nutrition* (2018)
- Chia-Wei Lee, **Jun-Jun Lee**, Yen-Feng Lee, Pei-Wen Wang, Tai-Long Pan, Wen-Neng Chang, Meng-Han Tsai."Clinical and molecular genetic features of cerebrotendinous xanthomatosis in Taiwan: Report of a novel CYP27A1 mutation and literature review." *Journal of Clinical Lipidology*, Nov-Dec 2019;13(6): 954-959.e1.
- Yu-Ju Huang, **Jun-Jun Lee**, Wen-Lan Fan, Che-Wei Hsu, Nai-Wen Tsai, Cheng-Hsien Lu, Wen-Neng Chang, Meng-Han Tsai. "A CD33 frameshift variant is associated with neuromyelitis optica spectrum disorders." *Biomedical Journal* https://doi.org/10.1016/j.bj.2020.07.007
- Chia-Yi Lien , **Jun-Jun Lee** , Wan-Chen Tsai , Shih-Ying Chen , Chi-Ren Huang , Chun-Chih Chien , Cheng-Hsien Lu , Wen-Neng Chang. "The clinical characteristics of spontaneous Gram-negative bacterial meningitis in adults: A hospital-based study." *Journal of Clinical Neuroscience* 64 (2019) 101–105
- Shih-Ying Chen, **Jun-Jun Lee**, Chun-Chih Chien, Wan-Chen Tsai, Cheng-Hsien Lu, Wen-Neng Chang, Chia-Yi Lien. "High incidence of severe neurological manifestations and high mortality rate for adult Listeria monocytogenes meningitis in Taiwan." *Journal of Clinical Neuroscience* 71 (2020) 177–185
- Wan-Chen Tsai, Chia-Yi Lien, **Jun-Jun Lee**, Wei-Che Lin, Che-Wei Hsu, Chi-Ren Huang, Nai-Wen Tsai*, et al.* "The Prognostic Factors of Hiv-Negative Adult Cryptococcal Meningitis with a Focus on Cranial Mri-Based Neuroimaging Findings." *Journal of Clinical Neuroscience* (2018) Jul 2. Sep; 55:57-61
- Wan-Chen Tsai, Chia-Yi Lien, **Jun-Jun Lee**, Chi-Ren Huang, Nai-Wen Tsai, Chiung-Chih Chang, Cheng-Hsien Lu, Wen-Neng Chang. "The clinical characteristics of adult cryptococcal meningitis patients who died within one year of treatment with a focus on those with early mortality/" *Journal of Clinical Neuroscience(*2019) Sep;67:80-84.
- Ya Ting Chang, Cheng-Hsien Lu, Ming-Kung Wu, Shih-Wei Hsu, Chi-Wei Huang, Wen-Neng Chang, Chia-Yi Lien, **Jun-Jun Lee,** and Chiung-Chih Chang. "Salience Network and Depressive Severities in Parkinson's Disease with Mild Cognitive Impairment: A Structural Covariance Network Analysis." *Frontiers in aging neuroscience* 9 (2017): 417.
- Ya-Ting Chang, Chi-Wei Huang, Shu-Hua Huang, Shih-Wei Hsu, Wen-Neng Chang, **Jun-Jun Lee**, and Chiung-Chih Chang. "Genetic Interaction Is Associated with Lower Metabolic Connectivity and Memory Impairment in Clinically Mild Alzheimer's Disease." *Genes, Brain and Behavior* (2018): e12490.
- Ya-Ting Chang, Chi-Wei Huang, Wen-Neng Chang, **Jun-Jun Lee**, Chiung-Chih Chang. "Altered Functional Network Affects Amyloid and Structural Covariance in Alzheimer's Disease. " *BioMed research international* (2018) Dec 2
- Ya-Ting Chang, Etsuro Mori, Maki Suzuki, Manabu Ikeda, Chi-Wei Huang, **Jun-Jun Lee**, Wen-Neng Chang, Chiung-Chih Chang. "APOE-MS4A genetic interactions are associated with executive dysfunction and network abnormality in clinically mild Alzheimer's disease." *Neuroimage Clinical*. 2019;21:101621
- Ya-Ting Chang, Shih-Wei Hsu, Shu-Hua Huang, Chi-Wei Huang, Wen-Neng Chang, Chia-Yi Lien, **Jun-Jun Lee**, Chen-Chang Lee, Chiung-Chih Chang. **"***ABCA7* polymorphisms correlate with memory impairment and default mode network in patients with *APOE*ε4-associated Alzheimer's disease." *Alzheimer's Research & Therapy* volume 11, Article number: 103 (2019)

Poster Presentations

- "Clinical characteristics and therapeutic outcomes of postneurosurgical bacterial meningitis in elderly patients over 65: A hospital-based study" **Jun-Jun Lee**, J Infect Dis Ther 2018, Volume 6 DOI: 10.4172/2332-0877-C1-039
- "Clinical significance of diffusion kurtosis imaging in patients with carbon monoxide intoxication – A comparison with diffusion tensor imaging of changes in white matter" **Jun-Jun Lee**, Wen-Neng Chang, Jung-Lung Hsu, Chung-Chih Chang, Taiwan Neurology Society 2018
- "TAU AND AMYLOID BURDEN IN EARLY ONSET ALZHEIMER'S DISEASE: A CASE REPORT" Sz-Fan Chen, Chiung-Chih Chang, Jung-Lung Hsu, **Jun-Jun Lee**, Taiwan Neurology Society 2018
- "Heterogeneity in the initial clinical and neuroimaging presentations of the familial members of familial neuromyelitis optica spectrum disorder: Report of one family and literature review" **Jun-Jun Lee**, Chung-Chih Chang, Wen-Neng Chang, Taiwan Neurology Society 2017

- "Acute Psychosis following Vagus Nerve Stimulation: experience from single institute" **Jun-Jun Lee**, Meng-Hen Tsai, Taiwan Neurology Society 2015

Pharmacologic Treatment inMigraine



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- Chronic Migraine Epidemiology and Outcome (CaMEO)
  - female, overweighted and have some psychiatric comorbidities
- In chronic migraine, the average per-person annual total costs is around 4.4-fold greater than episodic migraine
- In United States, estimated annual direct healthcare cost of chronic migraine is around $9.2 billion
- In 2005-2009, annual direct costs of Taiwanese patients with chronic migraine were NTD $52527, which was five times than costs of general population [
- indirect costs of chronic migraine, which are caused by disability-related missing work days or decreased productivity, plays greater role than direct costs.
- In Europe, more than 90% annual per-person costs of migraine was attributed to indirect costs cost for migraine
- Similar to Westen countries, in Taiwan, the estimated median annual number of missed workdays are about 2 days

Table 3. Selected Therapies for Acute Migraine.*

Class	Specific Treatments	Reported Mean Therapeutic Effects†	Common or Serious Adverse Effects	Comments
Triptans[26]	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	Pain relief by 2 hr, 16–51%; pain-free by 2 hr, 9–32%; free of headache for 24 hr, 9–27%	Chest or facial muscle tightness, lightheadedness; contraindicated in patients with coronary artery disease	Response to and side-effect profile of different triptans varies in individual patients; nasal or subcutaneous delivery may be more effective than oral delivery in patients with nausea or vomiting
Ergots[27,28]	DHE nasal spray, DHE injection	Pain relief by 2 hr, 20–40% (for DHE nasal spray; limited evidence)	Nausea, dizziness; contraindicated in patients with peripheral vascular disease or coronary artery disease	Intravenous DHE is commonly used for refractory migraine
Acetaminophen[29]				nore effective in combination with metic agent
NSAIDs[30]	Aspirin, diclofenac, ibupro ketorolac, naproxen			ffective individually or have additive fit when taken with triptan; different preparations (effervescent or powder) have improved efficacy
Combinations[31,32]	Acetaminophen–aspirin–caffeine, sumatriptan–naproxen	evidence); pain-free by 2 hr, 20–30%		containing preparations may have increased potential for overuse; combination therapy is more effective than individual agents in some patients
Antiemetic agents[23,29,30]	Chlorpromazine, metoclopramide, prochlorperazine	Pain relief by 2 hr with oral metoclopramide (plus aspirin or acetaminophen), 23%; pain relief by 1–2 hr with intravenous delivery in emergency department, 24–67%	Sedation, restlessness (akathisia), dystonic reactions	Phenothiazines plus metoclopramide have benefit for headache as well as nausea; ondansetron is commonly used for nausea, but evidence is lacking
Single-pulse TMS[33]	SpringTMS	Pain-free by 2 hr, 17%	No clinically significant adverse effects	Handheld device for patient-delivered therapy; currently FDA-approved for treatment of acute migraine with aura
CGRP receptor antagonists[34,35] (under investigation)	Rimegepant, ubrogepant	Pain-free by 2 hr, 14–18%	None reported; safety studies are ongoing	Phase 2 studies have been completed

急性止痛治療

* Shown are therapies that have high-quality supporting evidence or are highly recommended in guidelines from the American Headache Society,[22,23] the Canadian Headache Society,[24] and the European Federation of Neurological Societies[25] as well as other Food and Drug Administration (FDA)–approved or emerging therapies. Citations are for primary trial data within guidelines except as noted; trials were of variable quality. All approaches are FDA-approved for the treatment of acute migraine except antiemetics and calcitonin gene–related peptide (CGRP) receptor antagonists. DHE denotes dihydroergotamine, NSAIDs nonsteroidal antiinflammatory drugs, and TMS transcranial magnetic stimulation.

† Values are the percentage of patients with pain relief or freedom from pain after a single dose of the treatment minus the percentage with pain relief or freedom from pain after placebo administration. In most cases, therapy was administered when pain was already moderate or severe.

Table 4. Selected Preventive Therapies for Migraine.*

Class	Specific Treatments	Reported Mean Monthly Therapeutic Effects†	Common or Serious Adverse Effects	Comments
Tricyclic antidepressants[41]	Amitriptyline, nortriptyline	Data not available	Dry mouth, sedation, weight gain, urinary retention	Low doses are typically used (10 to 50 mg); may be useful in patients with insomnia
Beta-blockers[42,43]	Metoprolol, nadolol, propranolol,‡ timolol‡	Headache days, −0.4 (meta-analysis for propranolol)	Hypotension, exercise intolerance, sexual dysfunction	May be useful in patients with hypertension, tachycardia, or anxiety
Anticonvulsant agent[44]	Topiramate‡	Episodic migraine days, −1.1 to −1.3; chronic migraine days, −1.5 to −3.3	Paresthesias, weight gain, cognitive dysfunction, depression	Also used for weight loss; preparations with various half-lives are available
Anticonvulsant agent[45]	Divalproex sodium‡		t gain, hair loss, l-tube defects	May be efficacious, but adverse effects limit its use
Candesartan[43]			zziness	Side effects are generally acceptable
Flunarizine[41]			ht gain, depression	Not available in the United States
Nonprescription therapies[46]	Coenzyme Q10, magnesium, melatonin, petasites, riboflavin	Migraine attacks: −1.1 with coenzyme Q10, −0.5 to −0.9 with magnesium, −0.8 with petasites or riboflavin	Diarrhea with magnesium	Side effects are generally acceptable, but current evidence of efficacy is poor
Botulinum toxins[47]	OnabotulinumtoxinA‡	Chronic migraine headache days, −1.4 to −2.3; migraine days, −1.5 to −2.4	Muscle weakness, headache	Delivered by subcutaneous injection at multiple sites; approved for chronic migraine only
Supraorbital nerve stimulation[48]	Cefaly device‡	Migraine days, −2.1	Local discomfort, skin irritation	Headband with forehead stimulation; applied for 20 min daily
Monoclonal antibodies targeting CGRP or its receptor[49,50] (under investigation)	Eptinezumab, erenumab, fremanezumab, galcanezumab	Episodic migraine headache days, −1.0 to −1.2; high-frequency episodic migraine days, −2.8; days with chronic migraine headache, −2.5; hr with chronic migraine headache, −30.4	Injection-site reactions; safety studies are ongoing	Multiple phase 3 trials have been completed; administered subcutaneously or intravenously every 1 to 3 mo; rapid onset of efficacy; rates of response of 75% and in some cases 100% have been reported

預防治療

* Shown are therapies that have high-quality supporting evidence or are highly recommended in guidelines are from American Academy of Neurology and the American Headache Society,[39,40] the Canadian Headache Society,[41] and the European Federation of Neurological Societies[25] as well as other FDA-approved or emerging therapies. Citations for primary clinical-trial data are included in these guidelines except where noted. All studies were of episodic migraine unless otherwise specified. Episodic migraine is defined as less than 15 headache days per month; chronic migraine is defined as 15 or more headache days per month, with migraine features on at least 8 of those days.

† Values are the number of migraine attacks, or number of days or hours with symptoms, per month with the treatment minus the number with placebo; negative values indicate a benefit with the treatment. The mean monthly effect (typically after 3 months of treatment) is summarized.

‡ These therapies have been approved by the FDA as preventive therapies for migraine.

NEJM 377;6 August 10, 2017

MIDAS

附件 1. 偏頭痛失能評估問卷 (MIDAS 問卷)

填寫需知：請回答以下有關您過去三個月內**所有**頭痛的相關問題。將答案填寫於每個問題旁的空格內。假如您過去三個月沒有從事該項活動，請填 0 。

1. 過去三個月中，您有多少天因爲頭痛而無法上班或上課？……□□天

2. 過去三個月中，您有多少天因爲頭痛而造成工作或課業上的成效減少一半或一半以上（不要將第 1 題無法上班或上課的日數算在內）？……□□天

3. 過去三個月中，您有多少天因爲頭痛而無法做家事？……□□天

4. 過去三個月中，您有多少天因爲頭痛而做家事的成效減少一半或一半以上（不要將第 3 題無法作家事的日數算在內）？……□□天

5. 過去三個月中，您有多少天因爲頭痛而沒有辦法參加家庭、社交或休閒活動？……□□天

A. 過去三個月中，您有多少天曾經有過任何的頭痛（如果頭痛超過一天，則每日都要計算）？……□□天

B. 以 0 至 10 表示頭痛的程度（0＝完全不痛，10＝痛得最厲害），平均而言，這些頭痛程度是？……□□天

以MIDAS總分分類偏頭痛嚴重度

Grade	定義	MIDAS分數	醫療需求
I	極輕度失能	0-5	低
II	輕度失能	6-10	中
III	中度失能	11-20	高
IV	重度失能	21-	高

Stewart WF et al. Cephalalgia 1999; 19: 107–14.

Acute treatment for migraine

Mild to Moderate (MIDAS grade I/II)	→	NSAIDs PO Aspirin Acetaminophen (1000mg) Combination analgesics NSAIDs IV/IM
Moderate to Severe (MIDAS grade III/IV)	→	Triptans Ergotamine/caffeine
Status migrainosus	→	Parenteral steroids + IV fluids

Since 2005 台灣頭痛學會 Taiwan Headache Society

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Indications for preventives = F4+A

- Functional disability
- Frequency (>4 attacks/month, >8 days/month)
- Failure of contraindication of acute treatment
- Favor (patient preference)
- Aura (hemiplegic migraine, migraine with brainstem aura, prolonged aura)

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Preventive medications

***be aware of contraindications and possible AEs

A

Antiepileptics

- Topiramate
- Valproate
- Gabapentin

ACEI/**A**RB

- Lisinopril
- Candesartan

B

β-blockers

- Propranolol
- Atenolol
- Metoprolol
- Nadolol

Botulinum toxin A (Only for CM)

C

Ca^{2+} channel blockers

- Flunarizine
- Verapamil

CGRP mAb

D

anti**d**epressants

- Amitriptyline
- Nortriptyline
- Venlafaxine

Preventive treatment for migraine

Episodic migraine	Propranolol (20-160) Valproic acid (300-1500) Topiramate (50-200) Flunarizine (5-10) Amitriptyline (10-75)
Chronic migraine	Topiramate (50-200) OnabotulinumtoxinA
Menstrual migraine	NSAIDs Triptans

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Conventional treatment

Preventative medication for Migraine

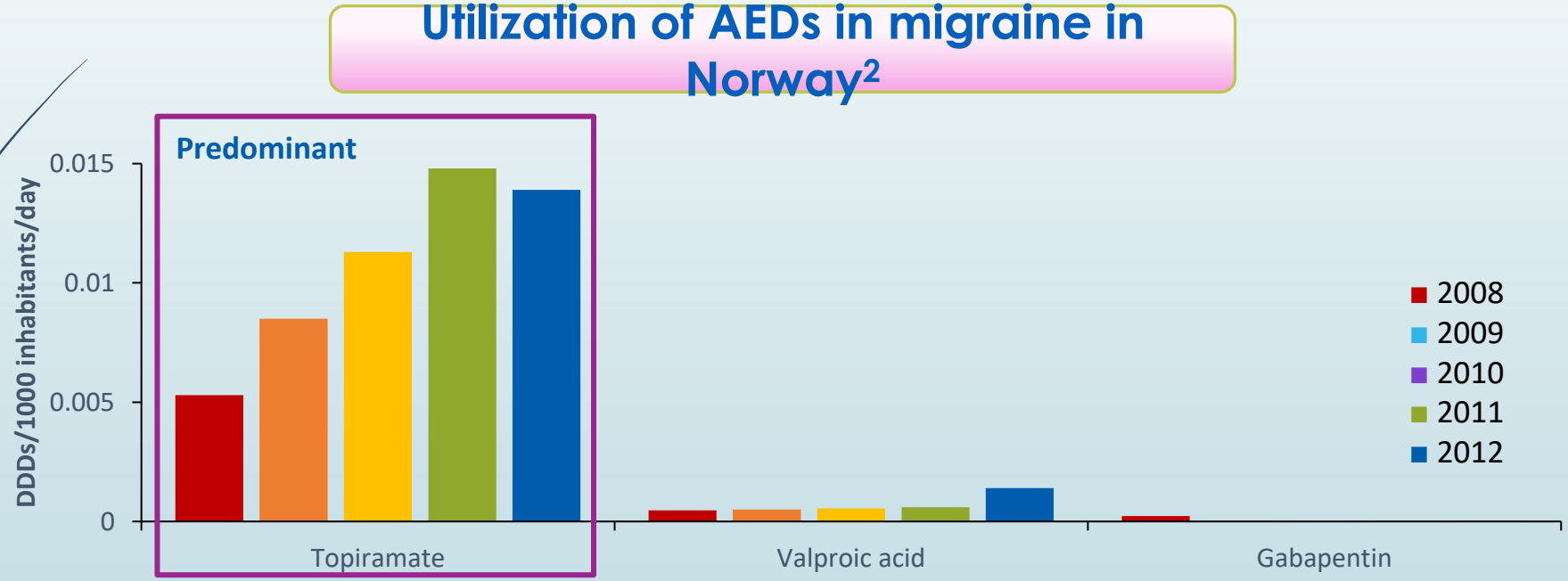
- TPM is level A established efficacy preventative treatment on Chronic Migraine.

Propranolol (PPN)	Flunarizine (FNZ)	Valproate (VPA)	Topiramate (TPM)
40-240mg/d	5-10mg/d	500-1800mg/d	PPN 80mg = VPA 400mg = TPM 50mg
50% Responder rate odd ratio 1.94	50% Responder rate FNZ ≒ PPN	50% Responder rate odd ratio 2.74	50% Responder rate odd ratio 3.27
Study withdrawal <5%	Weight gain	Pregnancy Category : X	

台灣頭痛學會
偏頭痛預防性藥物治療準則

Topiramate is a first-line agent for migraine prevention

AAN and AHS recommendations for migraine preventive therapy (level A evidence)[1]
AEDs: Topiramate, divalproex sodium, and sodium valproate



AAN=American Academy of Neurology; AED=Antiepileptic drug; AHS=American Headache Society; DDDs=defined daily doses.

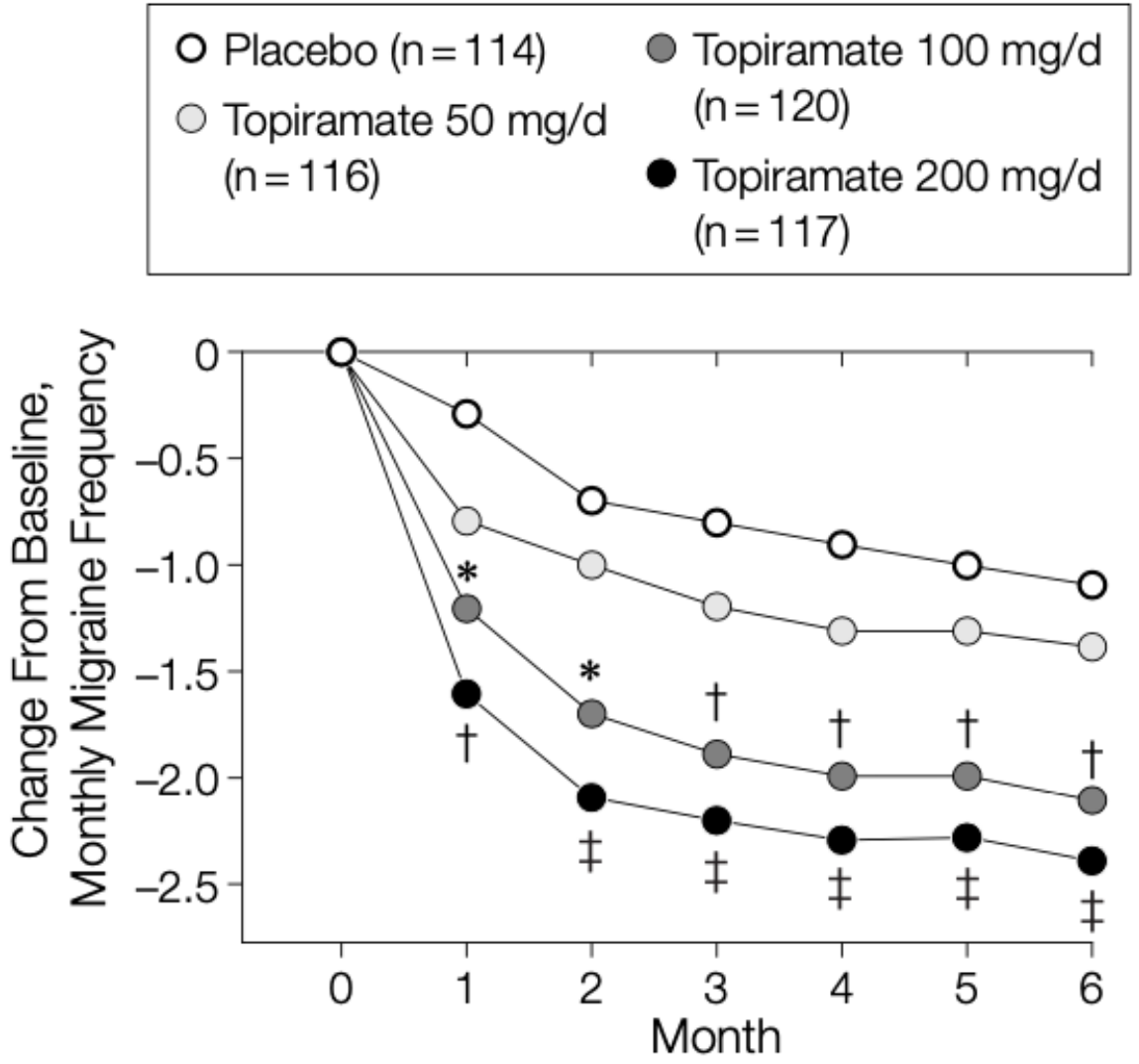
1. Silberstein SD, et al. Neurology. 2012;78(17):1337-45.
2. Baftiu A, et al. Eur J Clin Pharmacol. 2016;72(10):1245-54.

Table 1. Baseline Demographic and Migraine Characteristics

	Placebo (n = 114)	Topiramate 50 mg/d (n = 117)	Topiramate 100 mg/d (n = 120)	Topiramate 200 mg/d (n = 117)
Demographic characteristics				
Men, No. (%)	20 (18)	20 (17)	11 (9)	11 (9)
Women, No. (%)	94 (82)	97 (83)	109 (91)	106 (91)
Age, mean (SD) [range], y	38.3 (11.96) [12-64]	39.0 (12.09) [12-61]	39.1 (12.58) [12-65]	39.1 (12.71) [12-65]
Weight, mean (SD) [range], kg	74.1 (18.17) [44-134]	78.6 (20.70) [40-133]	78.7 (20.79) [41-136]	74.7 (18.11) [40-132]
Race, No. (%)				
White	101 (89)	99 (85)	108 (90)	103 (88)
Black	8 (7)	8 (7)	8 (7)	9 (8)
Asian	0	3 (3)	1 (1)	1 (1)
Other	5 (4)	7 (6)	3 (3)	4 (3)
Monthly migraine characteristics, mean (SD) [range]*				
Migraine frequency	5.6 (2.22) [1.5-13.1]	5.4 (2.42) [1.3-11.6]	5.8 (2.58) [1.7-14.5]	5.1 (2.02) [1.0-11.0]
Migraine days	6.7 (2.84) [2.2-18.0]	6.4 (2.88) [1.3-14.9]	6.9 (3.00) [1.7-15.4]	6.1 (2.54) [1.0-14.5]
Rescue medication use, d	5.8 (2.67) [0.8-15.4]	5.7 (2.72) [1.0-13.1]	6.2 (3.13) [0.7-17.0]	5.8 (2.52) [0.9-13.0]
Migraine duration, days per migraine	2.6 (1.85) [0.4-8.7]	2.3 (1.73) [0.1-8.3]	2.6 (1.73) [0.3-8.5]	2.1 (1.66) [0.2-8.5]
Monthly migraine severity†	2.2 (0.45) [1.0-3.0]	2.3 (0.38) [1.0-3.0]	2.2 (0.37) [1.3-3.0]	2.3 (0.39) [1.3-3.0]

*One patient in the 50 mg/d group provided no baseline headache information.
†Migraine severity was rated by patients on a scale of 1-3: 1 = mild, 2 = moderate, and 3 = severe.

Figure 3. Change From Baseline in Cumulative Monthly Migraine Frequency

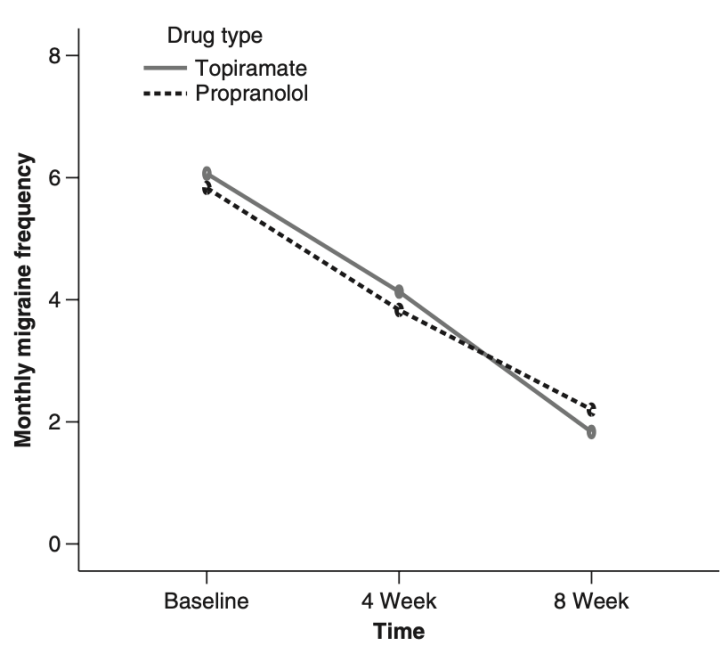


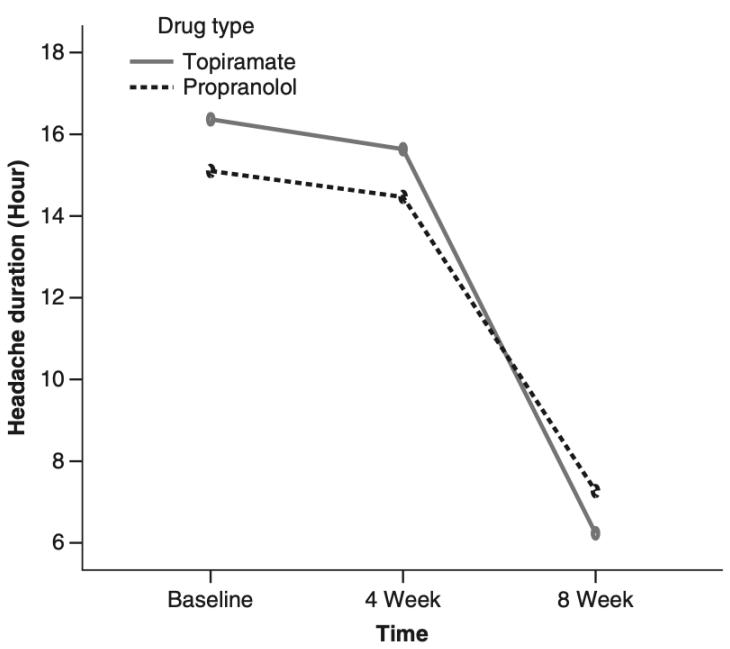
JAMA, February 25, 2004—Vol 291, No. 8

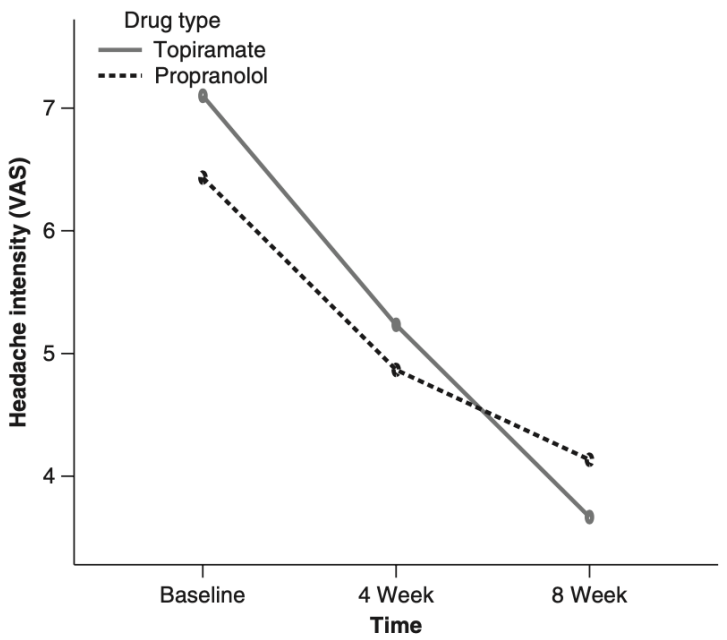
Acta Neurol Scand 2008: 118: 301–305 DOI: 10.1111/j.1600-0404.2008.01087.x

ACTA NEUROLOGICA
SCANDINAVICA

A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis







Clinical Therapeutics/Volume 31, Number 3, 2009

Topiramate Versus Amitriptyline in Migraine Prevention: A 26-Week, Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Noninferiority Trial in Adult Migraineurs

David W. Dodick, MD[1]; Fred Freitag, DO[2]; James Banks, MD[3]; Joel Saper, MD[4]; Jim Xiang, PhD[5]; Marcia Rupnow, PhD[5]; David Biondi, DO[5]; Steven J. Greenberg, MD[6]; and Joseph Hulihan, MD[5]; for the CAPSS-277 Investigator Group

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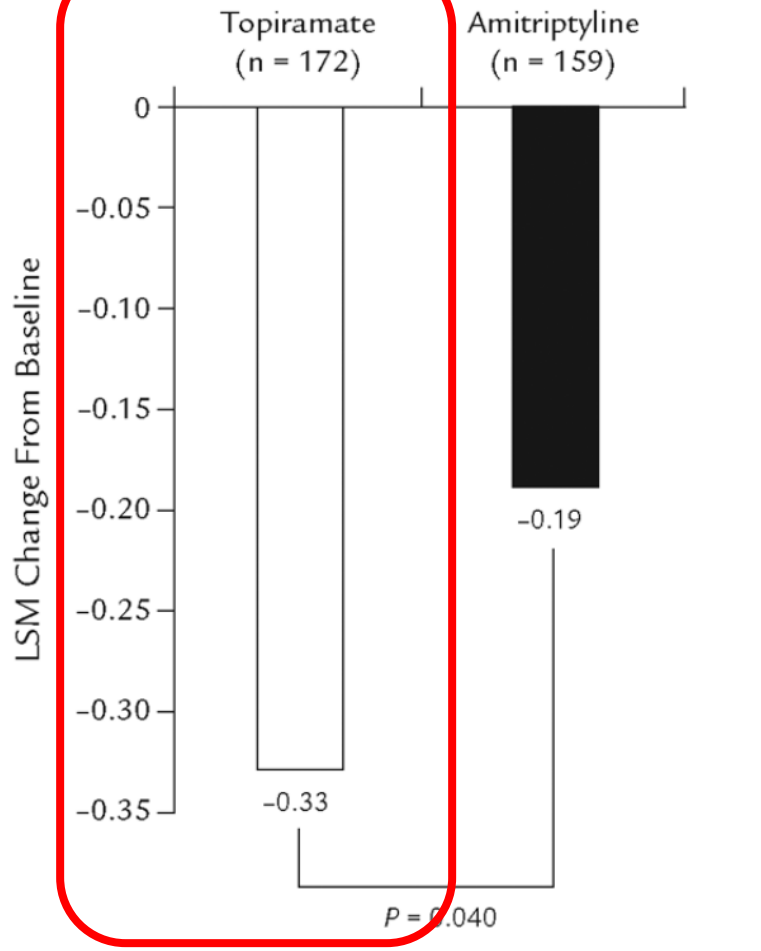


Figure 4. Least squares mean (LSM) change from baseline in mean migraine severity on the functional disability question (intent to treat).

Table VIII. Treatment-emergent adverse events reported in ≥5% of subjects (safety population).

Adverse Event	Topiramate (n = 177)	Amitriptyline (n = 169)	*P*
No. (%) of subjects with any adverse event*	152 (85.9)	150 (88.8)	0.519
Specific adverse events, no. (%)			
Paresthesia	53 (29.9)	8 (4.7)	<0.001
Fatigue	30 (16.9)	41 (24.3)	0.110
Somnolence	21 (11.9)	30 (17.8)	0.132
Hypoesthesia	19 (10.7)	6 (3.6)	0.012
Nausea	18 (10.2)	12 (7.1)	0.344
Dizziness	15 (8.5)	18 (10.7)	0.584
Sinusitis	14 (7.9)	18 (10.7)	0.459
Viral infection	14 (7.9)	11 (6.5)	0.681
Upper respiratory tract infection	14 (7.9)	11 (6.5)	0.681
Dry mouth	12 (6.8)	60 (35.5)	<0.001
Anorexia	12 (6.8)	8 (4.7)	0.493
Difficulty with concentration/attention	12 (6.8)	5 (3.0)	0.135
Taste perversion	10 (5.6)	6 (3.6)	0.446
Dyspepsia	9 (5.1)	14 (8.3)	0.283
Abnormal vision	9 (5.1)	9 (5.3)	1.000
Headache	9 (5.1)	0	0.004
Coughing	9 (5.1)	7 (4.1)	0.800
Pharyngitis	8 (4.5)	11 (6.5)	0.483
Constipation	6 (3.4)	14 (8.3)	0.065
Weight increase	0	23 (13.6)	<0.001

*Subjects with >1 occurrence of the same adverse event were counted only once for that event.

Agostoni *et al. The Journal of Headache and Pain* (2019) 20:92
https://doi.org/10.1186/s10194-019-1038-4

The Journal of Headache and Pain

REVIEW ARTICLE Open Access

Current and emerging evidence-based treatment options in chronic migraine: a narrative review

Elio Clemente Agostoni[1†], Piero Barbanti[2,3*†], Paolo Calabresi[4†], Bruno Colombo[5†], Pietro Cortelli[6,7†], Fabio Frediani[8†], Pietrangelo Geppetti[9†], Licia Grazzi[10†], Massimo Leone[10†], Paolo Martelletti[11†], Luigi Alberto Pini[12†], Maria Pia Prudenzano[13†], Paola Sarchielli[14†], Gioacchino Tedeschi[15†], Antonio Russo[15†] and The Italian chronic migraine group

Abstract

Background: Chronic migraine is a disabling condition that is currently underdiagnosed and undertreated. In this narrative review, we discuss the future of chronic migraine management in relation to recent progress in evidence-based pharmacological treatment.

Findings: Patients with chronic migraine require prophylactic therapy to reduce the frequency of migraine attacks, but the only currently available evidence-based prophylactic treatment options for chronic migraine are topiramate and onabotulinumtoxinA. Improved prophylactic therapy is needed to reduce the high burden of chronic migraine in Italy. Monoclonal antibodies that target the calcitonin gene-related peptide (CGRP) pathway of migraine pathogenesis have been specifically developed for the prophylactic treatment of chronic migraine. These anti-CGRP/R monoclonal antibodies have demonstrated good efficacy and excellent tolerability in phase II and III clinical trials, and offer new hope to patients who are currently not taking any prophylactic therapy or not benefitting from their current treatment.

Conclusions: Treatment of chronic migraine is a dynamic and rapidly advancing area of research. New developments in this field have the potential to improve the diagnosis and provide more individualised treatments for this condition. Establishing a culture of prevention is essential for reducing the personal, social and economic burden of chronic migraine.

Keywords: Chronic migraine, Fremanezumab, onabotulinumtoxinA, Prophylaxis, Topiramate, Anti-CGRP monoclonal antibodies

Neurol Sci (2016) 37:585–589
DOI 10.1007/s10072-015-2458-9

ORIGINAL ARTICLE

Topiramate-induced paresthesia is more frequently reported by migraine than epileptic patients

Behnaz Sedighi[1] · Kaveh Shafiei[1] · Iman Azizpour[1]

Table 1 Demographic data, clinical characteristics and frequency of topiramate-induced paresthesia

Demographic data	Migraine	Epilepsy	*P* value
Number of patients	160	160	
Mean age (years)	34.5 (9.9)	28.9 (13)	<0.05
Age range (minimum–maximum) years	12–61	7–61	
Female (percent)	92.5 %	40 %	<0.05
Duration of treatment (months)	8 (3.4)	10.2 (1.9)	<0.05
Topiramate dosage (mg)	33.2 (12.7)	62.3 (30)	<0.05
Paresthesia	53 %	15 %	<0.05

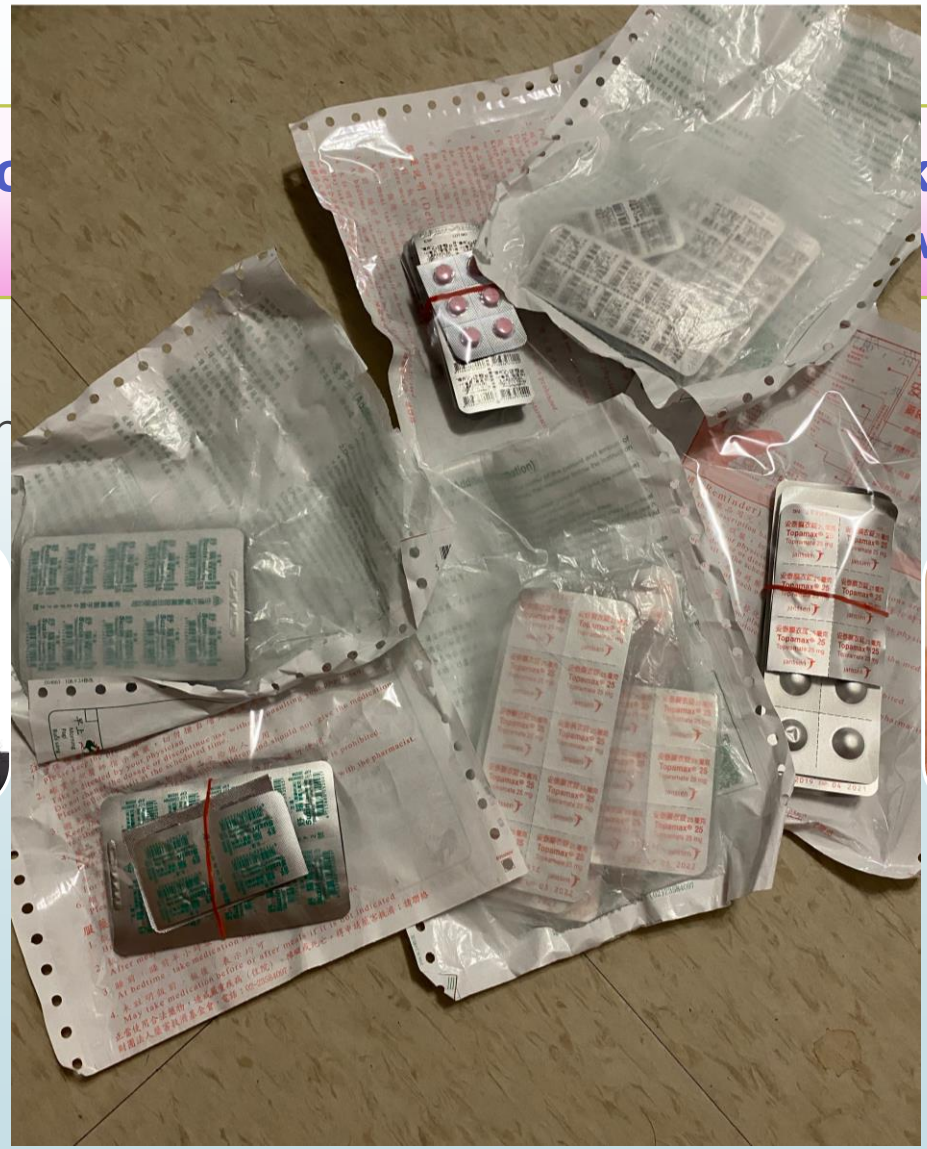
Numbers showed in parenthesis are standard deviation

Rationale for Extended-Release formulation

"Drugs do ke them."
verett Koop, MD

- Nonadherer

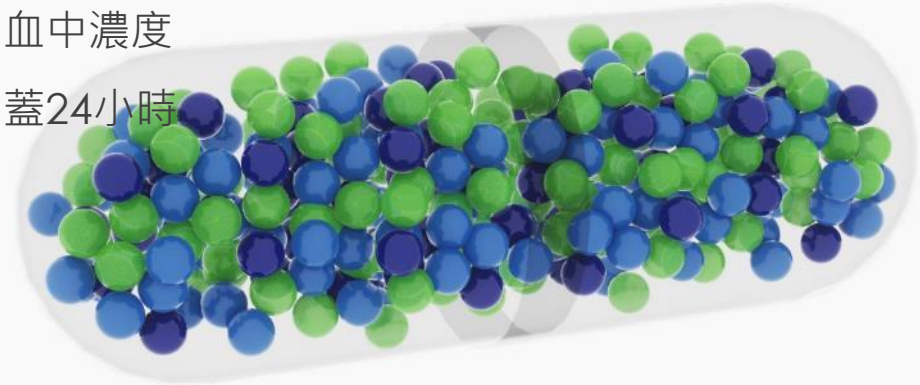
Forget

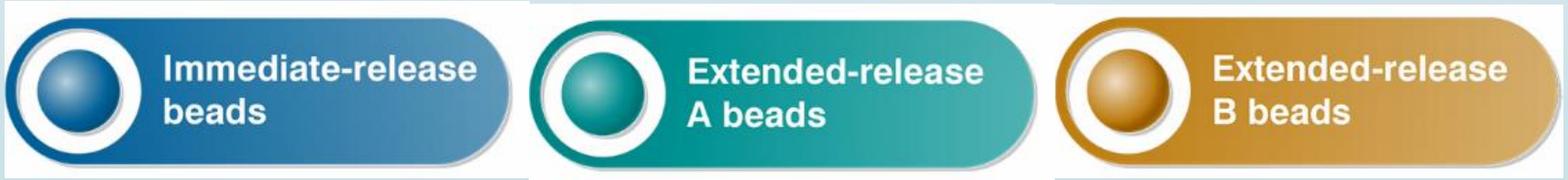


Persistency issues

Microtrol® 微粒控釋藥物系統

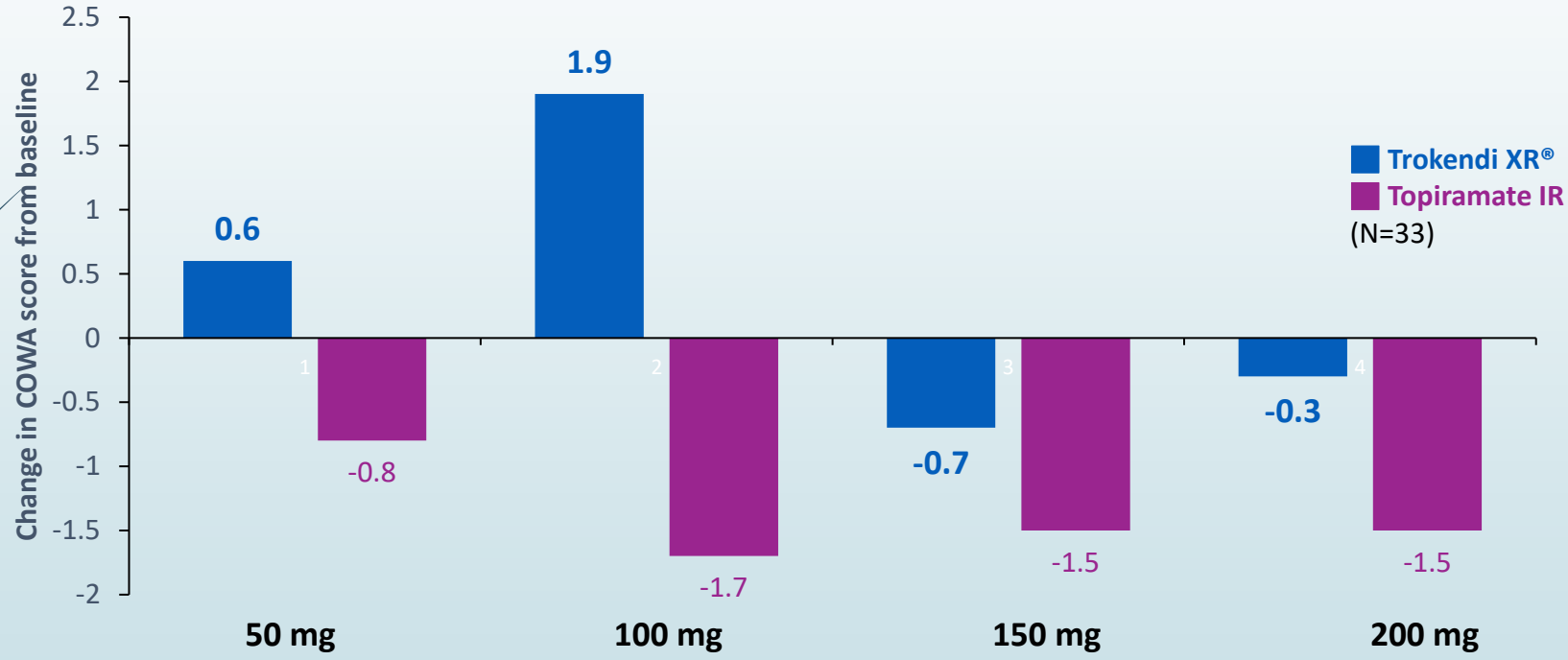
- Trokendi® XR的藥物優勢
  - 平穩的血中濃度
  - 藥效涵蓋24小時





Impact on Verbal Fluency of Trokendi XR®

- Trokendi XR® showed less negative impact on verbal fluency vs. TPM-IR. (P<0.05)



- Data were collected from 33 healthy volunteers tolerating therapy and completing both treatment arms.
- The COWA test assesses verbal fluency by requiring subjects to spontaneously articulate in a minute as many words as possible that begin with a particular letter (e.g., F or B).

COWA=Controlled Oral Word Association; IR=immediate-release; XR=extended-release.

Epilepsy Curr. 2014; 14 (Suppl. 1): 2.119.

Trokendi XR® significantly lower TEAE ($p < 0.001$)

- The incidence of cognitive symptoms was > 4-fold lower during Trokendi XR versus previous TPM-IR treatment

Table 4. Treatment-emergent adverse events in ≥5 patients during previous immediate-release topiramate or Trokendi XR® treatment.

	All patients (n = 192) n (%)		Migraine subset (n = 124) n (%)	
	TPM-IR	Trokendi XR	TPM-IR	Trokendi XR
Any TEAE	77 (40.1)	43 (22.4)†	59 (47.6)	29 (23.4)†
Cognitive symptoms	39 (20.3)	9 (4.7)†	35 (28.2)	7 (5.6)†
Paresthesia	15 (7.8)	4 (2.1)‡	15 (12.1)	3 (2.4) ‡
Somnolence	9 (4.7)	4 (2.1)	7 (5.6)	1 (0.8)
Appetite decreased/weight loss	6 (3.1)	3 (1.5)	4 (3.2)	3 (2.4)
Fatigue	5 (2.7)	2 (1.0)	2 (1.8)	1 (0.8)
GI problem	4 (2.1)	6 (3.1)	3 (2.4)	5 (4.0)

†Chi square; < 0.001 versus previous TPM-IR treatment.
‡Chi square; < 0.01 versus previous TPM-IR treatment.
GI: Gastrointestinal; TEAE: Treatment-emergent adverse event; TPM-IR: Immediate-release topiramate; Trokendi XR: Extended-release topiramate.

J.Comp. Eff. Res. doi: 10.2217/cer-2018-0074

Botox- 台灣健保現況

Sensory systems involved in CM

Peripheral sensory effect

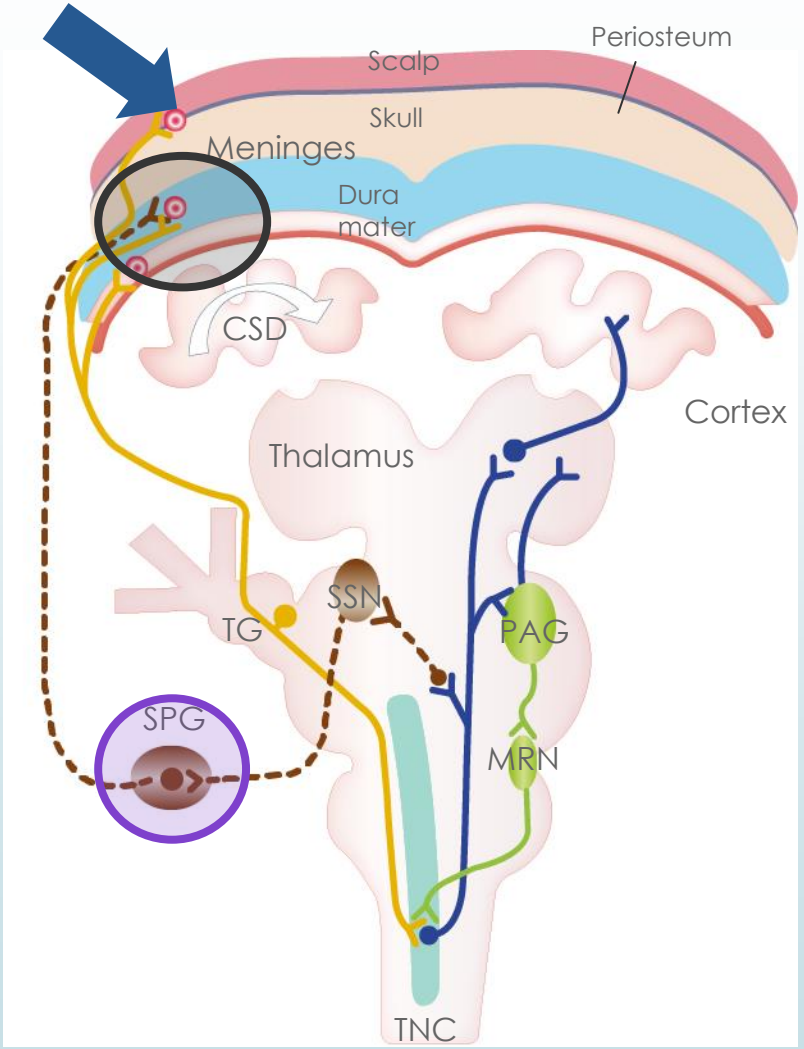
- Blocks release of neurotransmitters associated with peripheral sensitisation of sensory afferents
- By inhibiting peripheral sensitisation, BOTOX® may indirectly inhibit central sensitisation

Transcranial afferent effect

- Inhibits transmission in sensory nerves that traverse the cranium and have collateral dural branches

Trigeminal autonomic effect

- Inhibits sphenopalatine ganglion activation



PREEMPT phase III trial

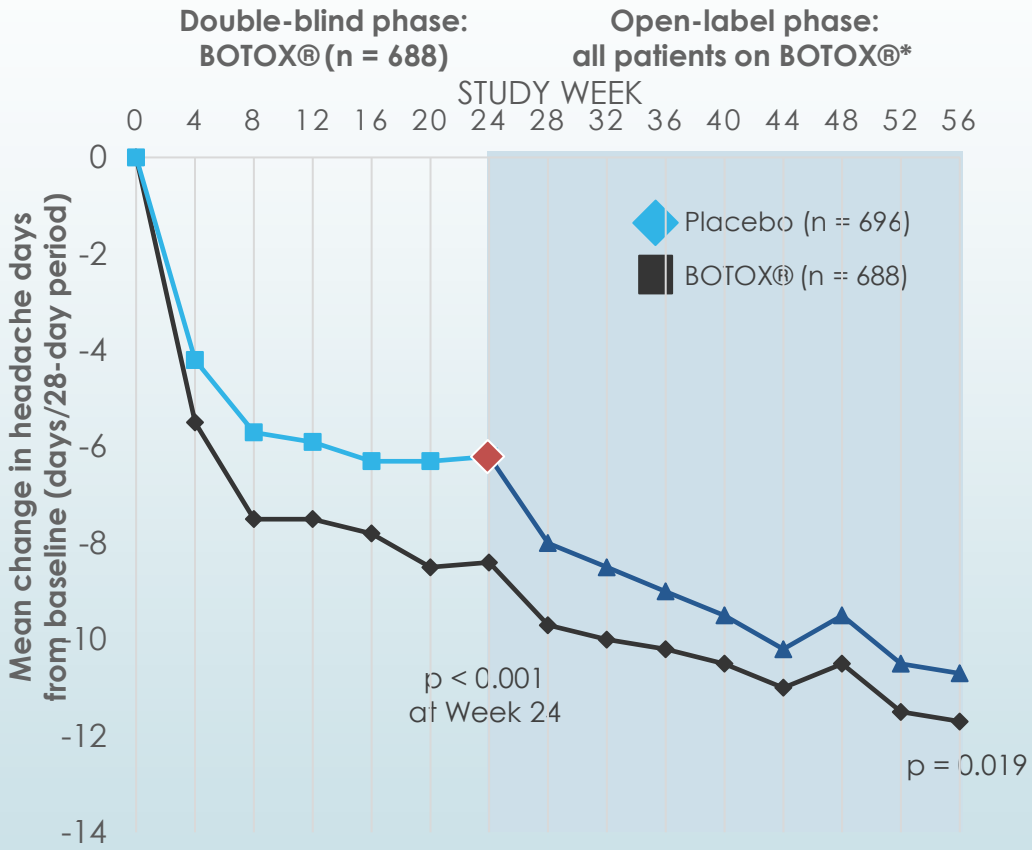
PREEMPT consisted of two phase III studies of patients with chronic migraine

- Global study across 122 sites in North America (106) and Europe (16) with 1384 patients
- 24-week, randomised, double-blind, placebo-controlled phase
- 32-week, open-label phase
- BOTOX® 155 U was administered as 31 fixed-site, fixed-dose injections
- An additional 40 U could be administered using a follow-the-pain strategy
- Headache symptoms and medications were recorded in a daily telephone diary

***Headache* 2011;51:1358-73**

PREEMPT pooled primary endpoint results (Weeks 24 and 56): frequency of headache days

- BOTOX® resulted in a significant improvement in frequency of headache days compared with placebo ($p < 0.001$ at 24 weeks)
- This improvement was sustained to the end of the 56-week open-label period ($p = 0.019$)



***Headache* 2011;51:1358-73**

Treatment-related adverse effect

Adverse events	BOTOX® (n = 687) (%)	Placebo (n = 692) (%)
Total treatment-related AEs	29.4	12.7
Neck pain	6.7	2.2
Muscular weakness	5.5	0.3
Eyelid ptosis	3.3	0.3
Musculoskeletal pain	2.2	0.7
Injection-site pain	3.2	2.0
Headache	2.9	1.6
Myalgia	2.6	0.3
Musculoskeletal stiffness	2.3	0.7

***Headache* 2011;51:1358-73**

全民健康保險藥物給付項目及支付標準共同擬訂會議

藥品部分第 40 次(108 年 10 月)會議紀錄

時　　間：108 年 10 月 17 日(星期四)上午 9 時 30 分

結論：

1. 慢性偏頭痛之預防性治療部分：根據台灣頭痛醫學會於 2017 年公布最新「偏頭痛預防性藥物治療準則」，Botox 藥品在預防性偏頭痛的治療，證據強度 A，推薦等級 I。台灣本土研究，亦顯示 Botox 藥品用於難治型慢性偏頭痛，仍然可以讓 40%的病人，達到降低頭痛天數 30%以上的效果，臨床有其需要性，同意納入給付範圍。

2020/1/1起實施

7.慢性偏頭痛之預防性治療

(○○/○○/1)

(1)需經事前審查核准後使用。

(2)限神經內科或神經外科專科醫師診斷及注射。

(3)需符合慢性偏頭痛診斷：至少有 3 個月時間，每個月≧15 天，每次持續 4 小時以上，且其中符合偏頭痛診斷的發作每個月≧8 天。(重要限制：Botox 對每個月頭痛天數≤14 天的陣發性偏頭痛之安全性及有效性，尚無證據證實其療效)。

(4)患者需經 3 種（含）以上偏頭痛預防用藥物（依據台灣頭痛學會發表之慢性偏頭痛預防性藥物治療準則之建議用藥，至少包括 topiramate）治療無顯著療效，或無法忍受其副作用

(5)每次注射最高劑量 Botox 155 單位，且每年最多 4 個療程。

(6)首次申請給付 2 個療程，2 個療程治療之後，評估每月頭痛天數，需比治療前降低 50%以上，方可持續給付。

(7)接續得申請一年療程，分為 4 次注射治療。療程完畢後半年內不得再次申請。

(8)若病況再度符合慢性偏頭痛診斷，得再次申請一年使用量時，需於病歷記錄治療後相關臨床資料，包括頭痛天數。

(9)神經內科、神經外科專科醫師需經台灣神經學學會訓練課程認證慢性偏頭痛診斷與 Botox PREEMPT 155U 標準注射法。

記錄日期：109 年 8 月 14 日

	頭痛程度	當日頭痛幾小時	是否伴隨以下症狀，請打V？
早上	1=輕微 ☑ 2=中度 ☐ 3=嚴重 ☐	9:10～1HR	☐噁心感/嘔吐 ☑對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☑身體活動會加重頭痛 ☑其他合併徵兆 太陽穴、眼球劇痛、右肩膀痛
下午	1=輕微 ☑ 2=中度 ☐ 3=嚴重 ☐	16:30～1HR	☐噁心感/嘔吐 ☑對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☑身體活動會加重頭痛 ☑其他合併徵兆 〃
晚上	1=輕微 ☑ 2=中度 ☐ 3=嚴重 ☐	22:20～½HR	☐噁心感/嘔吐 ☑對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☑其他合併徵兆 〃
睡眠	1=輕微 ☐ 2=中度 ☐ 3=嚴重 ☐	0H	☐噁心感/嘔吐 ☐對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☐其他合併徵兆

	使用頭痛相關藥物名稱及劑量	止痛藥有效嗎？(0=沒效；1=一點；2=有效；3=不痛)	影響到工作或日常生活	月經來的日子
早上	Lactam, Livalo Methy. cobul	1	否	
下午	Sprovel, Galvus Kinax, Suzin	1	是	X
晚上	Diapin	1	否	
睡眠				
備註				

記錄日期：109 年 8 月 15 日

	頭痛程度	當日頭痛幾小時	是否伴隨以下症狀，請打V？
早上	1=輕微 ☑ 2=中度 ☐ 3=嚴重 ☐	9:45～½HR	☑噁心感/嘔吐 ☑對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☑身體活動會加重頭痛 ☑其他合併徵兆 太陽穴、眼球劇痛
下午	1=輕微 ☑ 2=中度 ☐ 3=嚴重 ☐	12:40～2HRS 16:10～½HR	☐噁心感/嘔吐 ☐對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☐其他合併徵兆 〃
晚上	1=輕微 ☑ 2=中度 ☐ 3=嚴重 ☐	18:45～2HRS 21:20～1HR	☐噁心感/嘔吐 ☐對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☐其他合併徵兆 〃
睡眠	1=輕微 ☐ 2=中度 ☐ 3=嚴重 ☐	0H	☐噁心感/嘔吐 ☐對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☐其他合併徵兆

	使用頭痛相關藥物名稱及劑量	止痛藥有效嗎？(0=沒效；1=一點；2=有效；3=不痛)	影響到工作或日常生活	月經來的日子
早上	同前頁	1	否	
下午		0	否	
晚上			否	
睡眠				
備註				

記錄日期：10[1]年 8 月 31 日

	頭痛程度	當日頭痛幾小時	是否伴隨以下症狀，請打V？
早上	1=輕微 ☑ 張文能 2=中度 ☐ 3=嚴重 ☐	2	☐噁心感/嘔吐 ☐對光線/聲音敏感 ☑頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☐其他合併徵兆 _____
下午	1=輕微 ☐ 2=中度 ☑ 張文能 3=嚴重 ☐	3	☐噁心感/嘔吐 ☑對光線/聲音敏感 ☑頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☑其他合併徵兆 _____
晚上	1=輕微 ☐ 2=中度 ☐ 3=嚴重 ☑ 張文能	4	☐噁心感/嘔吐 ☐對光線/聲音敏感 ☑頭痛像脈搏一樣跳動 ☐單側開始 ☑身體活動會加重頭痛 ☑其他合併徵兆 _____
睡眠	1=輕微 ☐ 2=中度 ☐ 3=嚴重 ☑ 張文能	4	☐噁心感/嘔吐 ☐對光線/聲音敏感 ☑頭痛像脈搏一樣跳動 ☐單側開始 ☑身體活動會加重頭痛 ☐其他合併徵兆 _____

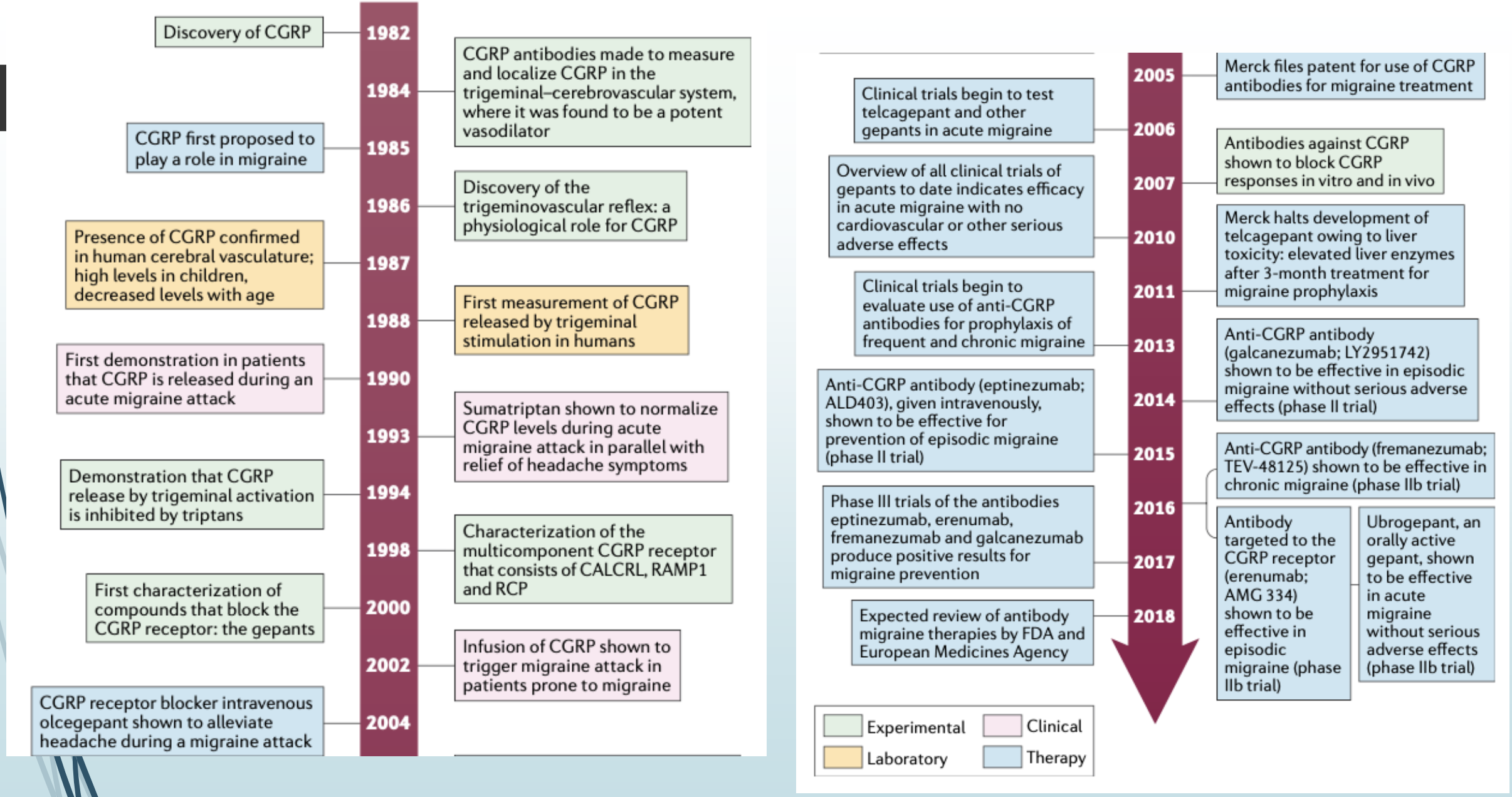
	使用頭痛相關藥物名稱及劑量	止痛藥有效嗎？(0=沒效；1=一點；2=有效；3=不痛)	影響到工作或日常生活	月經來的日子
早上	1 張文能	有 2	會	
下午	2 張文能	有 2	會	
晚上	1 張文能	有 2	會	
睡眠	1	有 2	會	
備註	增加劑量	有 2	有	

記錄日期：109 年 8 月 31 日

	頭痛程度	當日頭痛幾小時	是否伴隨以下症狀，請打V？
早上	1=輕微 ☑ 2=中度 ☐ 3=嚴重 ☐	3	☐噁心感/嘔吐 ☑對光線/聲音敏感 ☑頭痛像脈搏一樣跳動 ☐單側開始 ☑身體活動會加重頭痛 ☑其他合併徵兆 _____
下午	1=輕微 ☑ 2=中度 ☐ 3=嚴重 ☐	2	☐噁心感/嘔吐 ☑對光線/聲音敏感 ☑頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☑其他合併徵兆 _____
晚上	1=輕微 ☐ 2=中度 ☑ 3=嚴重 ☐	4	☑噁心感/嘔吐 ☐對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☐身體活動會加重頭痛 ☐其他合併徵兆 _____
睡眠	1=輕微 ☐ 2=中度 ☐ 3=嚴重 ☑	1	☑噁心感/嘔吐 ☐對光線/聲音敏感 ☐頭痛像脈搏一樣跳動 ☐單側開始 ☑身體活動會加重頭痛 ☐其他合併徵兆 _____

	使用頭痛相關藥物名稱及劑量	止痛藥有效嗎？(0=沒效；1=一點；2=有效；3=不痛)	影響到工作或日常生活	月經來的日子
早上	1 張文能	1	有	
下午	1 張文能	2	有	
晚上	1 張文能	2	有	
睡眠	1 張文能	1	有	
備註	1 張文能	1	痛時增加劑量	

Evolving treatment


1982
Discovery of CGRP
1984
CGRP antibodies made to measure and localize CGRP in the trigeminal–cerebrovascular system, where it was found to be a potent vasodilator
1985
CGRP first proposed to play a role in migraine
1986
Discovery of the trigeminovascular reflex: a physiological role for CGRP
1987
Presence of CGRP confirmed in human cerebral vasculature; high levels in children, decreased levels with age
1988
First measurement of CGRP released by trigeminal stimulation in humans
1990
First demonstration in patients that CGRP is released during an acute migraine attack
1993
Sumatriptan shown to normalize CGRP levels during acute migraine attack in parallel with relief of headache symptoms
1994
Demonstration that CGRP release by trigeminal activation is inhibited by triptans
1998
Characterization of the multicomponent CGRP receptor that consists of CALCRL, RAMP1 and RCP
2000
First characterization of compounds that block the CGRP receptor: the gepants
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Infusion of CGRP shown to trigger migraine attack in patients prone to migraine
2004
CGRP receptor blocker intravenous olcegepant shown to alleviate headache during a migraine attack
2005
Merck files patent for use of CGRP antibodies for migraine treatment
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Antibodies against CGRP shown to block CGRP responses in vitro and in vivo
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Overview of all clinical trials of gepants to date indicates efficacy in acute migraine with no cardiovascular or other serious adverse effects
Merck halts development of telcagepant owing to liver toxicity: elevated liver enzymes after 3-month treatment for migraine prophylaxis
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Clinical trials begin to evaluate use of anti-CGRP antibodies for prophylaxis of frequent and chronic migraine
2013
Anti-CGRP antibody (galcanezumab; LY2951742) shown to be effective in episodic migraine without serious adverse effects (phase II trial)
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Anti-CGRP antibody (eptinezumab; ALD403), given intravenously, shown to be effective for prevention of episodic migraine (phase II trial)
2015
Anti-CGRP antibody (fremanezumab; TEV-48125) shown to be effective in chronic migraine (phase IIb trial)
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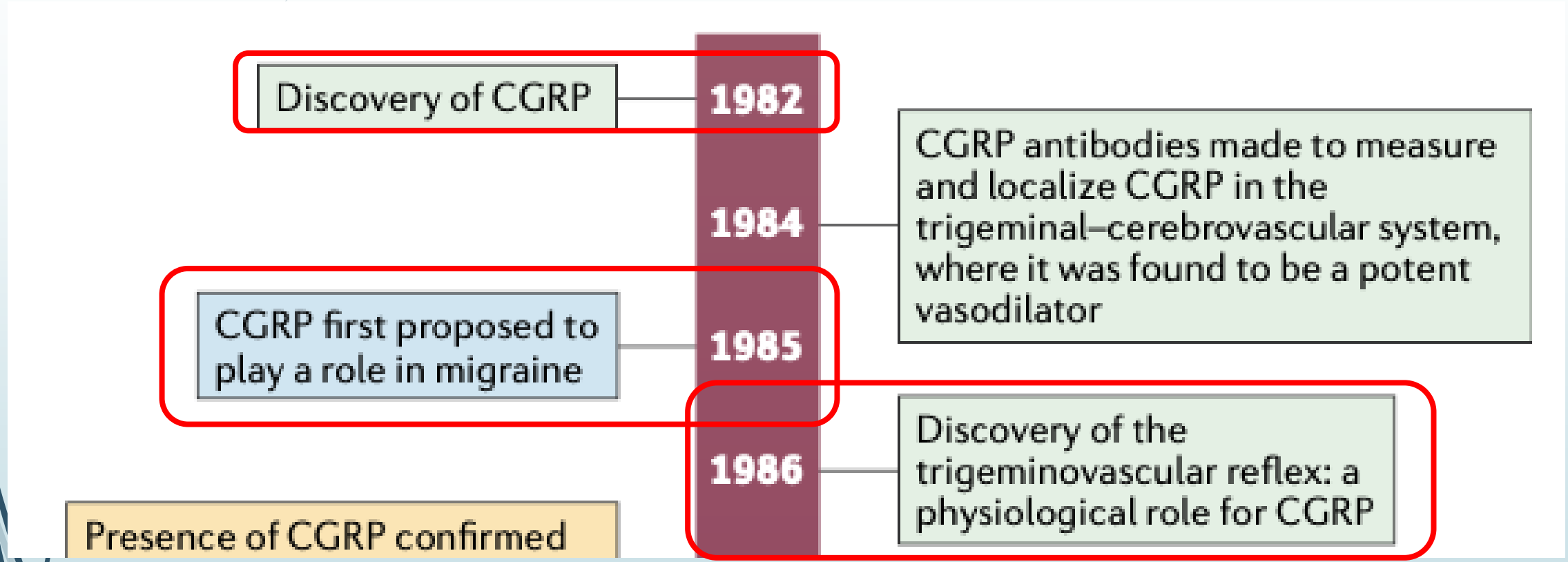
2018
Expected review of antibody migraine therapies by FDA and European Medicines Agency
Experimental
Clinical
Laboratory
Therapy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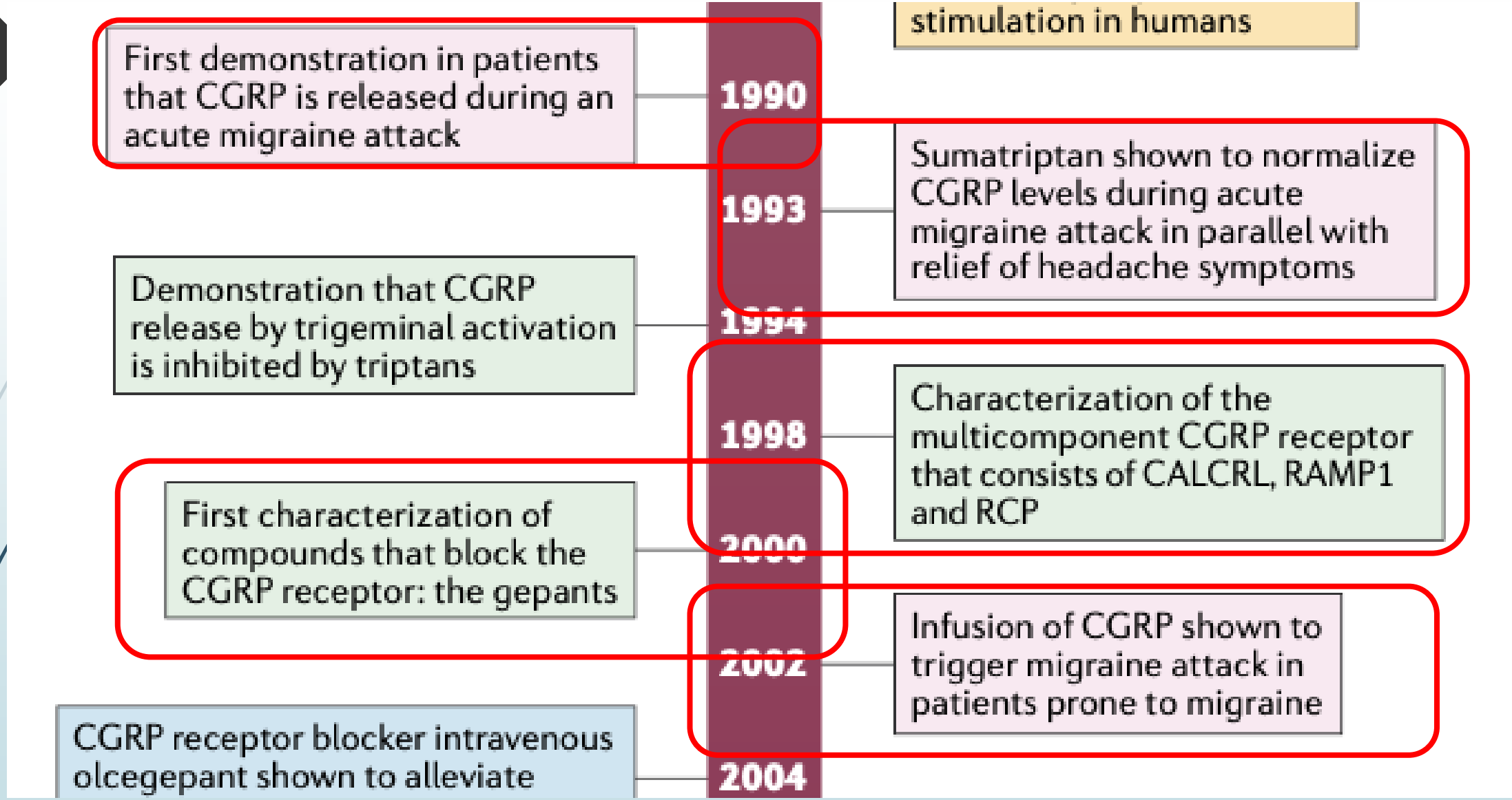
Presence of CGRP confirmed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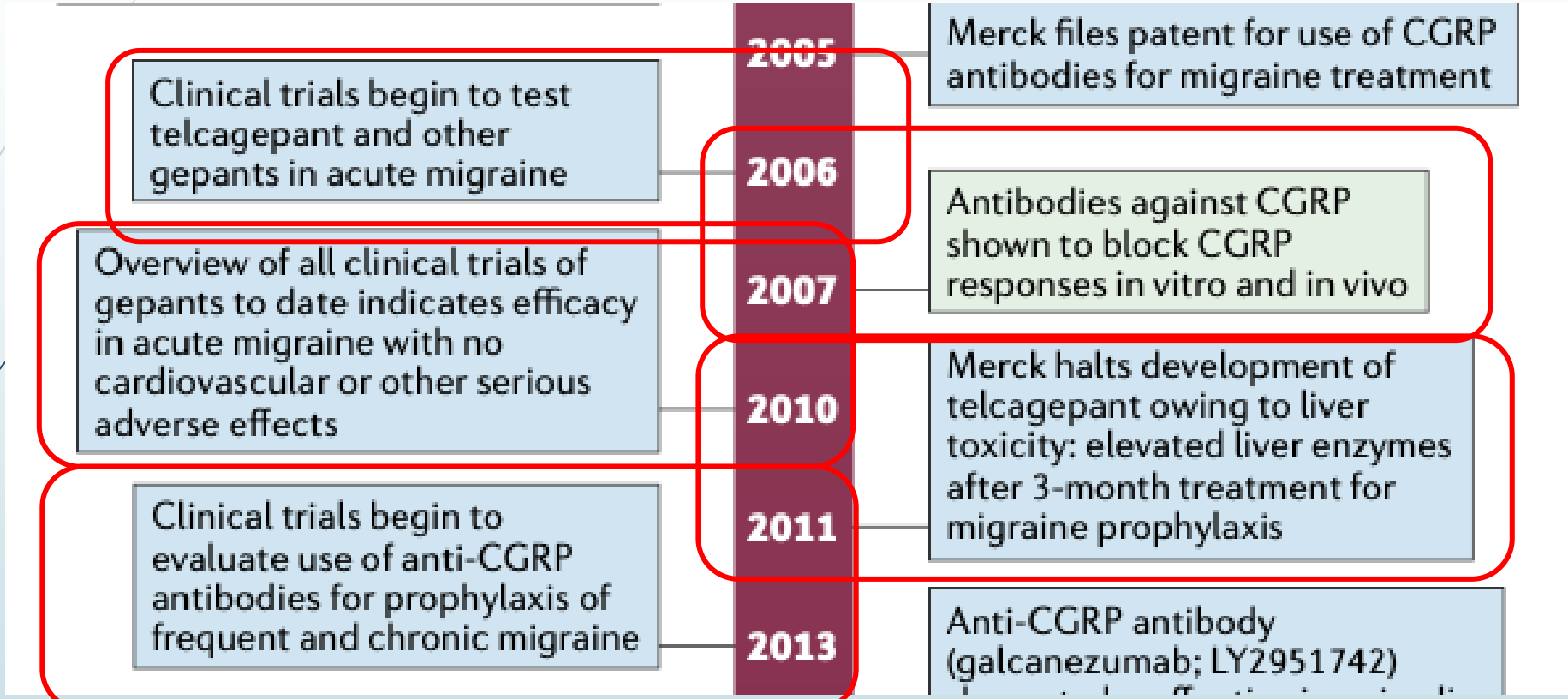
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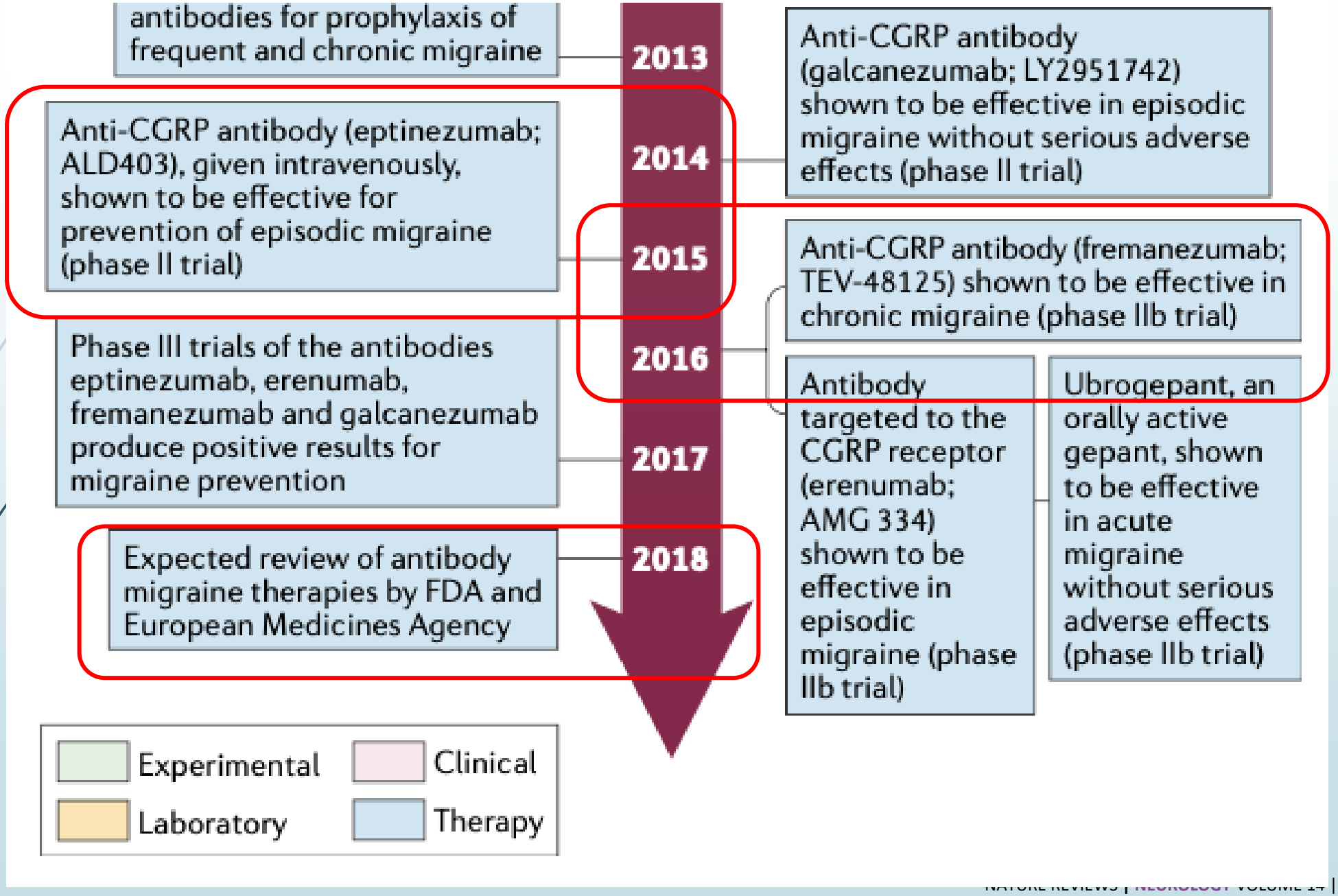
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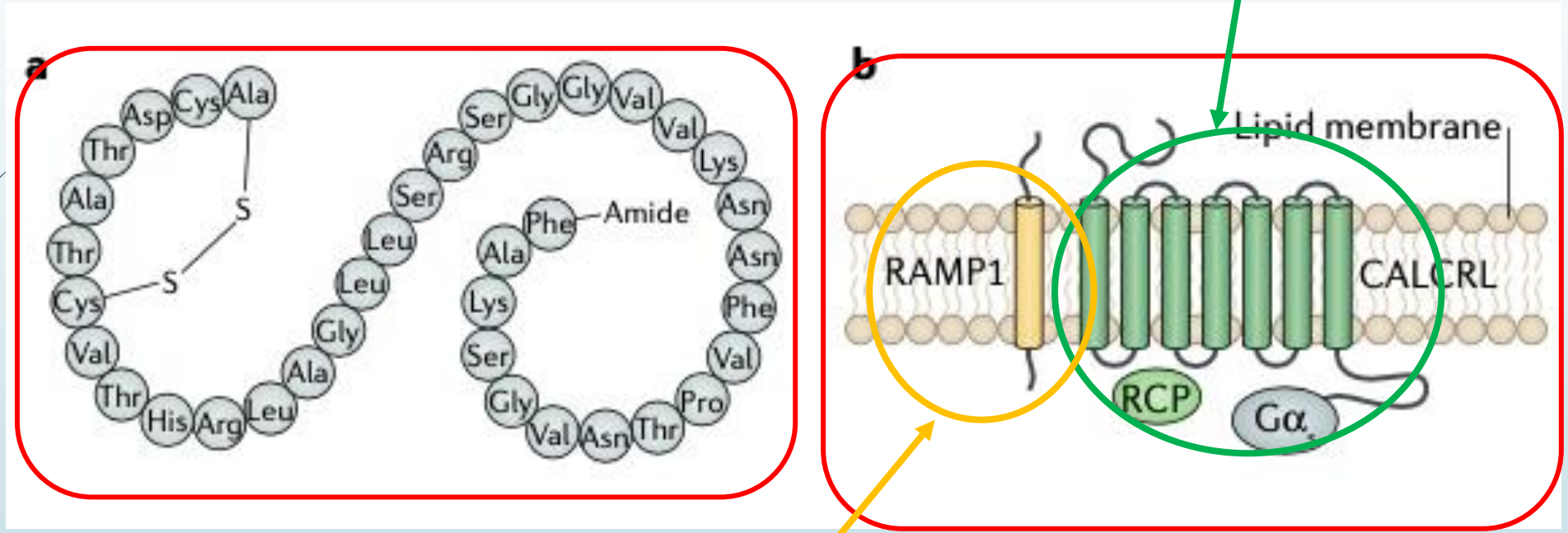
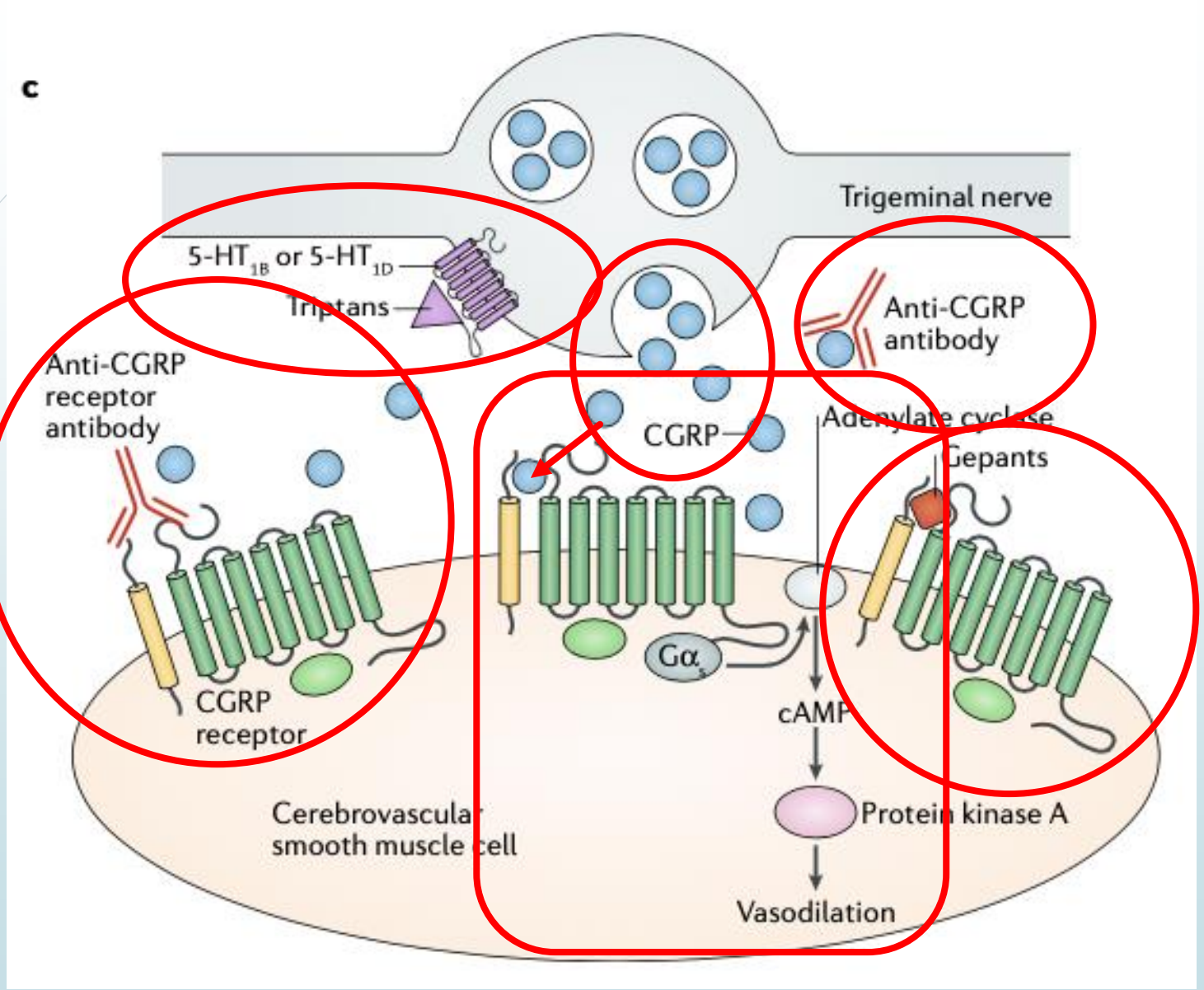
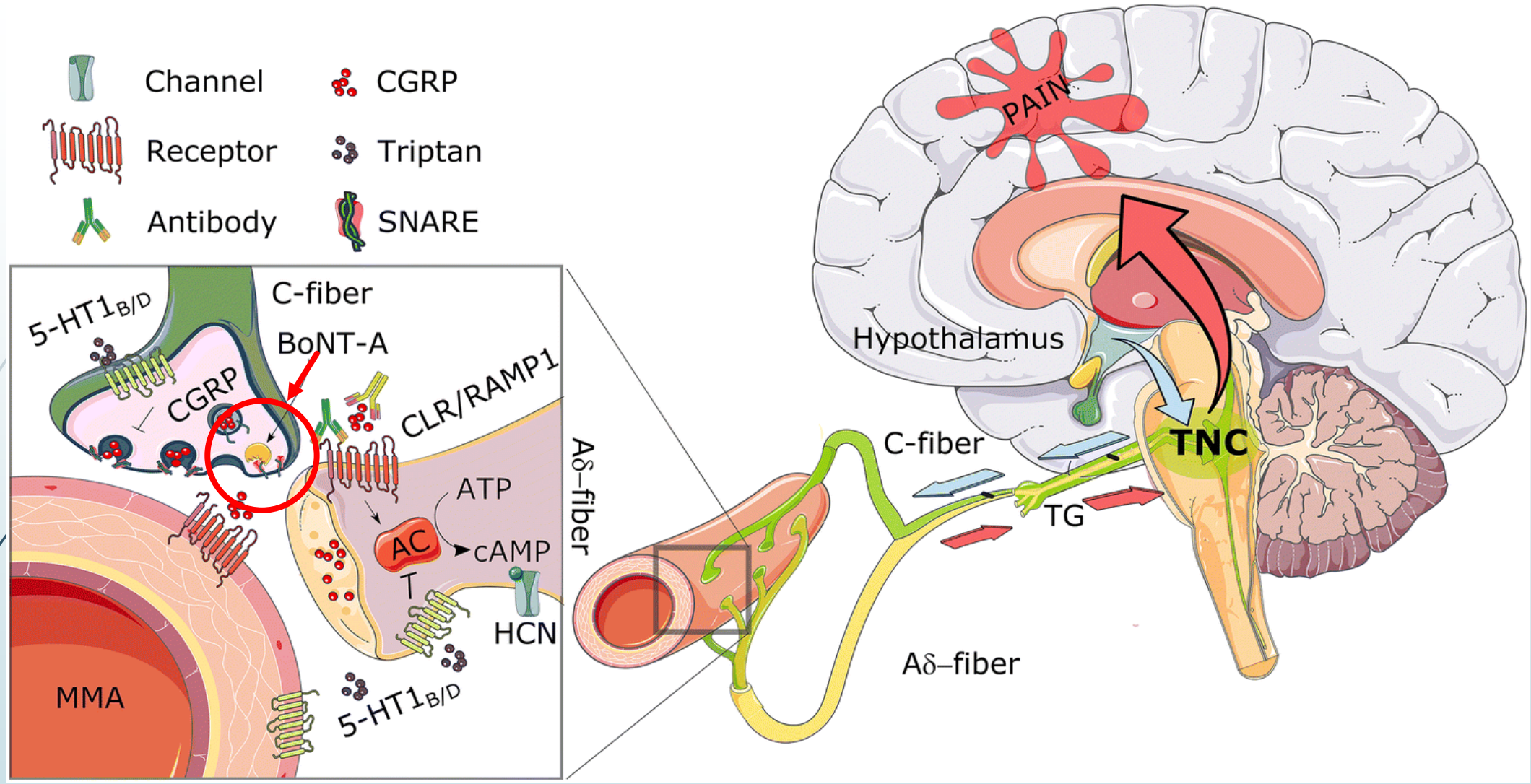
2017
Expected review of antibody migraine therapies by FDA and European Medicines Agency
2018
Experimental
Clinical
Laboratory
Therapy

multimeric complex made up of the 7 transmembrane GPCR designated CT receptor-like receptor (CLR) domains

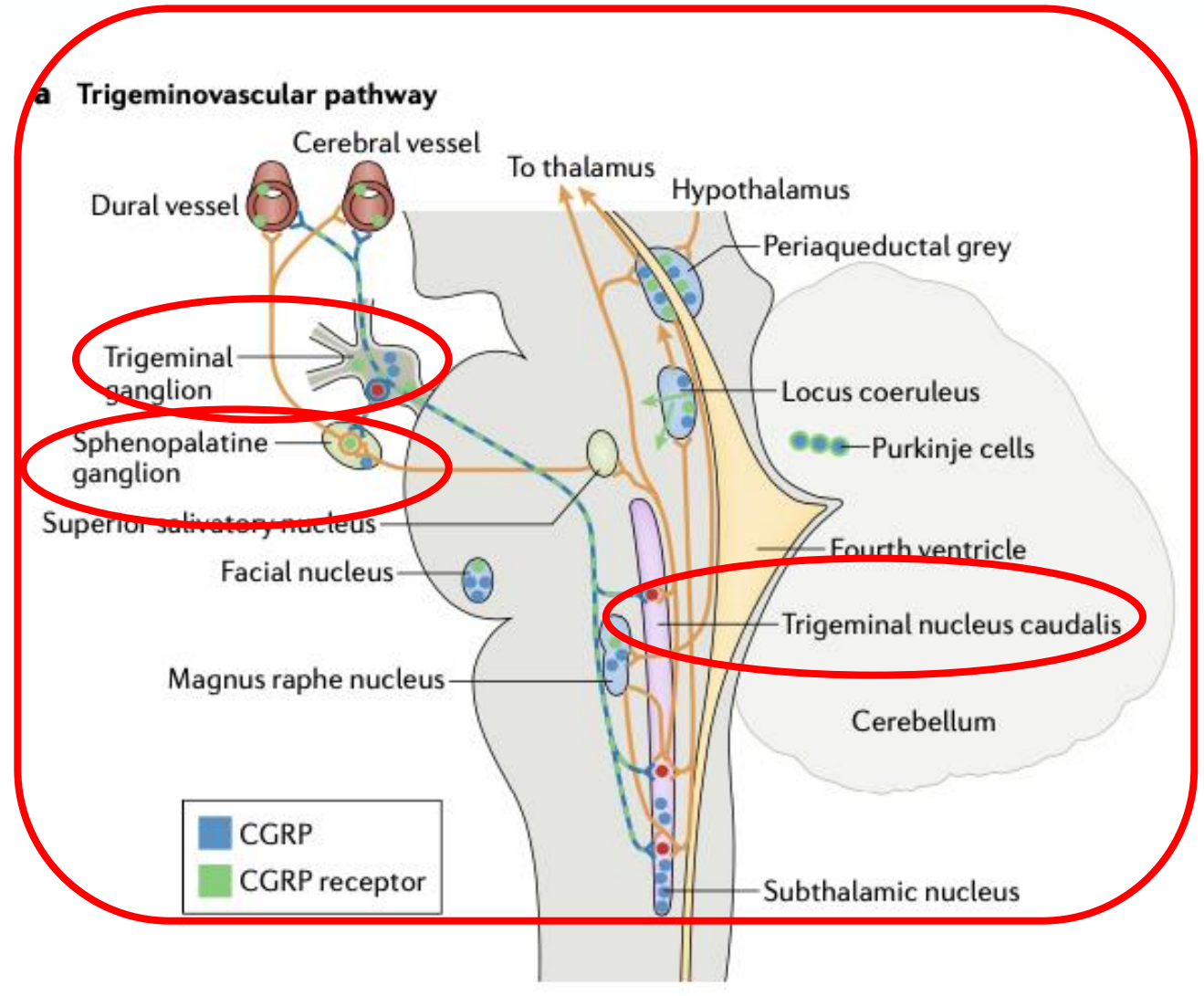


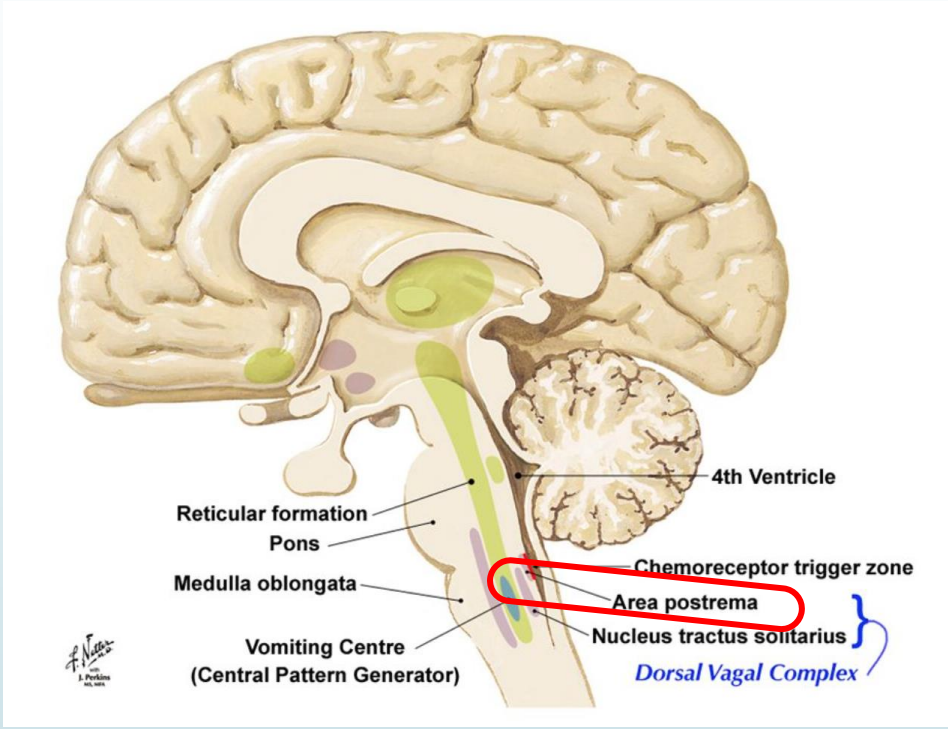
single transmembrane protein designated receptor activity modifying protein 1 (RAMP1)

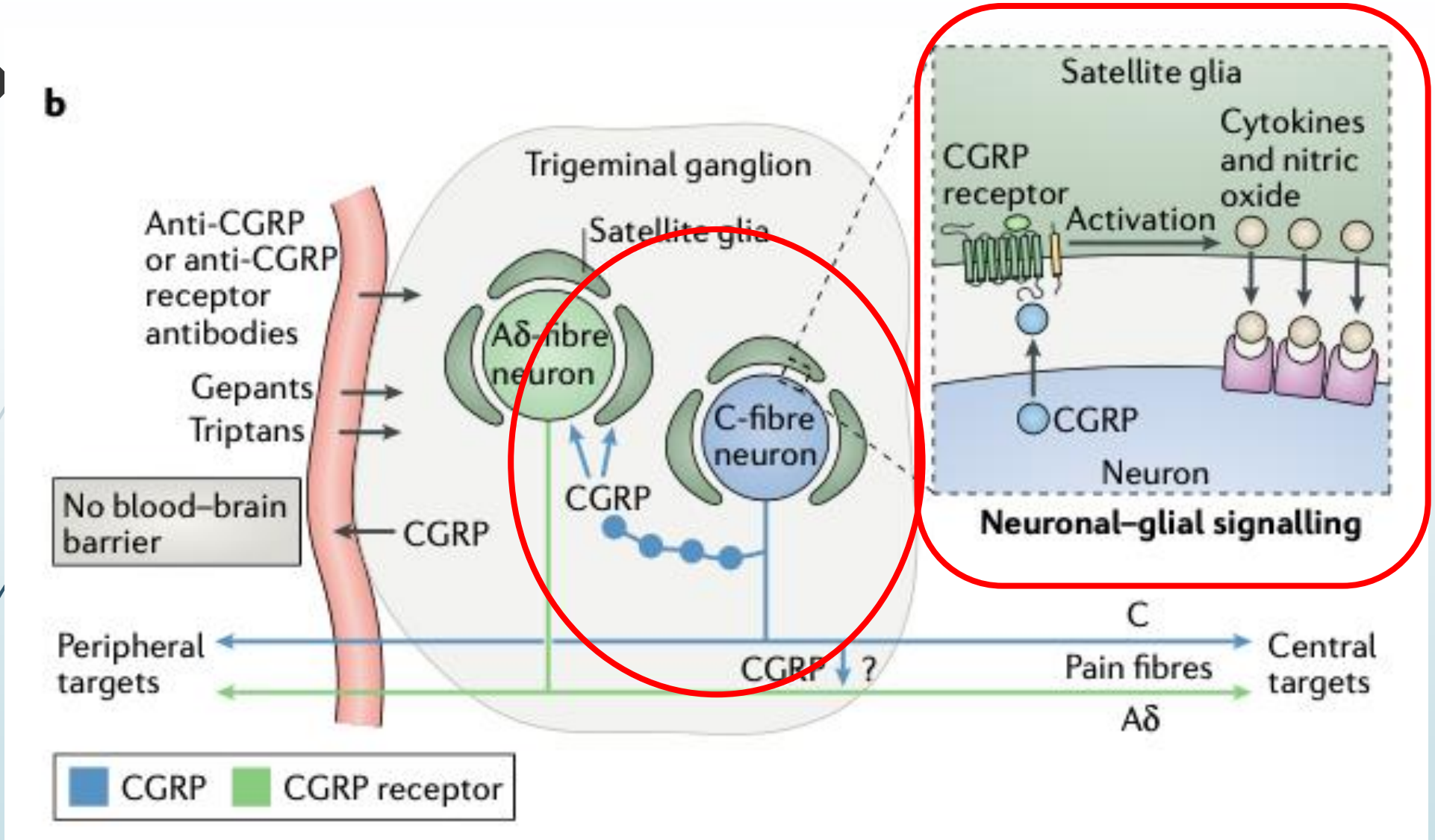

c
Trigeminal nerve
5-HT1B or 5-HT1D
Triptans
Anti-CGRP antibody
Anti-CGRP receptor antibody
CGRP
Adenylate cyclase
Gepants
Gαs
CGRP receptor
cAMP
Cerebrovascular smooth muscle cell
Protein kinase A
Vasodilation



CNS Drugs volume 33, pages525–537(2019)

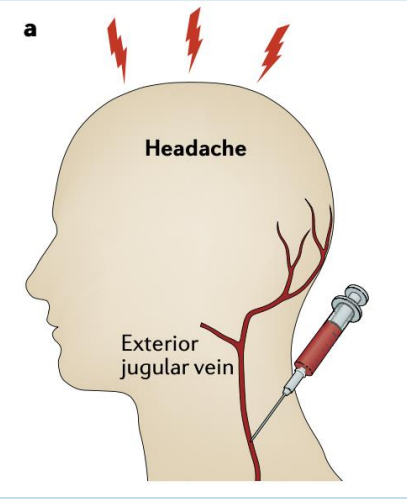

a Trigeminovascular pathway
Cerebral vessel
To thalamus
Hypothalamus
Dural vessel
Periaqueductal grey
Trigeminal ganglion
Locus coeruleus
Sphenopalatine ganglion
Purkinje cells
Superior salivatory nucleus
Fourth ventricle
Facial nucleus
Trigeminal nucleus caudalis
Magnus raphe nucleus
Cerebellum
CGRP
CGRP receptor
Subthalamic nucleus


4th Ventricle
Reticular formation
Pons
Chemoreceptor trigger zone
Medulla oblongata
Area postrema
Nucleus tractus solitarius
Vomiting Centre
(Central Pattern Generator)
Dorsal Vagal Complex


b
Trigeminal ganglion
Satellite glia
Anti-CGRP or anti-CGRP receptor antibodies
Gepants
Triptans
No blood–brain barrier
CGRP
Aδ-fibre neuron
C-fibre neuron
CGRP
Peripheral targets
CGRP
?
C
Pain fibres
Aδ
Central targets
CGRP
CGRP receptor
Satellite glia
CGRP receptor
Cytokines and nitric oxide
Activation
CGRP
Neuron
Neuronal–glial signalling

CGRP and migraine

- CGRP increased in external jugular venous blood during a migraine attack compared to non-migraine controls
- CGRP was reduced concomitant with migraine headache relief by sumatriptan
- IV CGRP to migraine patients during a headache free phase
  → induced not only an immediate moderate headache but also a delayed headache that completely mimicked their migraine
  → but no pain in other body parts



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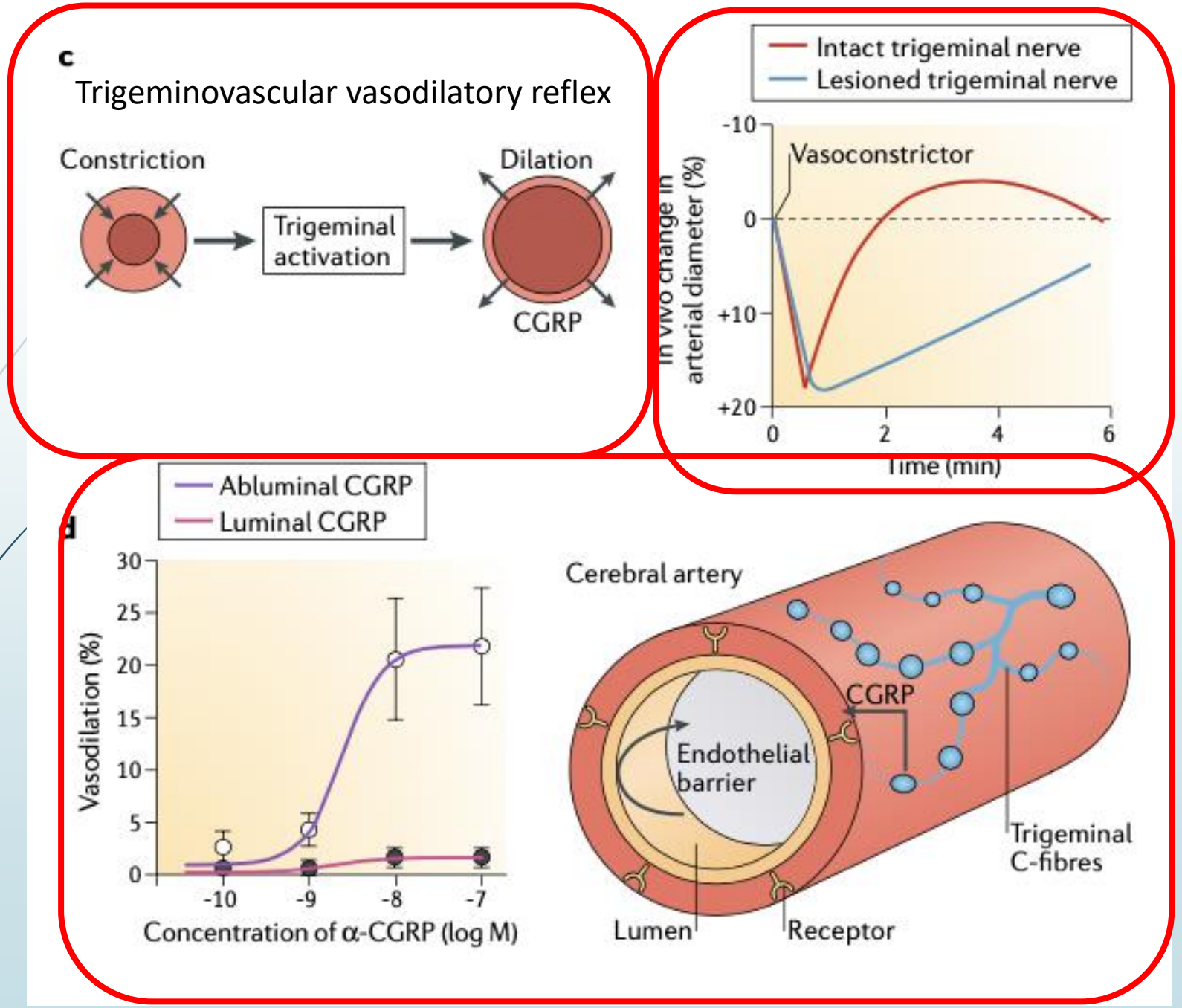
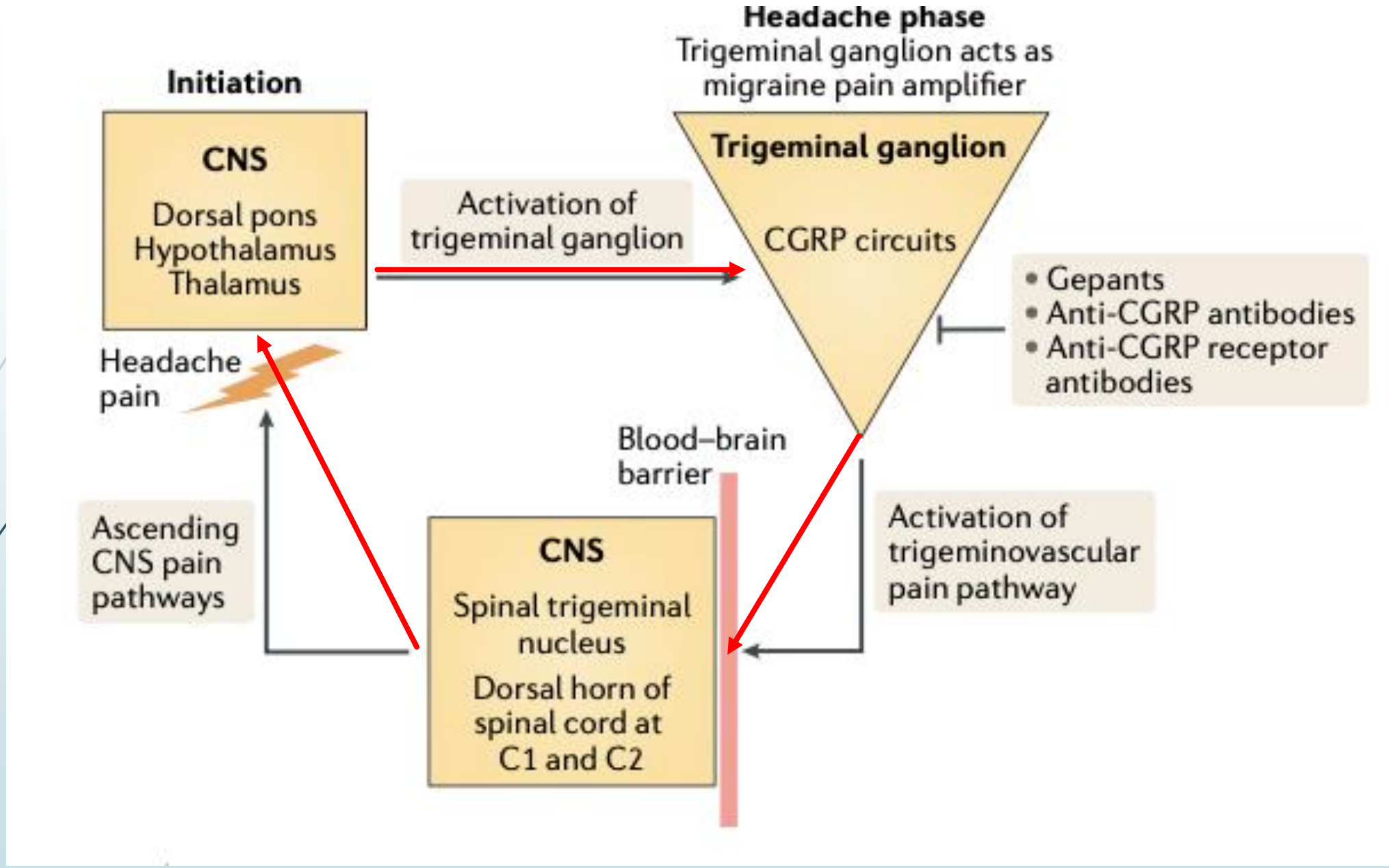

c
Trigeminovascular vasodilatory reflex
Constriction
Trigeminal activation
Dilation
CGRP
Intact trigeminal nerve
Lesioned trigeminal nerve
In vivo change in arterial diameter (%)
Vasoconstrictor
-10
0
+10
+20
0
2
4
6
Time (min)
d
Abluminal CGRP
Luminal CGRP
Vasodilation (%)
30
25
20
15
10
5
0
-10
-9
-8
-7
Concentration of α-CGRP (log M)
Cerebral artery
CGRP
Endothelial barrier
Trigeminal C-fibres
Lumen
Receptor


Initiation
Headache phase
Trigeminal ganglion acts as migraine pain amplifier
CNS
Dorsal pons
Hypothalamus
Thalamus
Activation of trigeminal ganglion
Trigeminal ganglion
CGRP circuits
• Gepants
• Anti-CGRP antibodies
• Anti-CGRP receptor antibodies
Headache pain
Blood–brain barrier
Ascending CNS pain pathways
CNS
Spinal trigeminal nucleus
Dorsal horn of spinal cord at C1 and C2
Activation of trigeminovascular pain pathway

CGRP-related therapy

Gepants

Table 2.—Comparison of the Binding Affinity and Functional Activity of Small Molecule CGRP-RAs at CGRP and Amylin 1 Receptors

Small Molecule CGRP Receptor Antagonist	CGRP Receptor (CLR + RAMP1) Ligand Binding SK-N-MC Cells	CGRP Receptor (CLR + RAMP1) Functional cAMP SK-N-MC† HEK-293‡ Cell Types	AMY_1 Receptor (CTR + RAMP1) Ligand Binding HEK-293† COS-7‡ SK-N-MC§ Cell Types	AMY_1 Receptor (CTR + RAMP1) Functional cAMP COS-7† HEK-297‡ Cell Types	Fold CGRP vs AMY_1 Receptor Selectivity Binding: Functional
Olcegepant (BIBN4096BS)	0.05 nM	0.11 nM†	n.a.	36 nM†	327 (functional)
Telcagepant (MK-0974)	0.8 nM	0.5 nM‡	190 nM†		238 (binding)
MK-3207	0.02 nM	0.1 nM‡	0.8 nM‡		40 binding
Rimegepant (BMS-927711)	0.027 nM	0.14 nM†	n.a.	n.a.	n.a.
Ubrogepant (MK-1602)†	0.07 nM	0.08 nM‡	8.2 nM§	8.4 nM‡	117:105
Atogepant (AGN-241689: MK-8031)†	0.015 nM	0.026 nM‡	1.8 nM§	2.4 nM‡	120:92

Ligand binding was performed in cells expressing human CGRP or AMY1 receptors using ^{125}I-CGRP or ^{125}I-Amylin, respectively. Functional potency was determined in cells by estimating human CGRP or amylin-stimulated cAMP responses in the presence and absence of antagonist.

Data were summarized from review citation 8 or received as a personal communication from Allergan.†

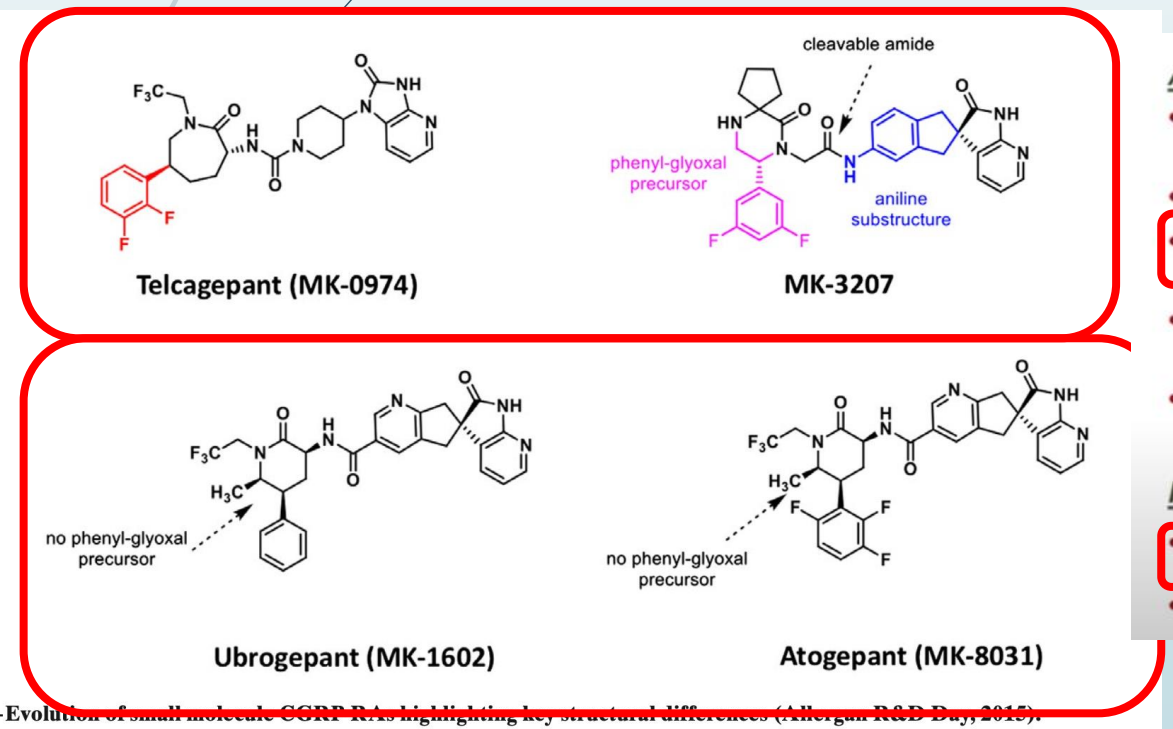


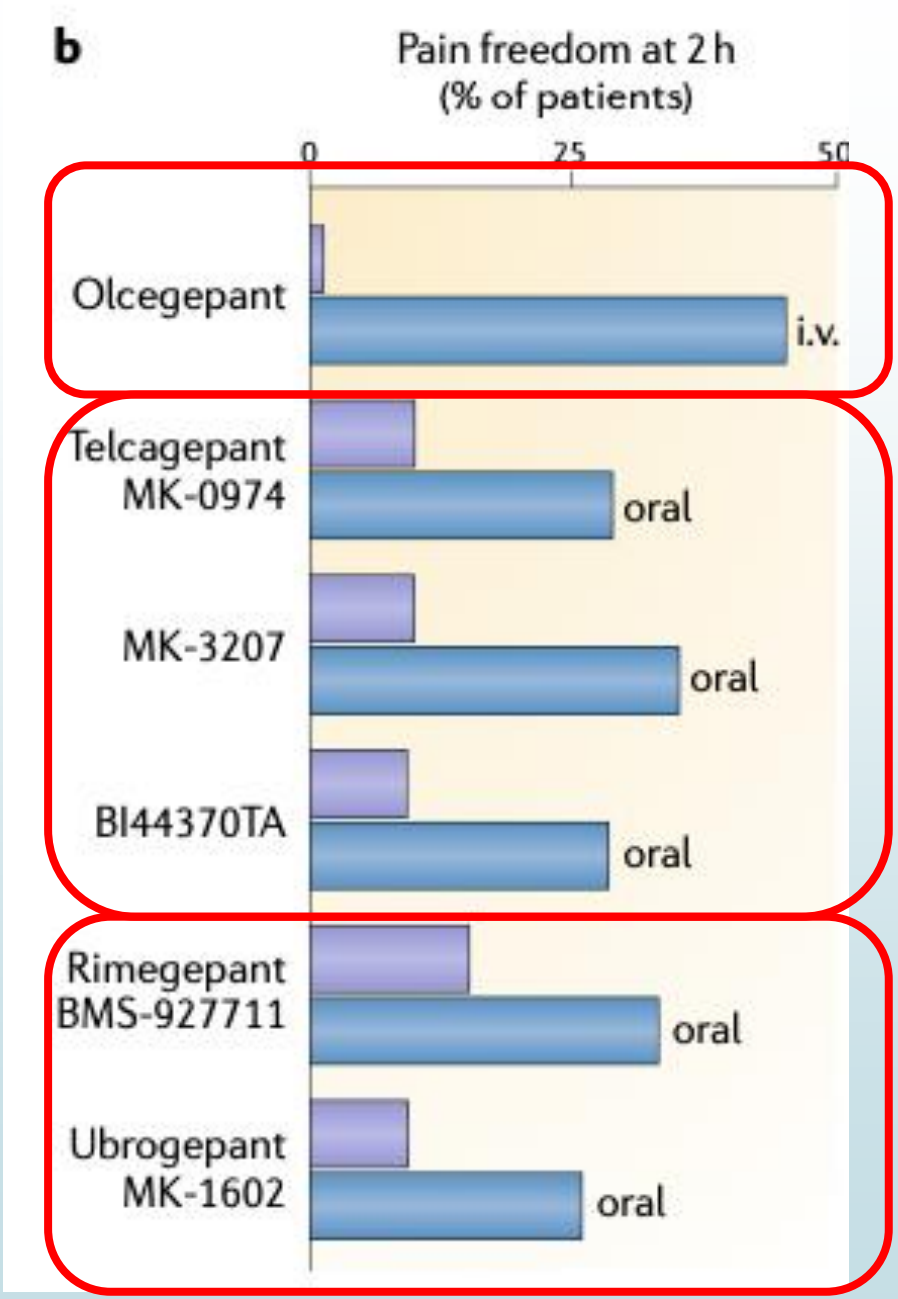
Fig. 2.—Evolution of small molecule CGRP-RAs highlighting key structural differences (Allergan R&D Day, 2015).

Acute Treatment of Episodic Migraine

- There have been six gepants tested which demonstrated efficacy in acute migraine treatment, olcegepant, BI 44370 TA, telcagepant, MK-3207, rimegepant, and ubrogepant
- BI 44370 TA, telcagepant, and MK-3207 all reportedly liver toxic
- **Ubrogepant** and **rimegepant** are completing the last phase of regulatory trials and will likely be submitted to the FDA for acute treatment of migraine this year
- They do not cause blood vessels to constrict, so, unlike triptans, they should be safe in those with vascular disease
- They work more like naratriptan (Amerge) than sumatriptan (Imitrex): gentle and slow in onset

Preventive Treatment of Episodic Migraine

- **Atogepant** vs placebo is underway in Phase 2 for migraine prevention
- **BHV-3500** will be tested for prevention in Phase 2


b
Pain freedom at 2 h
(% of patients)
0
25
50
Olcegepant
i.v.
Telcagepant
MK-0974
oral
MK-3207
oral
BI44370TA
oral
Rimegepant
BMS-927711
oral
Ubrogepant
MK-1602
oral

If small molecular cause hepatotoxicity, how about big molecular ?

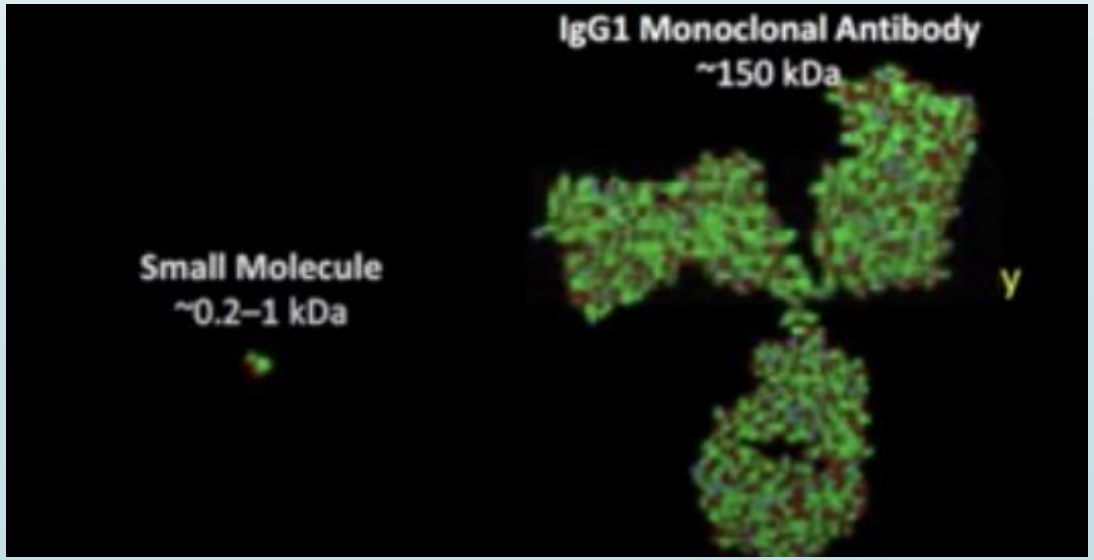


Table 1 | **CGRP-related therapies for migraine and other headache disorders**

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
Acute therapy				
Ubrogepant	Relief from acute migraine attack	Oral, as needed	CGRP receptor antagonist	Positive phase IIb results[49]; phase III trials ongoing

cCH, chronic cluster headache; CGRP, calcitonin gene-related peptide; CM, chronic migraine; eCH, episodic cluster headache; EM, episodic migraine; EMEA, European Medicines Evaluation Agency. [a]Prevention is defined as a reduction in headache days.

Table 3.—Monoclonal Antibodies Against CGRP or the CGRP Receptor Currently in Development

Marketed Name	AIMOVIG®	EMGALITY®	AJOVY®	TBD
Generic name	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab†
Characteristics	Human	Humanized	Humanized	Humanized
Sponsor	Amgen/Novartis	Lilly	Teva	Alder
Being studied for	Episodic migraine Chronic migraine Treatment resistant migraine (hot flashes)	Episodic migraine Chronic migraine Episodic cluster Chronic cluster‡ Treatment resistant migraine	Episodic migraine Chronic migraine Refractory migraine Episodic cluster Chronic cluster‡ Posttraumatic headaches	Episodic migraine Chronic migraine
Dosing	Monthly SC 70 or 140 mg	Loading dose 240 mg then 120 mg monthly SC	225 mg Monthly SC 675 mg Quarterly SC	Quarterly IV Final doses TBD
Target	CGRP receptor	CGRP peptide	CGRP peptide	CGRP peptide

†Produced in yeast.

‡Studies in chronic c

CGRP mAbs
- the common considerations

CGRP mAbs - benefits [1]

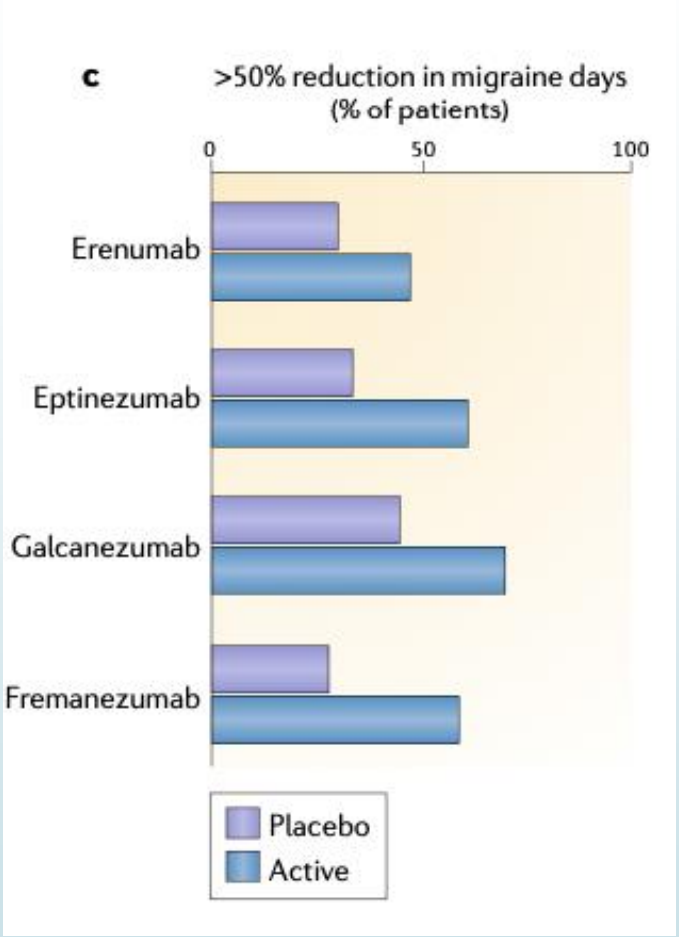
- Some benefits over small molecule drugs, especially in chronic indications:
  - (1) long-circulating plasma half-lives (weeks)
    ↔ small molecules (hours)
    → infrequent administration ➔better adherence
  - (2) lack liver toxic metabolites
  - (3) no metabolic drug-drug interactions
  - (4) exquisite target selectivity

CGRP mAbs - benefits [2]

- 1. Quick onset of effect, separating from placebo within 1 week
- 2. Clinically meaningful responses observed after 1 month
- 3. A subgroup of "super responders" (≥50% improvement and higher)
- 4. Responses not limited by past failure to other preventive medications
- 5. Safety and tolerability appear generally similar to placebo except for GI side effects

How about the effect?

- Erenemab:
  - ➔ ↓ 6.7 days reduction in monthly migraine days
  - ➔ ↓ 79 migraine days per year
- Galcanezumab and eptinezumab
  - ➔ 1/3 patients:
    - ↓ >75% monthly migraine days



Lancet Neurol. 2017 Jun;16(6):425-434
SKLAREVSKI AHS MEETING JUNE 2017
NATURE REVIEWS | NEUROLOGY VOLUME 14 | JUNE 2018

Clinical considerations

Current problems with prevention of migraine

- Current medication for other therapeutic use
- Even on the best dose and the best medication for several months, the likelihood of having a 50% reduction rate in headache days is less than half
- More than 80% patient quit from current preventive medication

Cephalalgia. 2015 May;35(6):478-88

European headache federation guideline: expert's opinion

When should treatment with anti-CGRP monoclonal antibodies be offered to patients with migraine?

- In patients with episodic migraine
  - who have failed at least two of the available medical treatments or
  - who cannot use other preventive treatments because of comorbidities, side effects or poor compliance

  ➔ we suggest the use of erenumab, fremanezumab, or galcanezumab
- In patients with chronic migraine
  - who have failed at least two of the available medical treatments or
  - who cannot use other preventive treatments because of comorbidities, side effects or poor compliance

  ➔ we suggest the use of erenumab, fremanezumab, or galcanezumab

The Journal of Headache and Pain (2019) 20:58

How should other preventive treatments be managed when using anti-CGRP monoclonal antibodies in patients with migraine?

- In patients with episodic migraine
  before starting erenumab, galcanezumab or fremanezumab we suggest to stop oral preventive drugs unless the patient had a previous history of chronic migraine before prevention; in this case, we suggest to add the anti-CGRP monoclonal antibody to the ongoing treatment and to re-assess the need of treatment withdrawal
- In patients with chronic migraine
  - who are on treatment with any oral drug with inadequate treatment response we suggest to add erenumab, fremanezumab, or galcanezumab and to consider later withdrawal of the oral drug
  - who are on treatment with onabotulinumtoxinA with inadequate treatment response we suggest to stop onabotulinumtoxinA before initiation of erenumab, fremanezumab, or galcanezumab
  - who are on treatment with erenumab, fremanezumab, or galcanezumab and who may benefit from additional prevention we suggest to add oral preventive drugs

The Journal of Headache and Pain (2019) 20:58

When should treatment with anti-CGRP monoclonal antibodies be stopped in patients with migraine?

- In patients with episodic migraine
  - we suggest to consider to stop treatment with erenumab, fremanezumab, and galcanezumab after 6–12 months of treatments
- In patients with chronic migraine
  - we suggest to consider to stop treatment with erenumab, fremanezumab, and galcanezumab after 6–12 months of treatments

The Journal of Headache and Pain (2019) 20:58

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

The Journal of Headache and Pain (2019) 20:58

In which patients anti-CGRP monoclonal antibodies are not to be used?

- In patients with migraine, we suggest to avoid anti-CGRP monoclonal antibodies in
  - pregnant or nursing women,
  - individuals with alcohol or drug abuse,
  - cardio and cerebrovascular diseases, and
  - with severe mental disorders

The Journal of Headache and Pain (2019) 20:58

Should binding and/or neutralizing antibodies be monitored?

- In patients with migraine on treatment with anti-CGRP monoclonal antibodies, we suggest not to test binding and/or neutralizing antibodies in daily clinical practice; we suggest to further study the possible implications of binding and/or neutralizing antibodies

The Journal of Headache and Pain (2019) 20:58

Take-home message

Current situation

Current preventive medications:

- were designed for other therapeutic areas
- have numerous side effects
- take 2-4 months to be effective
- Work in less than half of people
- sometimes don't even lower acute medication use

Future potential for MABs

- They were designed for primary migraine prevention
- They work in all migraine types
- Speed: time to onset: less than one month for most
- Tolerability: similar to placebo
- Safety: no safety signal
- Up to 1/3 have at least a 75% migraine day decrease
- Lower acute med use

The MABs may fundamentally change the way we treat migraine!
They are the first designer migraine preventive medications in our lifetime!

First Gepant Drug OK'd for Acute Migraine

— Oral CGRP receptor antagonist wins approval

by Judy George, Senior Staff Writer, MedPage Today December 23, 2019

WASHINGTON -- Ubrogepant (Ubrelvy) became the first oral calcitonin gene-related peptide (CGRP) receptor antagonist (gepant) drug to win approval for migraine, the FDA announced Monday.

The agency approved ubrogepant tablets for acute treatment of migraine with or without aura. The drug is not indicated for migraine prevention, the agency stated.

"The FDA is pleased to approve a novel treatment for patients suffering from migraine and will continue to work with stakeholders to promote the development of new safe and effective migraine therapies," said Billy Dunn, MD, acting director of the Office of Neuroscience in the FDA's Center for Drug Evaluation and Research, in a statement.

October 16, 2020

Rimegepant Under Review for Migraine Prevention

Brian Park, PharmD

A PDUFA target action date for the application has been set for the second quarter of 2021.

The Food and Drug Administration (FDA) has accepted for review the supplemental New Drug Application (sNDA) for rimegepant (Nurtec™ ODT; Biohaven) for the preventive treatment of migraine.

The sNDA is supported by data from a randomized, double-blind, placebo-controlled phase 2/3 study that assessed the efficacy and safety of rimegepant, a calcitonin gene-related peptide receptor antagonist, in adults who had migraines for at least 1 year and 4 to 18 moderate to severe migraine attacks per month over 3 months prior to enrollment. Patients were randomized to receive either rimegepant 75mg orally every other day (n=348) or placebo (n=347). The primary end point was the change from baseline in mean migraine days per month over the 12-week period.

AbbVie Announces Positive Phase 3 Data for Atogepant in Migraine Prevention

- Phase 3 ADVANCE trial evaluating atogepant meets primary endpoint of statistically significant reduction from baseline in mean monthly migraine days, compared to placebo, for all doses evaluated across a 12-week treatment period

- Trial also demonstrates statistically significant improvements in all six secondary endpoints in the 30 mg and 60 mg once-daily treatment arms

- Data from this trial and previous Phase 2/3 trial will be the basis for regulatory submissions in the U.S. and other countries

- These results support AbbVie's commitment to providing multiple treatment options, including BOTOX® (onabotulinumtoxinA) for the prevention of chronic migraine and UBRELVY™ (ubrogepant), to treat migraine

NEWS PROVIDED BY
AbbVie →
Jul 29, 2020, 08:45 ET

Lilly's REYVOW™ (lasmiditan), The First and Only Medicine in a New Class of Acute Treatment for Migraine, Receives FDA Approval

- The approval of REYVOW is significant because it represents the first new class of acute migraine treatment approved by the FDA in more than two decades

NEWS PROVIDED BY
Eli Lilly and Company →
Oct 11, 2019, 15:48 ET

SHARE THIS ARTICLE

INDIANAPOLIS, Oct. 11, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today

Thank you for your attention.

Feb 2021

Chi Ieong Lau 劉子洋

MD, MSc(Res), MSc, PhD Candidate

chiieong.lau@ndcn.oxon.org
website: https://www.ucl.ac.uk/icn/research/research-groups/applied-cognitive-neuroscience

EDUCATION

2015-present	**University College London, Queen Square, UK** PhD candidate, Cognitive Neuroscience
2011-2013	**University Of Oxford, UK** Masters of Science by Research in Clinical Neurosciences
2010-2011	**University College London, Queen Square, UK** Masters of Science in Cognitive Neuroscience (Distinction)
1997-2004	**National Defence Medical Center, Taiwan** Doctor of Medicine

CURRENT POSITIONS AND WORK EXPERIENCE

2019 - present	**Director**	Dementia Center, Shin Kong WHS Hospital, Taiwan
2004 - present	**Attending Neurologist** (Consultant Neurologist)	Shin Kong WHS Hospital, Taiwan
2020 - present	**Assistant Professor**	Institute of Biophotonics, National Yang-Ming University, Taiwan
2021 - present	**Assistant Professor**	College of Medicine, Fu-Jen Catholic University, Taiwan
2017 - present	**Director/ Supervisor of Board**	Taiwan Headache Society
2014 – 2017	**Secretary-General**	Taiwan Headache Society
2011 - 2013	**Research Fellow**	Nuffield Department of Clinical Neurosciences, University of Oxford
2010 - 2011	**Research Fellow**	Institute of Cognitive Neuroscience, Queen Square, UCL, London, UK

PROFESSIONAL QUALIFICATIONS

2019	Fellowship of the Macau Academy of Medicine (Neurology)
2015	Certificate of Headache Master (certificate no. 37) - accreditated by the International Headache Society
2009	Taiwan Registered Neurocritical Care Specialist
2007	Taiwan Registered Neurology Specialist
2004	Taiwan Registered Medical Doctor

PRIZES AND HONOURS (selected)

2020	Research Award, Shin Kong Wu Ho-Su Memorial Hospital
2010-2011	**British Chevening Scholar** (UK Government Scholarships)
2015	**Oral Poster Presentation Award**, the 5th Asian Regional Conference for Headache, Chiangmai International Headache Society
2014	Award of **Best Supervisors** of Postgradate year 1 (PGY1) Physicians
2011/12	**Study Award**, Keble Association Grants, University of Oxford
2005	Outstanding Medical Student Teaching Award, College of Medicine, Fu-Jen Catholic University

CURRENT RESEARCH AND INTERESTS

My research interests focus on understanding the neural mechanisms underpinning migraine and neurodegenerative diseases, specifically the potential of brain stimulation in therapeutics. With transcranial electrical stimulation (tES), my work includes modulating cortical excitability in migraine, boosting slow-wave-sleep-related memory consolidation in healthy subjects as well as enhancing cognition and gait in demented subjects. My recent research also involves decision-making and big data analysis in migraine. To investigate these issues, I use a variety of methods including tES, EEG, neuroimaging, epidemiological and neuropsychological approaches.

PUBLICATIONS

30 SCI peer-reviewed journal articles, 19 articles as first/corresponding author

PUBLICATIONS (peer-reviewed journal articles)

2021
- Jao CW[+]; **Lau CI**[+]; Lien LM; Tsai YF; Chu KE; Hsiao CY; Yeh JH ***;** Wu YT*. Using Fractal Dimension Analysis with the Desikan-Killiany Atlas to Assess the Effects of Normal Aging on Subregional Cortex Alterations in Adulthood. ***Brain Sciences.*** 2021 Jan 14;11(1):107. doi: 10.3390/brainsci11010107. (IF: 2.786. first author, equal contribution+)

2020
- Jao CW, Yeh JH; Wu YT; Lien LM; Tsai YF; Chu KE; Hsiao CY; Wang PS; **Lau CI***. Alteration of Intra- and Inter-Lobes Connectivity of Brain Structural Network in Normal Aging. ***Entropy***. 2020, 22, 826; doi:10.3390/e22080826. (IF: 2.494. CORRESPONDING AUTHOR)
- **Lau CI**, Liu MN, Chen WH, Walsh V, Wang SJ*. Clinical and biobehavioral perspectives: Is medication overuse headache a behavior of dependence? ***Prog. Brain Res***. 2020 Jun. doi.org/10.1016/bs.pbr.2020.05.019. (IF: 2.961)
- **Lau CI***, Chen WH, Walsh V. The visual system as target of non-invasive brain stimulation for migraine treatment: Current insights and future challenges. ***Prog. Brain Res***. 2020 Jun. doi.org/10.1016/bs.pbr.2020.05.018. (IF: 2.961)
- Liu MN, Yeh HL, Kuan AS, Tsai SJ, Liou YJ, Walsh V, **Lau CI***. High-frequency external muscle stimulation reduces depressive symptoms in older male veterans—a pilot study. ***J Geriatr Psych Neur***. 2020 Apr 3;891988720915524. doi: 10.1177/0891988720915524. (IF: 2.747. CORRESPONDING AUTHOR).
- Lin KY, Liu MN, Wang PH, **Lau CI***. Positive magnetic resonance imaging evidence of transient global amnesia following the use of sildenafil. ***Clin. Neuropharmacol*** Mar/Apr 2020;43(2):52-53.doi: 10.1097/WNF.0000000000000383. (IF: 1.272. CORRESPONDING AUTHOR).
- Li JR, **Lau CI**, Huang MH, Hu LY, CF Tsai and Liu MN. Language impairment as diagnostic clue to lvPPA in a young-onset dementia patient mimicking bvFTD. ***Aust Nz J Psychiat*** 2020 Aug 28;4867420950797. doi: 10.1177/0004867420950797 (IF: 4.657)

2019
- **Lau CI**, Liu MN, Chang KC, Chang A, Bai CH, Tseng CS, Walsh V, Wang HC. Effect of single-session tDCS on cognition in Parkinson's disease. ***CNS Neurosci Ther***. Aug 19. doi: 10.1111/cns.13210. (IF: 3.394)
- Liu MN, **Lau CI**, Lin CP. Precision Medicine for Frontotemporal Dementia. ***Front Psychiatry***. 2019 Feb 21;10:75. doi: 10.3389/fpsyt.2019.00075. eCollection 2019 (IF: 3.532)
- Cheng YC, Yeh JH, Yeh HL, Lien LM, Chen WY, Hsiao CY, Liu YH, Chen CL, Chen SY, **Lau CI*.** Eccentric target sign in CNS toxoplasmosis: a rare presentation of Good's syndrome. ***Neurology***. 2019;92:1-3. doi:10.1212/WNL.0000000000006862 (IF: 8.32. CORRESPONDING AUTHOR)
- **Lau CI,** Walsh V, Hsu TY. Does tDCS modulate visual cortical excitability—a proof of concept study for migraine prevention. ***Cephalalgia***. 2019, Vol. 39(1S) 40. DOI: 10.1177/0333102419859835 (Abstract)

2017
- **Lau CI,** Lin CC, Chen HJ, Wang HC, Chen WH, Liang JA. Increased risk of essential tremor in migraine: A population-based retrospective cohort study. PLoS One. 2017 Mar 13;12(3):e0173586. (IF: 3.057)
- **Lau CI,** Hsu TY, Tseng LY, Chen WH. Visual evoked potentials in episodic and chronic migraine – a pilot study. Cephalalgia. 2017 Sep;37(1_suppl): 52-171. (Abstract)

2016
- Hsu CL, Yeh JH, **Lau CI*.** Persistent hyperthermia in a patient with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. J Clin Neurol 2016;12(6):515-516. (IF: 1.876, CORRESPONDING AUTHOR)
- Wang HC, **Lau CI,** Lin CC, Chang A, Kao CH. Group A Streptococcal Infections Are

Associated With Increased Risk of Pediatric Neuropsychiatric Disorders: A Taiwanese Population-Based Cohort Study. J Clin Psychiatry. 2016 Jul;77(7):e848-54. (IF: 5.847)

2015
- **Lau CI**, Lin CC, Chen WH, Wang HC, Kao CH. Increased risk of chronic fatigue syndrome in migraine: a population-based cohort study. Journal of Psychosomatic Research. 79 (2015) 514–518. (IF: 2.736)
- Bridge H, Stagg CJ, Near J, **Lau CI,** Zisner A and Cader MZ. Altered neurochemical coupling in the occipital cortex in migraine with visual aura. Cephalalgia. 2015 Oct;35(11):1025-30. Epub 2015 Jan 28 (IF: 4.121)
- Wang HC, Lin CC, **Lau CI**, Chang A, Kao CH. Angiotensin-converting enzyme inhibitors and bacterial pneumonia in patients with Parkinson disease. Mov Disord. 2015 Apr;30(4):593-6. (IF: 5.634)

2014
- Garside P, Arizpe J, **Lau CI**, Goh C, Walsh V. Cross-hemispheric alternating current stimulation during a nap disrupts slow wave activity and associated memory consolidation. Brain Stimulation. Epub 2014 Dec 31. (IF: 5.432)
- **Lau CI**, Lin CC, Chen WH, Wang HC, Kao CH. Association between migraine and irritable bowel syndrome: a population-based retrospective cohort study. Eur J Neurol. 2014 May 17. [Epub ahead of print] (IF: 3.852)
- Wang HC, Lin CC, **Lau CI,** Chang A, Sung FC, Kao CH. Risk of accidental injuries amongst Parkinson disease patients. Eur J Neurol. 2014 Jun;21(6):907-13. Epub 2014 Mar 17. (IF: 3.852)
- **Lau CI,** Chiu HC. The Circadian Rhythm and the Non-image Forming Visual System. Formosan J Med. 2014.

2013
- **Lau CI**, Wang HC, Hsu JL. Does the dopamine hypothesis explain schizophrenia? Rev Neurosci. 2013;24(4):389-400. (IF: 3.314)

2012
- **Lau CI** (2012). Light, photophobia and headache: an investigation of visually-induced migraine. MSc by Research. Bodleian Libary, University of Oxford.
- Hsieh YC et al. Collaborators. Epistasis analysis for estrogen metabolic and signaling pathway genes on young ischemic stroke patients. PLoS One. 2012;7(10):e47773. Epub 2012 Oct 24. (IF: 3.534)

2011
- **Lau CI**, Wang HC, Yeh HL, Li CH. Isolated Orbito-cerebral mucormycosis. Neurologist. 2011 May;17(3). (IF: 1.078)
- **Lau CI**, Wang HC, Tsai MD et al. Acute Parkinsonian syndrome after ventriculoperitoneal shunt malfunction caused by a roller coaster ride. Clinical Neurology and Neurosurgery. 2011 Jun;113(5):423-5. (IF: 1.248)
- **Lau CI,** Lien LM, Chen WH. Brainstem Hyperperfusion Syndrome after Intravenous Thrombolysis: Case Report. J Neuroimaging. 2011 Jul;21(3):277-9. Epub 2010 Mar 17. (IF: 1.818)

2010
- **Lau CI**, Wang HC, Hsu WC. Hypoglycemic Encephalopathy as the Initial Presentation of Hepatic Tumor-a case report. Neurologist. 2010 May;16(3):206-7. (IF: 1.078)
- Get With the Guidelines-Stroke performance indicators: surveillance of stroke care in the Taiwan Stroke Registry: Get With the Guidelines-Stroke in Taiwan. Hsieh FI, Lien LM, Chen ST, Taiwan Stroke Registry Investigators et al. Circulation. 2010 Sep 14;122(11):1116-23. Epub 2010 Aug 30. (IF: 14.948)

2008
- Cheng PL, Hung SW, Lin LW, Chong CF, **Lau CI.** Amantadine-induced serotonin syndrome in a patient with renal failure. ***Am J Emerg Med***. 2008 Jan;26(1):112.e5-6. (IF: 1.152)

Non-pharmacological Treatments in Migraine

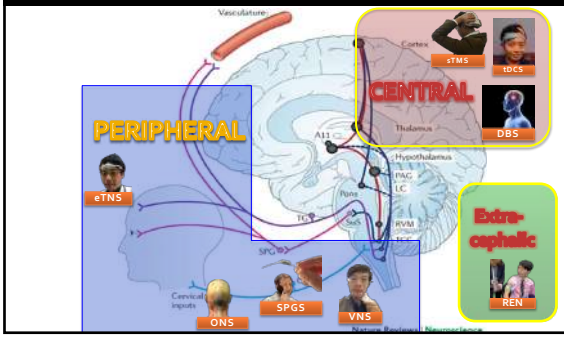
the role of non-invasive brain stimulation

劉子洋
Chi-ieong David Lau
MD, MSc(Res) (Oxon), MSc, MSc (UCL)

Assistant Professor
Consultant Neurologist
National Yang-Ming Chiao Tung University
Fu Jen Catholic University
Shin Kong WHS Memorial Hospital, Taipei, Taiwan

1

Where & How



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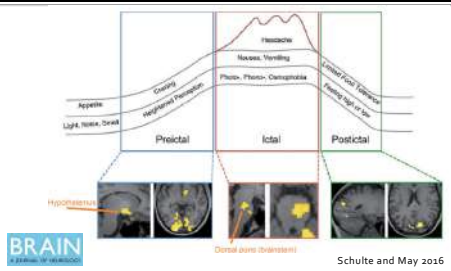
When—a dynamic target?



Schulte and May 2016

3

Neuromodulation for treating migraine
The One Million Dollar Questions

Bergmann et al. NeuroImage 2016

4

The visual network in migraine pathophysiology

CSD | Photophobia | Visual Snow

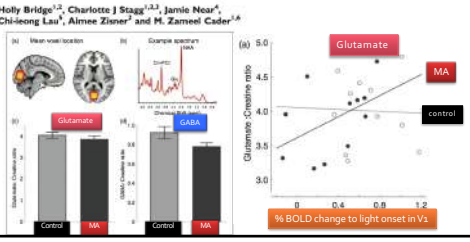
fMRI, Hadjikhani, 2001 | Noseda R et al. 2010 | Puledda et al. 2019

5

Cephalalgia 2015

Altered neurochemical coupling in the occipital cortex in migraine with visual aura

Holly Bridge[1,2], Charlotte J Stagg[1,2,3], Jamie Near[4], Chi-ieong Lau[1], Aimee Zisner[2] and M. Zameel Cader[1,5]



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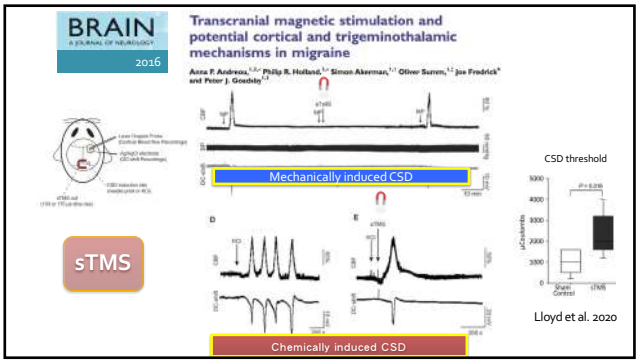
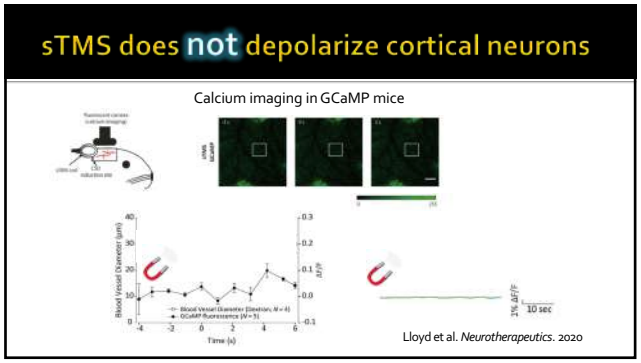
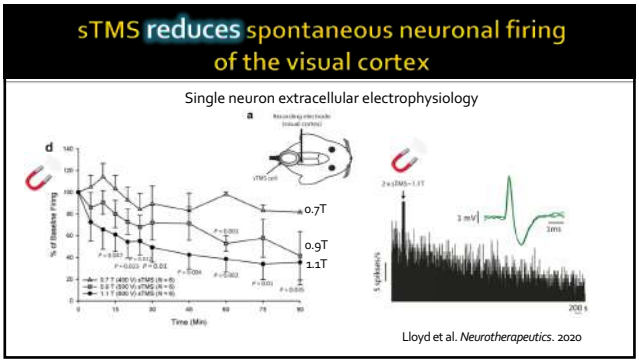

BRAIN
A JOURNAL OF NEUROLOGY
2016
Transcranial magnetic stimulation and potential cortical and trigeminothalamic mechanisms in migraine
Mechanically induced CSD
sTMS
CSD threshold
Chemically induced CSD
Lloyd et al. 2020

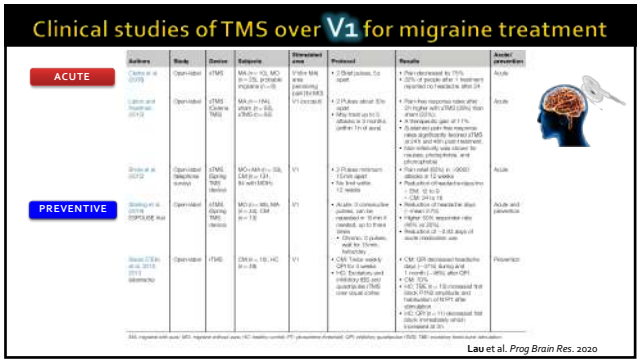
7


sTMS does not depolarize cortical neurons
Calcium imaging in GCaMP mice
10 sec
Lloyd et al. Neurotherapeutics. 2020

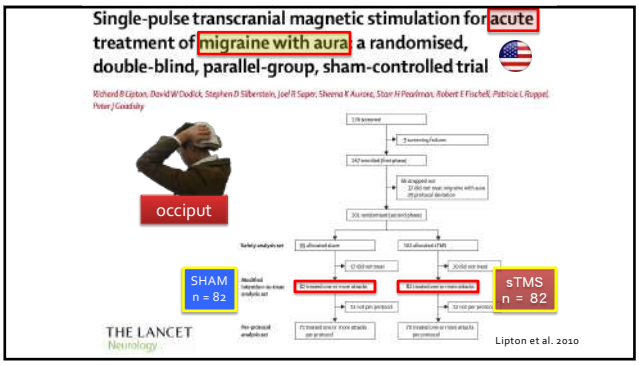
8


sTMS reduces spontaneous neuronal firing of the visual cortex
Single neuron extracellular electrophysiology
0.7T
0.9T
1.1T
Lloyd et al. Neurotherapeutics. 2020

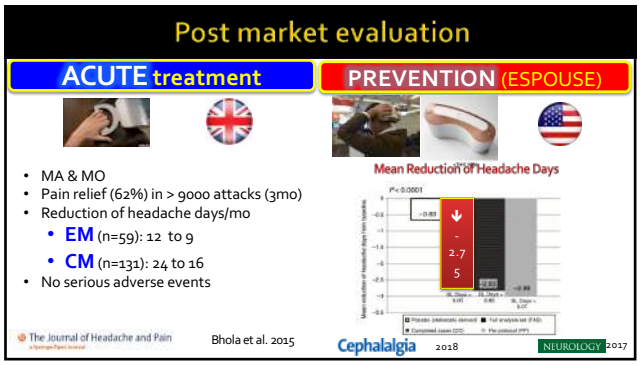
9


Clinical studies of TMS over V1 for migraine treatment
ACUTE
PREVENTIVE
Lau et al. Prog Brain Res. 2020

10

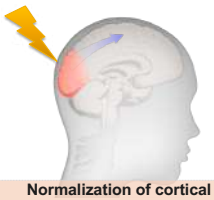

Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial
occiput
SHAM n = 82
sTMS n = 82
THE LANCET Neurology
Lipton et al. 2010

11


Post market evaluation
ACUTE treatment
PREVENTION (ESPOUSE)
MA & MO
Pain relief (62%) in > 9000 attacks (3mo)
Reduction of headache days/mo
EM (n=59): 12 to 9
CM (n=131): 24 to 16
No serious adverse events
Mean Reduction of Headache Days
-2.7
5
The Journal of Headache and Pain
Bhola et al. 2015
Cephalalgia 2018
NEUROLOGY 2017

12

Neuromodulation studies targeting at V1



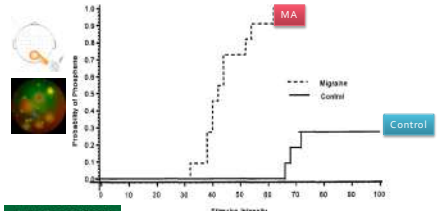
Normalization of cortical hyperexcitability?
deactivating CSD in the visual cortex

Goadsby *Headache*. 2005; Afridi SK et al. *Arch Neurol*. 2005

13

Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine

S.K. Aurora, MD; B.K. Ahmad, MD; K.M.A. Welch, MD; P. Bhardhwaj, MD; and N.M. Ramadan, MD



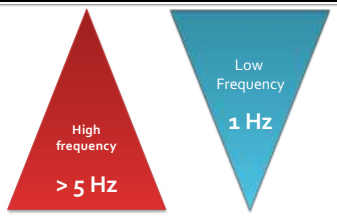
NEUROLOGY

Aurora et al. 1998

14

14

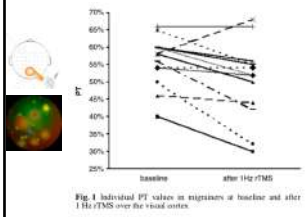
Neuromodulation by rTMS



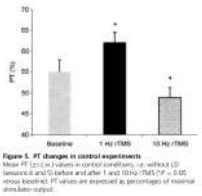
Maeda F, Keenan JP, Tormos JM, Topka H, Pascual- Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000; 111: 800–5.
Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 2001; 112: 1367–77.

15

Bidirectional modulation of visual cortex excitability with rTMS



Brighina et al. 2002



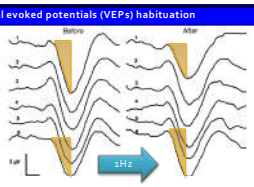
Fierro et al. 2005

16

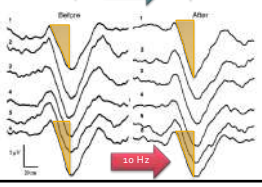
16

Visual evoked potentials (VEPs) habituation

Healthy subjects



Migraineurs



BRAIN

Bohotin et al. 2002

17

Failure of rTMS for Migraine Prevention – Why ?

Table 2. *Efficacy of rTMS for Migraine Prevention*

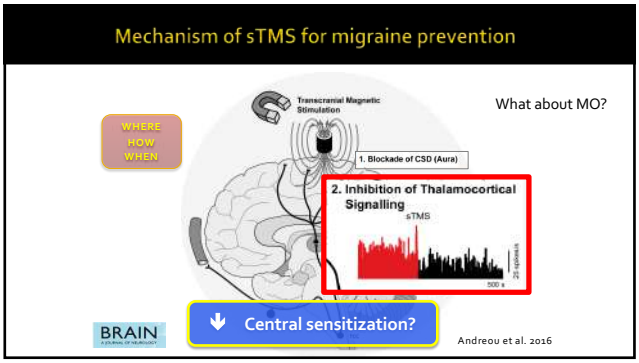
rTMS-Preventive Tx	Study Design	Number of Patients	Device/Site of Application	Dose and Frequency	Response/Primary Endpoint
Teepker et al.,[97] 2009 Migraine >4 attacks per month	Pre-post design	n = 27	Tabletop NS	500 pulses; 1 Hz for 5 days	27.5% reduction in number of migraine attacks versus baseline ($p = 0.007$; NS vs sham $p = 0.216$)
Brighina et al.,[96] 2006 Chronic migraine	Randomized, double-blind, sham control	n = 11	Tabletop/ dorsolateral prefrontal cortex NS	10 trains or 2 s duration; 30 s intervals; 12 sessions on alternate days	Improvement over baseline in attack frequency, acute treatment use, headache index; NS versus sham

rTMS = repetitive transcranial magnetic stimulations; NS = not significant; Tx = treatment.

Neurotherapeutics, Vol. 7, No. 2, 2010

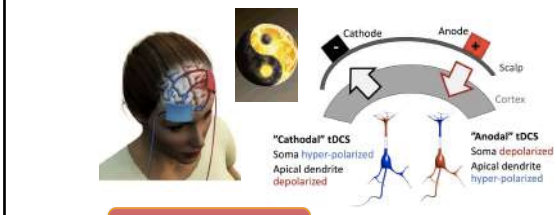
18

Mechanism of sTMS for migraine prevention



19

Transcranial Direct Current Stimulation (tDCS)



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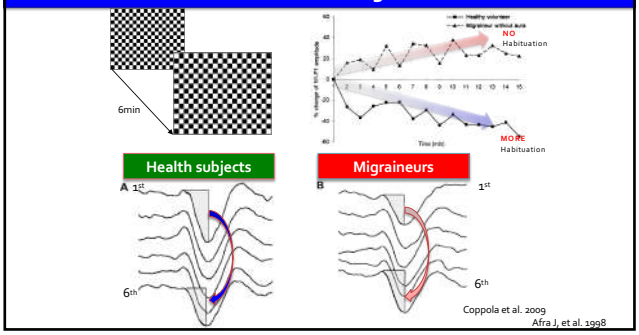
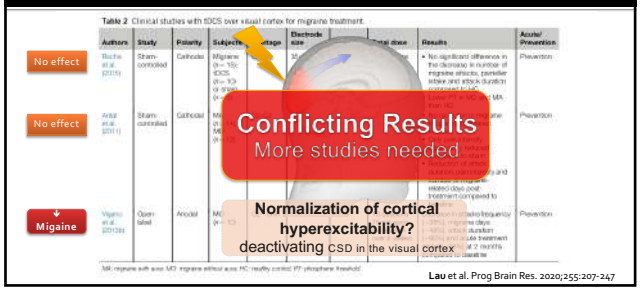
Lack of habituation in Migraine - VEPs



21

tDCS studies targeting at V1



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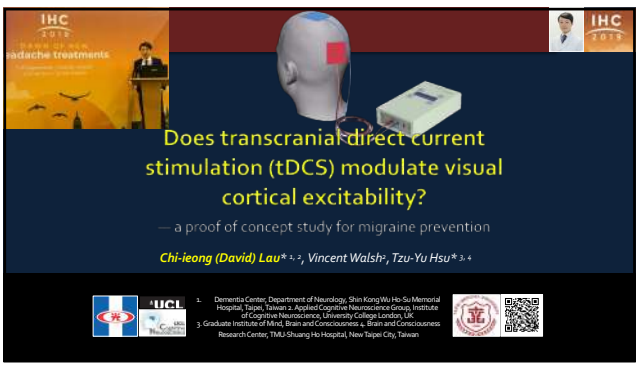
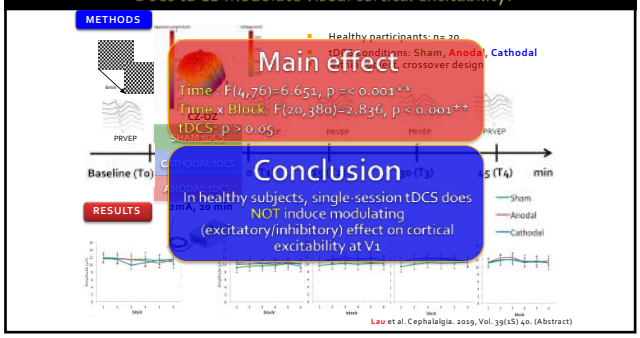


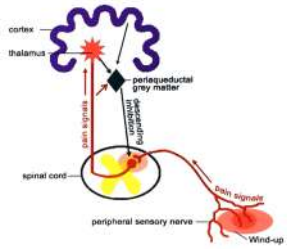
23

Does tDCS modulate visual cortical excitability?



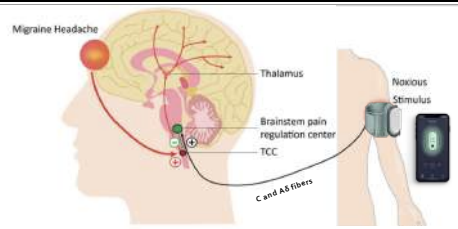
24

Endogenous analgesia



25

How does it work?
Conditioned Pain Modulation



HEADACHE

Above depolarization thresholds
Below perceived pain threshold

Yarnitsky et al. 2019

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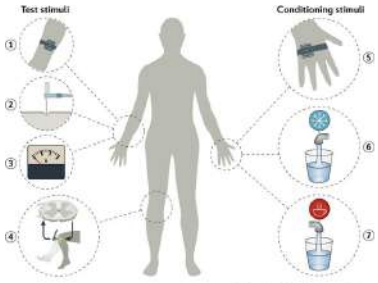
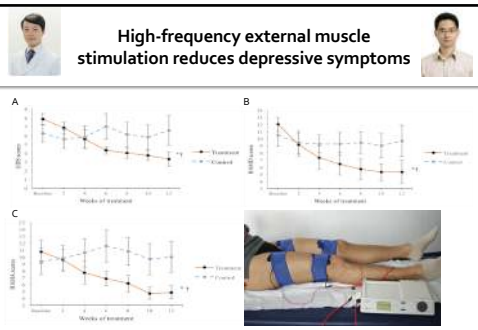
Conditioned Pain Modulation



27

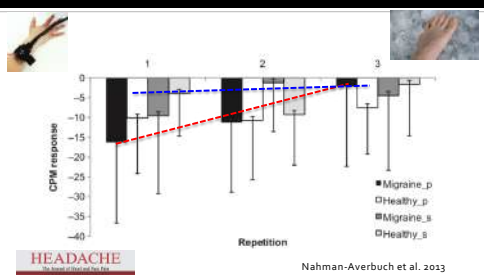
High-frequency external muscle stimulation reduces depressive symptoms



Liu…& **Lau.** J Geriatr Psychiatry Neurol. 2021

28

CPM in migraine wanes over time



HEADACHE

Nahman-Averbuch et al. 2013

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PILOT

Nonpainful remote electrical stimulation alleviates episodic migraine pain

NEUROLOGY

Yarnitsky et al. 2017

PILOT
Double-blind, randomized, crossover, sham-controlled trial

PIVOTAL

Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

HEADACHE

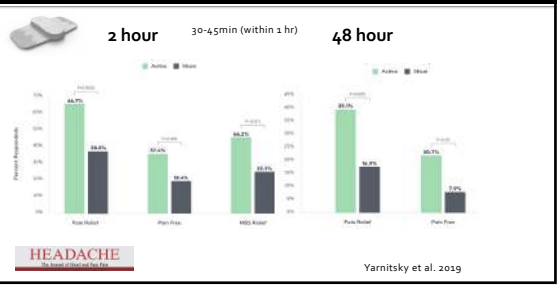
Yarnitsky et al. 2019

PIVOTAL
Double-blind, randomized, sham-controlled, multicenter trial

30

PIVOTAL Pain responses 2 & 48hr post-treatment

Double-blind, RCT, multicenter trial (n =252)



Yarnitsky et al. 2019

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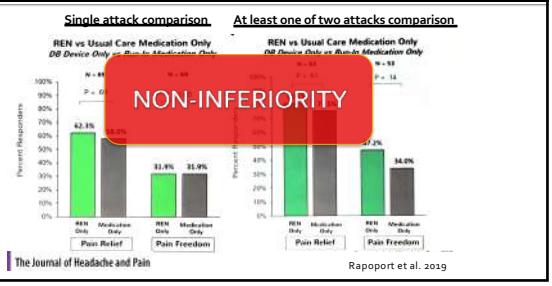
Efficacy of acute treatments for migraine

Treatment	Pain relief at 2 hours	Pain-free at 2 hours
Nerivio	67% (therapeutic gain 28%)	37% (therapeutic gain 19%)
Triptans	58% (therapeutic gain 31%)	29% (therapeutic gain 18%)
Gepants	59% (therapeutic gain 16%)	21% (therapeutic gain 10%)
Lasmiditan	59% (therapeutic gain 17%)	32% (therapeutic gain 17%)
Cefaly	N/A	17% (therapeutic gain 10%)
gammaCore	41% (therapeutic gain 13%)	30% (therapeutic gain 11%)
sTMS	72% (therapeutic gain 5%)	39% (therapeutic gain 17%)

32

REN only vs Medication only



Rapoport et al. 2019

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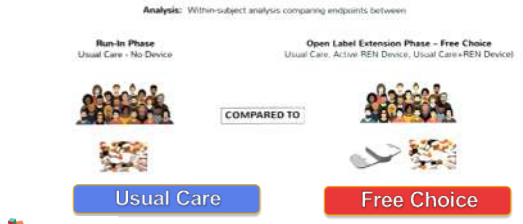
Real World - Incorporating REN Into Usual Care Reduces Acute Migraine Medication Use



Marmura et al. 2020

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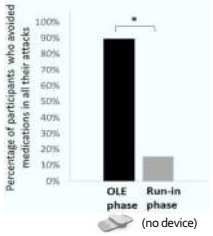
Real World - percentage of participants who avoided medications with REN

117 participants who had treated at least one migraine attack with REN



Marmura et al. 2020

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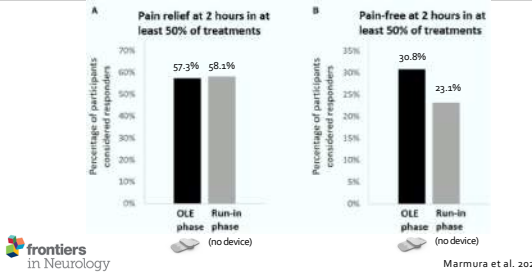
REN is non-inferior to usual care



Marmura et al. 2020

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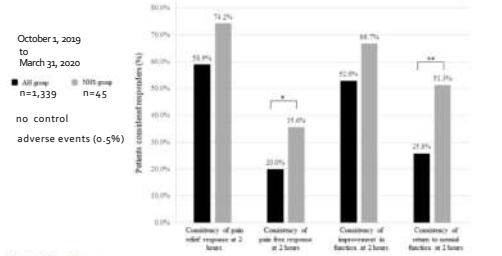
Real-world experience with REN in the acute treatment of migraine



Tepper et al. 2020

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REN vs TENS

Parameter	Remote Electrical Neuromodulation (REN) Conditioned Pain Modulation (CPM)	Transcutaneous Electrical Nerve Stimulation (TENS) Gate Theory
MOA	Descending Pain Inhibition	Ascending Pain Inhibition
Nerve Fibers	C and Aδ Fibers	Aβ Fibers
Stimulated Sensory Tract	Nociceptive	Touch
Location	Remote from Pain Location	At the Same Spinal Segment
Typical Pulse Frequency	100 - 120 Hz	60 - 100 Hz
Typical Pulse Width	400 μS	50 - 300 μS
Impact	Global	Local

theranica

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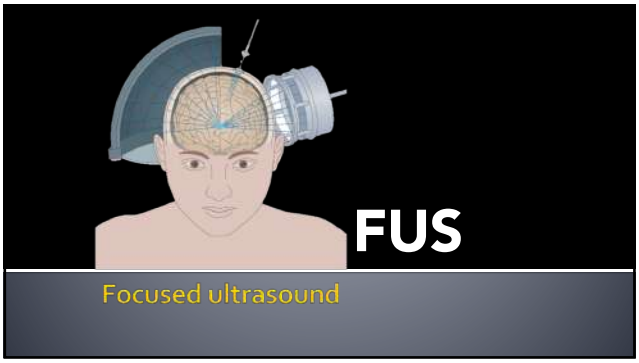

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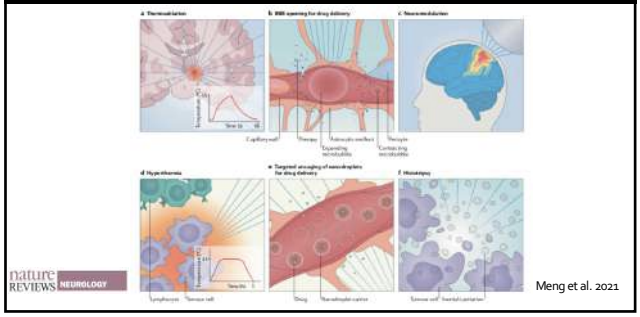
Biological effects of FUS



Meng et al. 2021

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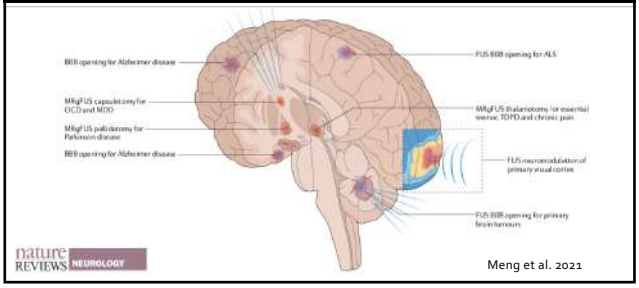
Intracranial applications of FUS in humans



Meng et al. 2021

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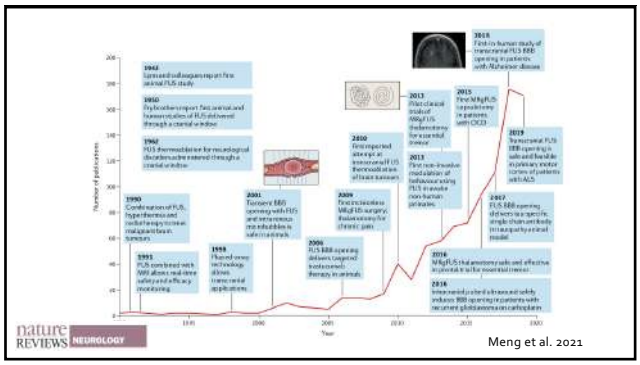

Meng et al. 2021

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Mechanisms

- ✓ most likely candidate is the acoustic radiation force (ARF)
- ✓ amplitude envelope
- X fundamental frequency
- ✓ (mechano-sensitive) ion-channels
- ✓ cytoskeleton
- ✓ membrane capacitance
- X cavitation
- X thermal effect
- ? membrane waves
- ? sonoporation

Jerusalem, Verhagen et al., 2019
Blackmore et al., 2019

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History context of FUS

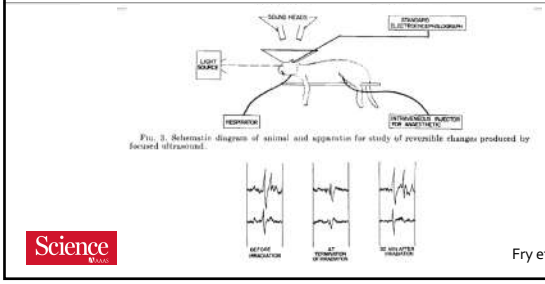

Fig. 3. Schematic diagram of animal and apparatus for study of reversible changes produced by focused ultrasound.

Science

Fry et al. 1958

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Dampening effects of human skull

" 76% loss in intensity"

Deffieux T, Konofagou EE. Numerical study of a simple transcranial focused ultrasound system applied to blood-brain barrier opening. IEEE transactions on ultrasonics, ferroelectrics, and frequency control. 2010 Dec;57(12):2637-53.

" 3.7- 4.1 fold drop in intensity"

Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, Tyler WJ. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. Nature neuroscience. 2014 Feb;17(2):322.

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Frequency and Attenuation

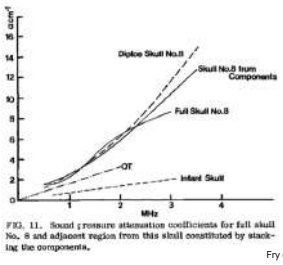

FIG. 11. Sound pressure attenuation coefficients for full skull No. 8 and adjacent region from this skull constituted by stacking the components.

Fry et al. J.Acoust Soc.Am. 63(5),May 1978

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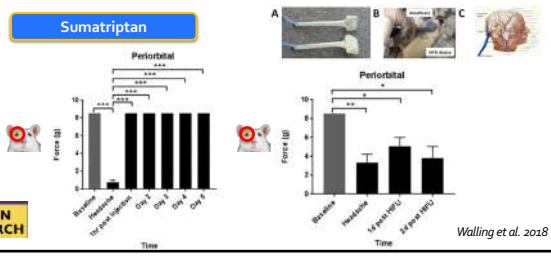
Focused ultrasound alleviates cutaneous allodynia associated with chronic migraine

headache rats underwent daily infusions of Inflammatory Mediators (IM) to induce allodynia

Sumatriptan



BRAIN RESEARCH

Walling et al. 2018

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劉子洋

Thank you

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48

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相關發表

- 2015 Annual Meeting of Taiwan Neurological Society. Poster. Alien Hand Syndrome with Initial Presentation of Language Disturbance: A Case Report
- 2016 Annual Meeting of Taiwan Neurological Society. Poster. The Role of High Altitude in Cerebral venous sinus thrombosis: A Case Report.
- 2018 Annual Meeting of Taiwan Neurological Society. Poster. Spontaneous Intracranial Hypotension-related Cerebral Venous Sinus Thrombosis : Case Series

The Psychological Treatment for Headache Disorder

成大醫院神經部 杜宜憲

共病
(Psychi)

Epidemiology
Mechanism

療效
(Headache)

Efficacy

療效
(Migraine)

CBT / Relaxation
Biofeedback
Exercise

共病
(Psychi)

療效
(Headache)

療效
(Migraine)

Epidemiology and mechanism of psychiatric comorbidity

Definition of co-morbidity

- 1st definition by Feinstein (1970): any distinct additional clinical entity that has existed during the clinical course of a patient who has the index disease *(J Chronic Dis. 1970 Dec;23(7):455-68.)*

Definition of co-morbidity

- Concordant conditions that have the same pathophysiological risk profile and management plan and discordant conditions *(Lancet Neurol. 2016 Jan;15(1):32.) (Ann Fam Med. Jul-Aug 2009;7(4):357-63.)*

- Concurrent or successive *(J Child Psychol Psychiatry. 1999 Jan;40(1):57-87.)*

- A broad concept, including complications or effects, and causes, s/s of the index disease *(J Chronic Dis. 1970 Dec;23(7):455-68.) (Psychopathology. Jul-Aug 2005;38(4):206-10.)*

Tension-type headache (TTH)

- 60% had anxiety and 32% had depression *(Arq Neuropsiquiatr. 2003 Dec;61(4):991-4.)*
- The main predictor for depression and anxiety *(Am J Epidemiol. 2005 Jun 1;161(11):1066-73.)*

- cTTH: 3-15 times to receive a diagnosis of anxiety or mood disorder *(Headache. 2000 Jan;40(1):3-16.)*
- cTTH: significantly higher neuroticism score and a significantly higher level of psychological distress than the general population *(Acta Neurol Scand. 2011 Dec;124(6):375-82.)*

Migraine

- Several psychiatric comorbidities *(J Neurol Neurosurg Psychiatry. 2016 Jul;87(7):741-9.)*
  - Depression (41-47%)
  - Anxiety disorders (51-58%)
  - Bipolar disorder
  - PTSD (9-43%)
  - Personality disorders
  - Suicide attempts

The relationship with migraine chronification

- Depression was a significant predictor of onset of chronic migraine (CM) (OR=1.65, 95% CI 1.12 to 2.45) *(J Headache Pain. 2012 Nov;13(8):615-24.)*

- Risk of CM onset increased with depression severity *(J Headache Pain. 2012 Nov;13(8):615-24.) (Headache. 2008 Sep;48(8):1157-68.)*

Migraine + depression

- Depression is 2-2.5 times more common, than general population *(Headache. 2008 Apr;48(4):501-16.)(Neurology. 2003 Apr 22;60(8):1308-12.)(Neurology. 2000 Sep 12;55(5):629-35.)*

- 40% migraineurs also report depression *(Neurology. 2000 Sep 12;55(5):629-35.)*

- Bidirectional association *(Neurology. 2000 Jan 25;54(2):308-13.) (Neurology. 2003 Apr 22;60(8):1308-12.)*
  - P’t w/ migraine: 5-fold higher risk of depression than general population
  - P’t w/ depression: 3-fold higher risk of migraine than general population

Migraine + anxiety

- 50% of cumulative lifetime incidence of ≥1 anxiety disorder *(J Neurol Neurosurg Psychiatry. 2016 Jul;87(7):741-9.)*

- Anxiety disorders are 2-5 times more prevalent than in the general population *(J Neurol Neurosurg Psychiatry. 2016 Jul;87(7):741-9.)*
- Anxiety disorders are much more common in CM than EM *(Cephalalgia. 1998 Aug;18 Suppl 22:56-8; discussion 58-61.)*

- Bidirectional relationship *(Headache. 2013 Jan;53(1):23-45.)*

Migraine + anxiety

- Generalized anxiety disorder (GAD), OCD, panic disorder *(Headache. 2006 Oct;46 Suppl 3:S76-87.)*

- Migraine is associated with a 4- to 5-fold increase in the risk of GAD *(J Neurol. 2013 Aug;260(8):1960-9.)*

- Migraine is associated with 3-10 times the risk of panic disorder *(Headache. 2013 Jan;53(1):23-45.)*

Migraine + sleep disorder

- >50% migraine P't report sleep difficulties *(Headache. Jul-Aug 2005;45(7):904-10.)*
- >1/3 migraine P't suffer from chronic short sleep (≤6h/night) *(Headache. Jul-Aug 2005;45(7):904-10.)*
- Bidirectional relationship *(Semin Pediatr Neurol. 2015 Jun;22(2):105-12.)*
  - Sleep disturbances (excess, lack, irregular) as triggers and risk factors
  - Migraines interfere with quality of sleep

In childhood and adolescence headache

- In a recent meta-analyses *(Cephalalgia. 2013 Jan;33(2):112-22.)*
  - Assessing internalizing (anxiety, depression) and externalizing (behavioral problems) symptoms
  - Internalizing: high level in either migraine or TTH
  - Externalization: high level in migraine
  - No significant differences between the headache groups

In childhood and adolescence headache

- Higher levels of internalizing symptoms are driven by other somatic complaints (nausea, dizziness, tiredness) *(Cephalalgia. 2013 Jan;33(2):112-22.)*

- Internalizing symptoms may represent a consequence of having headache rather than a sign of psychological dysfunctioning. *(Cephalalgia. 2013 Jan;33(2):112-22.)*

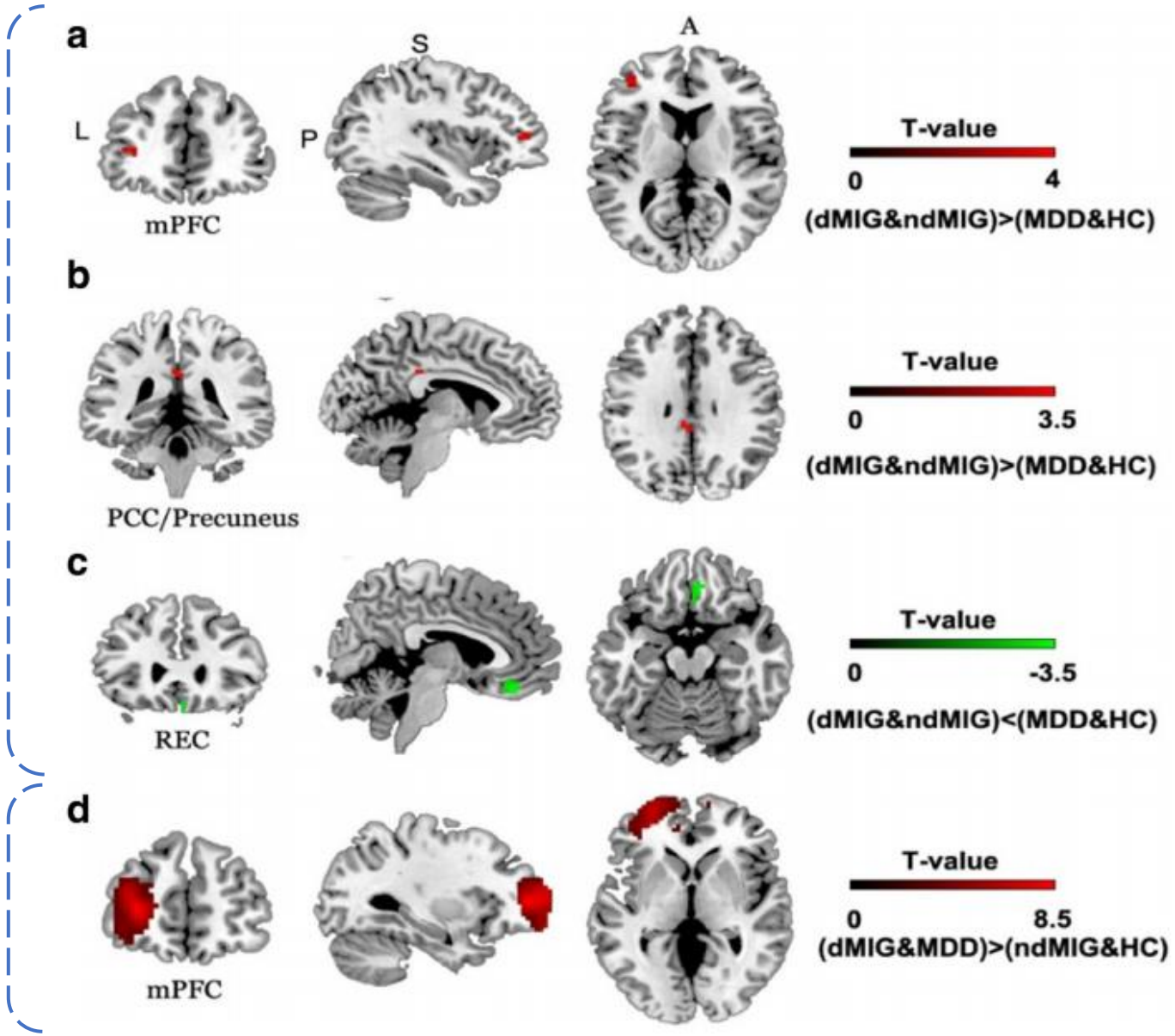
Effects of psychiatric comorbidities

- Decreased quality of life *(Int J Psychiatry Med. 2016 Jul;51(5):442-455.)*
- Modifiable trigger factor in primary headache disorder, notably stress and sleep *(Cephalalgia. 2018 May;38(6):1188-1198.)*

Mechanism in development of psycho-pathology

- Still un-determined

- The abnormal mPFC may contribute to determining the common symptoms in migraine and depression *(J Headache Pain. 2018 Jun 26;19(1):48.)*
  - Amplitude of low-frequency fluctuation (ALFF) to measure regional intrinsic brain activity to explore the pathophysiology



Migraine

Depression

mPFC: medial prefrontal cortex

REC: rectus gyrus

PCC: posterior cingulate cortex

dMIG: migraine w/ depression

ndMIG: migraine w/o depression

MDD: major depressive disorder

HC: healthy controls

Mechanism of psychological Tx

- Preventive effect by management and regulation of major trigger factors of headache, or comorbid psychopathology which interact with headache bi-directionally

- Physiological changes from psychological treatment
  - Endogenous opioids system *(Am J Med. 2016 Jul;129(7):755-8.)*
  - Sympathetic activity *(Headache. 1993 Sep;33(8):439-41.)*
  - Pain-related brain neuroplasticity. *(Neural Plast. 2017;2017:2038573.)*

Efficacy of psychological Tx (headache)

Psychological Tx (incomprehensive)

- Psychotherapy
- Cognitive behavior therapy (CBT)
- Biofeedback therapy (BFT), Neurofeedback
- Relaxation training (RT)
- Autogenic training
- Meditation
- Mindfulness-based treatment (MBT)

Pros and cons of psychological Tx

- Long-lasting Tx efficacy
  - 5yrs after completing biofeedback and/or relaxation, 91% of migraine P’ts and 78% of TTH continued to improve significantly *(Headache. 1987 Nov;27(10):580-3.)*
  - Biofeedback and relaxation have shown a similar Tx response immediately after Tx and significantly better response 1-year Tx than did those using propranolol for migraine *(Complement Ther Med. 2005 Sep;13(3):165-74.)*

- Time-consuming
- Need more motivation

Current recommendation-1 (migraine)

- 2019 AHS *(Headache. 2019 Jan;59(1):1-18.)*
  - Biobehavioral therapy: effective in the acute and preventive Tx. Alone or in conjunction
  - Grade A evidence for prevention

- 2019 Cochrane Library *(Cochrane Database Syst Rev. 2019 Jul 2;7(7):CD012295.)*
  - No high-quality evidence to determine whether psychological interventions are effective in managing migraine in adults

Current recommendation-2

- TTH *(JAMA. 2001 May 2;285(17):2208-15.)*
  - CBT: comparable with tricyclic antidepressants
  - Combination more effective

- Primary HA (2012 NICE guideline)
  - Not to make a recommendation on the use of psychological therapies for the prophylactic treatment of primary headaches
  - Not enough evidence to form a recommendation for or against its use

Efficacy of psychological treatment for headache disorder: a systematic review and meta-analysis

J Headache Pain. 2019 Feb 14;20(1):17.

Hye Jeong Lee[1], Jin Hyeok Lee[1], Eun Young Cho[2], Sun Mi Kim[3] and Seoyoung Yoon[1*]

Methods

English databases
- EMBASE, MEDLINE, Cochrane Library
- SCOPUS, Science Direct, Web of Science
- CINAHL, PsycArticles

Korean database
- KoreaMed, and KMBASE

Primary efficacy measure
- HA frequency (HA days/mth)

Secondary efficacy measure
- HA frequency (HA attacks/wk)
- Headache index (HI)
- Tx response rate (>50% improvement from baseline on the HI and MIDAS)

Heterogeneity
- I^2 statistic (>50%: meaningful)

Sensitivity analysis
- Excluding one study at a time from the meta-analysis to test the robustness of the effects of a single study

Risk of bias
- Tool (Higgins & colleagues); Funnel plot

Subgroup analysis

Headache type
- restricted to migraine vs. TTH vs. cluster headache vs. MOH vs. primary headache with no restriction on headache type

Type of intervention
- CBT vs. BFT vs. MBT vs. other Tx-type without a previously mentioned Tx components

Study location

Model

Fixed-effect model
- Low heterogeneity among the studies included in the identified meta-analysis

Random-effect model
- High heterogeneity among the studies included in the identified meta-analysis

Efficacy of psychological treatment for headache disorder: a systematic review and meta-analysis

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Hye Jeong Lee[1], Jin Hyeok Lee[1], Eun Young Cho[2], Sun Mi Kim[3] and Seoyoung Yoon[1*]

HA frequency (HA days/mth)

-0.70 (95% CI [− 1.22, − 0.18], P = 0.01)

Heterogeneity analysis

not heterogeneous (I^2 = 36%, P = 0.12)

Sensitivity analysis

one study nearly robust

− 0.54 (95% CI [− 1.08, 0.00], P = 0.05)

1

HA frequency (HA attack/wk)

-1.14 (95% CI [− 1.61, − 0.66, P < 0.001)

Heterogeneity analysis

not heterogeneous (I^2 = 32%, P = 0.19)

Sensitivity analysis

no single robust study

2

Headache index

-0.92 (95% CI [− 1.40, − 0.44], P < 0.001)

Heterogeneity analysis

not heterogeneous (I^2 = 0%, P = 0.92)

Sensitivity analysis

no single robust study

3

Treatment response

Pooled RR **3.13** (95% CI [2.24, 4.37], P < 0.001)

Heterogeneity analysis

not heterogeneous (I^2 = 0%, P = 0.67)

Sensitivity analysis

no single robust study

4

Disability due to HA

MIDAS **-2.52** (95% CI [− 5.27, 0.23], **P = 0.073**)

Heterogeneity analysis

significantly heterogeneous (**I^2 = 74%**, P < 0.01)

Sensitivity analysis

one robust study. **-3.15** (95% CI [− 6.04, − 0.27], P = 0.03) after correction

5

Efficacy of psychological treatment for headache disorder: a systematic review and meta-analysis

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Hye Jeong Lee[1], Jin Hyeok Lee[1], Eun Young Cho[2], Sun Mi Kim[3] and Seoyoung Yoon[1*]

1

HA frequency (HA days/mth)

-0.70 (95% CI [− 1.22, − 0.18], P = 0.01)

Subgroup analysis
- By headache type: no significant difference (P = 0.23)
- By intervention type: no significant difference (P = 0.67)
- By country: significant difference (P = 0.02)

Headache type
- Migraine: significant difference than placebo −0.59 (95% CI [− 1.12, − 0.05])
- TTH or no restriction: no significant differences between control

Intervention type
- No specific intervention type showed significant efficacy over control

Country
- US and European countries: no significant difference between groups
- Other countries: significantly better results than control −2.80 (95% CI [− 4.36, −1.24])

2

HA frequency (attack/wk)

-1.14

3

Headache index

-0.92

4

Tx response

Pooled RR **3.13**

5

HA Disability

MIDAS **-2.52**

Efficacy of psychological treatment for headache disorder: a systematic review and meta-analysis

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Hye Jeong Lee[1], Jin Hyeok Lee[1], Eun Young Cho[2], Sun Mi Kim[3] and Seoyoung Yoon[1*]

1

HA frequency (HA days/mth)

-0.70

2

HA frequency (attack/wk)

-1.14 (95% CI [− 1.61, − 0.66, P < 0.001)

Subgroup analysis

- By headache type: no significant differences (P = 0.55)
- By intervention type: no significant differences (P = 0.26)
- By country: no significant differences (P = 0.93)

Headache type

- migraine: significant difference over placebo, −0.91 (95% CI [− 1.53, − 0.30])
- TTH: significant difference over placebo, −1.43 (95% CI [− 2.19, − 0.66])

Intervention type

- BFT: significant difference over control, −0.70 (95% CI[− 1.37, − 0.02]
- CBT: significant difference over control, −3.00 (95% CI [− 5.43, − 0.57])
- MBT: significant difference over control, −1.39 (95% CI [− 2.13, 0.64])
- Other treatments: no significant differences

Country

- US: significant difference than control, −0.94 (95% CI [− 1.72, − 0.15])
- Other: significant difference than control, −1.26 (95% CI [− 1.86, − 0.66])

3

Headache index

-0.92

4

Tx response

Pooled RR **3.13**

5

HA Disability

MIDAS **-2.52**

Efficacy of psychological treatment for headache disorder: a systematic review and meta-analysis

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Hye Jeong Lee[1], Jin Hyeok Lee[1], Eun Young Cho[2], Sun Mi Kim[3] and Seoyoung Yoon[1*]

1

HA frequency (HA days/mth)

-0.70

2

HA frequency (attack/wk)

-1.14

3

Headache index

-0.92 (95% CI [− 1.40, − 0.44], P < 0.001)

Subgroup analysis
- By headache type: no significant differences (P = 0.81)
- By intervention type: no significant differences (P = 0.83)
- By country: cannot perform (all from the US)

Headache type
- TTH: significant difference than control group, −0.99 (95% CI [− 1.79, − 0.19])
- No restriction: significant difference than control group, −0.83 (95% CI [− 1.45, − 0.20])
- Migraine(1): no significant difference

Intervention type
- BFT: significant difference over the control, −0.86 (95% CI[− 1.35, − 0.36])
- Other intervention* (including CBT): no significant difference

4

Tx response

Pooled RR **3.13**

5

HA Disability

MIDAS **-2.52**

Efficacy of psychological treatment for headache disorder: a systematic review and meta-analysis

J Headache Pain. 2019 Feb 14;20(1):17.

Hye Jeong Lee[1], Jin Hyeok Lee[1], Eun Young Cho[2], Sun Mi Kim[3] and Seoyoung Yoon[1*]

1

HA frequency (HA days/mth)

-0.70

2

HA frequency (attack/wk)

-1.14

4

Tx response

Pooled RR **3.13** (95% CI [2.24, 4.37], P < 0.001)

Subgroup analysis

- By headache type: no significant difference (P = 0.54)
- By intervention type: no significant difference (P = 0.38)
- By country: no significant difference (P = 0.76)

Headache type

- Migraine: significant difference, pooled RR of 3.94 (95% CI [1.80, 8.62])
- TTH: significant difference, pooled RR of 4.16 (95% CI [1.70, 10.19])
- No restriction: significant difference, pooled RR of 2.70 (95% CI [1.80, 4.03])

Intervention type

- CBT: significant difference than control, pooled RR of 4.75 (95% CI [2.03, 11.12])
- BFT: significant difference than control, pooled RR of 2.74 (95% CI [1.70, 4.42])
- CBT and BFT: significant difference than control, pooled RR of 2.13 (95% CI [1.08, 4.21])
- Others: significant difference than control, pooled RR of 4.78 (95% CI [1.79, 12.75])

Country

- US: significant difference than control, pooled RR = 2.52, 95% CI [1.70, 3.74]),
- European: significant difference than control, pooled RR = 5.10, 95% CI [1.93, 13.48])
- Other: significant difference than control, pooled RR = 3.05, 95% CI [1.10, 8.40])

3

Headache index

-0.92

5

HA Disability

MIDAS **-2.52**

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1

HA frequency (HA days/mth)

-0.70

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HA frequency (attack/wk)

-1.14

3

Headache index

-0.92

4

Tx response

Pooled RR **3.13**

5

HA Disability

MIDAS **-2.52** (95% CI [− 5.27, 0.23], **P = 0.073**)

Subgroup analysis

- By headache type: no significant difference (P = 0.98)
- By intervention type: no significant difference (P = 0.05)
- By country: significant difference between subgroups (P = 0.03)

Headache type

- All subgroup: no significant difference over control group

Intervention type:

- MBT: significant difference over control, −13.00, 95% CI [− 21.08, − 4.92])
- BFT, CBT and other: no significant differences

Country

- US and European: no significant differences
- Other countries: difference over control group, − 5.72 (95% CI [− 8.44, − 3.0])

Efficacy of psychological treatment for headache disorder: a systematic review and meta-analysis

J Headache Pain. 2019 Feb 14;20(1):17.

Hye Jeong Lee[1], Jin Hyeok Lee[1], Eun Young Cho[2], Sun Mi Kim[3] and Seoyoung Yoon[1*]

Limitation

Diversity of treatment modality
Heterogeneity of protocol in each modality
Lack of standardized outcome measure in RCTs

Source of bias

Hard to blind
High drop-out rate

Conclusion

Reduced headache frequency and the suffering
Possible option for primary headache; alone or in combination
Need standardized outcome measures and strategies to reduce bias
Need standardized protocol or manual

Efficacy of psychological Tx (migraine)

CBT

1

Biofeedback

2

Relaxation training

3

Physical exercise

4

Cognitive behavioral therapy (CBT)

- Therapists teach patients how to identify and address maladaptive thoughts, beliefs, and triggers associated with headache, as well as various behavioral strategies for modifying behaviors. *(Neurol Clin. 2019 Nov;37(4):789-813.)*

- Patient need: well-educated, devoting

Cognitive behavioral therapy (CBT)

- A recent meta-analysis across a broad range of behavioral interventions *(Headache. 2018 Jun;58(6):913-925.)*
  - Aids in reducing stress by 4-12%
  - Reduced frequency of medication use by 20-25%
  - Improve self-efficacy
  - Reduce pain catastrophizing
  - Enhanced clinical outcomes and quality of life

- Effectiveness in reducing HA frequency is more variable *(Br J Pain. 2015 Nov;9(4):213-24.)*

Biofeedback (BF)

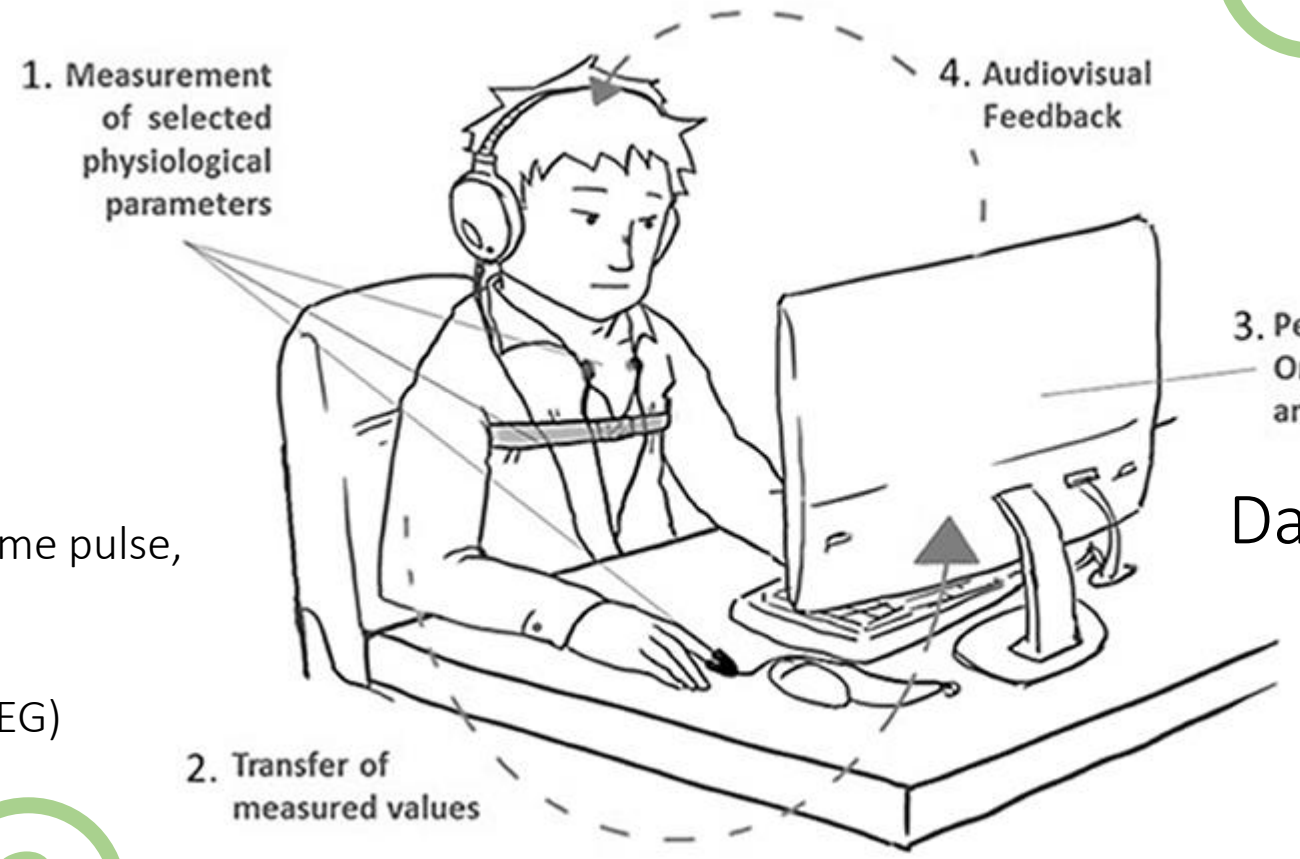
- Self-regulatory technique whose purpose is to enable P't to gain voluntary control of varied physiologic functions *(Neurol Clin. 2019 Nov;37(4):789-813.)*

- 4 components: a biosensing unit, a data transfer unit, a data processing unit, and a feedback unit. *(Yu B, Funk M, Hu J, Wang Q and Feijs L (2018) Biofeedback for Everyday Stress Management: A Systematic Review. Front. ICT 5:23.)*

1 Biosensing

Early parameters
- overall arousal,
- chiefly muscle tension,
- limb temperature,
- skin conductance

Advance parameters
- temporal artery blood volume pulse,
- respiration,
- heart rate variability (HRV),
- electroencephalography (EEG)



Feedback 4

Data process 3

2 Data transfer

Biofeedback (BF)

- Reduce headache duration and more limited support for reductions in prophylactic medications *(Appl Psychophysiol Biofeedback. 2008 Sep;33(3):125-40.) (Pain. 2007 Mar;128(1-2):111-27.)*

- Reduce headache frequency by 21-67% *(J Neurol. 2016 Dec;263(12):2369-2377.)*

- Superior to placebo, and generally comparable with most prophylactic medication (with insufficient evidence comparing CGRP antagonists) *(Neurol Sci. 2014 May;35 Suppl 1:121-7.) (Pain. 1990 Jul;42(1):1-13.)*

Biofeedback (BF)

- Comprehensive efficacy review *(Appl Psychophysiol Biofeedback. 2008 Sep;33(3):125-40.)*
  - Average of 11 sessions to show clinically significant improvements (headache parameters, anxiety, depression, self-efficacy)
  - Results enduring (14mths)

- BF + standard pharmacologic Tx > either alone *(Pain. 1990 Jul;42(1):1-13.) (JAMA. 2013 Dec 25;310(24):2622-30.)*

Relaxation training (RT)

- Not only to relax muscle tension but also to decrease the sympathetic nervous system's response to stress *(Neurol Clin. 2019 Nov;37(4):789-813.)*

- Several approaches successfully applied for migraine *(Neurol Clin. 2019 Nov;37(4):789-813.)*
  - Guided imagery (導引式圖像)
  - Deep or diaphragmatic breathing (腹式呼吸)
  - Progressive muscle RT (PMRT) (漸進式肌肉放鬆)

- PMRT can significantly reduce migraine frequency and day/mth by approximately 41% and 43%, respectively *(J Headache Pain. 2016;17:37.)*

Relaxation training (RT)-Mindfulness Meditation

› JAMA Intern Med. 2020 Dec 14;e207090. doi: 10.1001/jamainternmed.2020.7090.
Online ahead of print.

Effectiveness of Mindfulness Meditation vs Headache Education for Adults With Migraine: A Randomized Clinical Trial

Rebecca Erwin Wells [1], Nathaniel O'Connell [2], Charles R Pierce [1], Paige Estave [3], Donald B Penzien [1 4 5], Elizabeth Loder [6], Fadel Zeidan [7], Timothy T Houle [8]

Relaxation training (RT)-Mindfulness (正念)

- Mindfulness-based stress reduction (MBSR), a standardized mind-body treatment that teaches momentary awareness with decreased sensory percept judgment *(JAMA Intern Med. 2020 Dec 14;e207090.)*

- Mindfulness may be particularly helpful for migraine, as it diminishes affective responses to stress *(J Clin Psychiatry. 2013 Aug;74(8):786-92.)* *(Psychoneuroendocrinology. 2014 Jun;44:1-12.)*

- Double-blinded RCT of MBSR vs headache education for migraine

Relaxation training (RT)-Mindfulness (正念)

- Inclusion criteria
  - Migraine (ICHD-2)
  - 4-20 migraine day/mth
  - Hx of migraine for at least 1 yr
  - At least 18 y/o
  - Availability for 8 weekly classes
- Exclusion criteria
  - Unstable medical or psychiatric illness
  - Severe clinical depression (PHQ-9 > 20)
  - Nonmigraine chronic pain
  - MOH (ICHD-2)
  - Pregnancy (current /planned)
  - Use of new migraine Mx within 4 wks
  - Inability to maintain stable Mx
  - Incomplete baseline headache log
  - Absence of pain ratings to noxious (49 °C) stimuli

Relaxation training (RT)-Mindfulness (正念)

- Primary outcome (baseline to 12 wks)
  - Migraine frequency change (day/mth)

- Secondary outcome (baseline to 12, 24, 36 wks)
  - Headache day frequency, intensity, unpleasantness, duration
  - Disability, QoL, self-efficacy
  - Pain catastrophizing, depression scores
  - Experimentally induced pain intensity and unpleasantness

Relaxation training (RT)-Mindfulness (正念)

- Primary outcome (baseline to 12 wks)
  - Both migraine frequency↓ (no statistical differences between groups)

- Secondary outcome (baseline to 12, 24, 36 wks)
  - 12 wks: both headache frequency↓ (no statistical differences between groups)
  - 36 wks: both migraine frequency↓ (no statistical differences between groups)
  - 36 wks: both headache frequency↓ (no statistical differences between groups)
  - No significant changes over time or group differences on headache pain unpleasantness, intensity, or duration

Pain Catastrophizing

Disability

Self-Efficacy

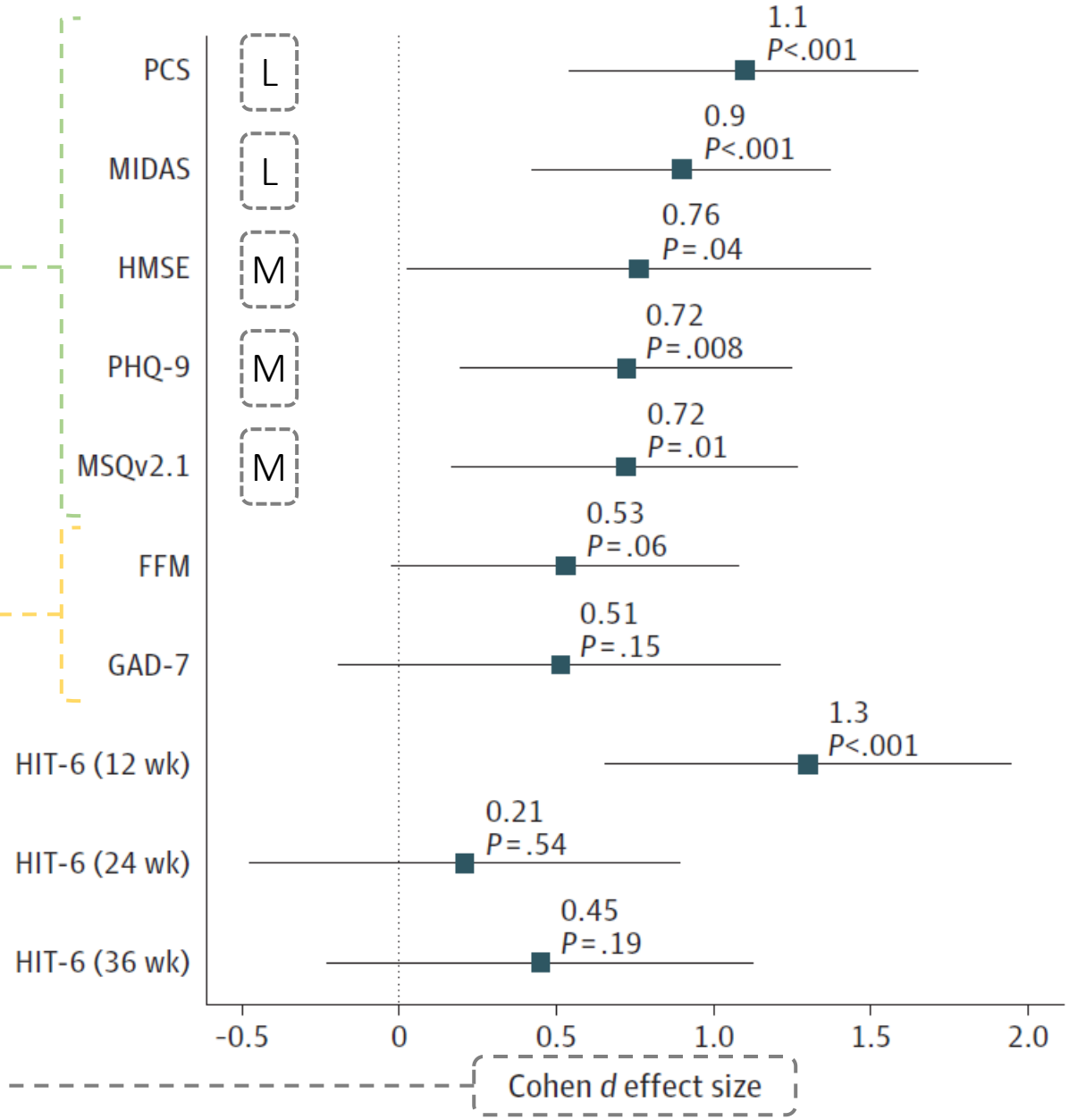
Depression

Quality of Life

Mindfulness

Anxiety

0.2(small)..... S
0.5(medium)..... M
0.8(large)..... L
1.2(very large)



Relaxation training (RT)-Mindfulness (正念)

- MBSR did not improve migraine frequency more than headache education

- MBSR improved disability, QoL, self-efficacy, pain catastrophizing, and depression out to 36 wks

Physical exercise

- Significant reduction in pain intensity, frequency and duration, w/o worsening of migraine *(Cephalalgia. 2003 Dec;23(10):972-6.) (Headache. 2009 Apr;49(4):563-70.) (Headache. 2002 Oct;42(9):845-54.) (Clin Rehabil. 2003 Sep;17(6):624-30.) (Clin J Sport Med. 2008 Jul;18(4):363-5.) (J Headache Pain. 2014 Feb 14;15(1):11.) (Arq Neuropsiquiatr. 2014 Nov;72(11):851-5.)*

- Aerobic training ≈ strength training *(Arq Neuropsiquiatr. 2011 Feb;69(1):39-43.)*

- RCT: significant frequency reduction in the yoga vs self-care ($p < 0.001$) *(Headache. 2007 May;47(5):654-61.)*

CBT

Need eligible P’t
Efficacy (stress/Mx use/QoL)
Frequency reduction variable

1

Biofeedback

Effective (duration/frequency)
Enduring result (14mths)
Combination better

2

Relaxation training

Effective (frequency)
Several types (MBSR, PMRT…)
Additional benefits (QoL…)

3

Physical exercise

Effective (duration/frequency/intensity)
Aerobic ≈ strength training
Yoga also effective

4

Conclusion

Prevalent

- Common psychiatric comorbidities
- Migraine chronification, QoL↓; Modifiable factors
- Mechanism?

Promising

- Effective/enduring in primary HA and migraine
- CBT, biofeedback, relaxation (MBSR/PMRT), exercise
- Standardized protocol and outcome measures

Participating

- Holistic care
- Pharmacological + non-pharmacological
- Teamwork (physician, therapist referral, P’t)

References of major importance

- Minen et al. Migraine and its psychiatric comorbidities. *J Neurol Neurosurg Psychiatry*. 2016 Jul;87(7):741-9. doi: 10.1136/jnnp-2015-312233.
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- Amin et al. The association between migraine and physical exercise. *J Headache Pain*. 2018 Sep 10;19(1):83. doi: 10.1186/s10194-018-0902-y.

Thank You for Your Time