Emicrania cronica:
la diagnosi e il trattamento con tossina botulinica

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Disclosures

- Participation in advisory boards for Allergan, ElectroCore, Eli Lilly, Novartis, Teva
- Lecturer for Allergan, Eli Lilly, Novartis, Teva
- PI or collaborator in randomised controlled trials for ElectroCore, Eli-Lilly, Teva, Alder

Outline

- Chronic migraine
- MoA of onabotulinumtoxinA in chronic migraine
- Efficacy

Migraine attack: pain and more

Vomiting

Nausea

Photophobia

Headache

Osmophobia

Neck stiffness

Movement hypersensitivity

Aura

Cognitive difficulties

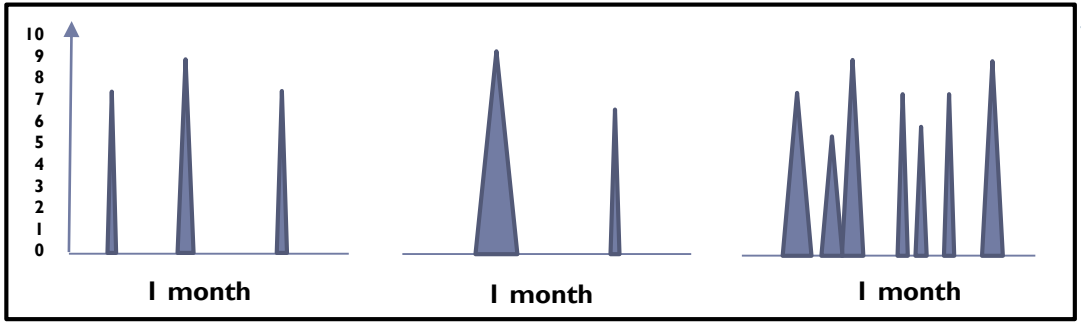
Vertigo

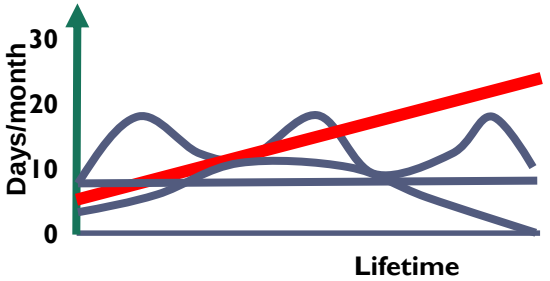
Duration: 4 to 72 hours

A severe migraine attack is as disabling as quadriplegia, schizophrenia or dementia

The severity of Migraine and its progression

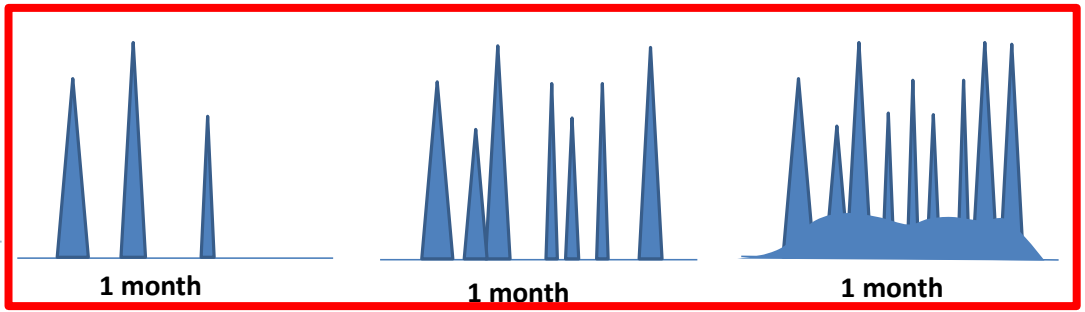
Within and between subjects: duration and intensity of attacks, temporal pattern





More aggressive and less aggressive biological subtypes of migraine

Aggravating/causative role for the overuse of acute medications



- ✓ **≥15 giorni al mese da almeno 3 mesi**
- ✓ **caratteristiche emicraniche in almeno 8 giorni/mese**

ICHD 2015

The typical CM patient

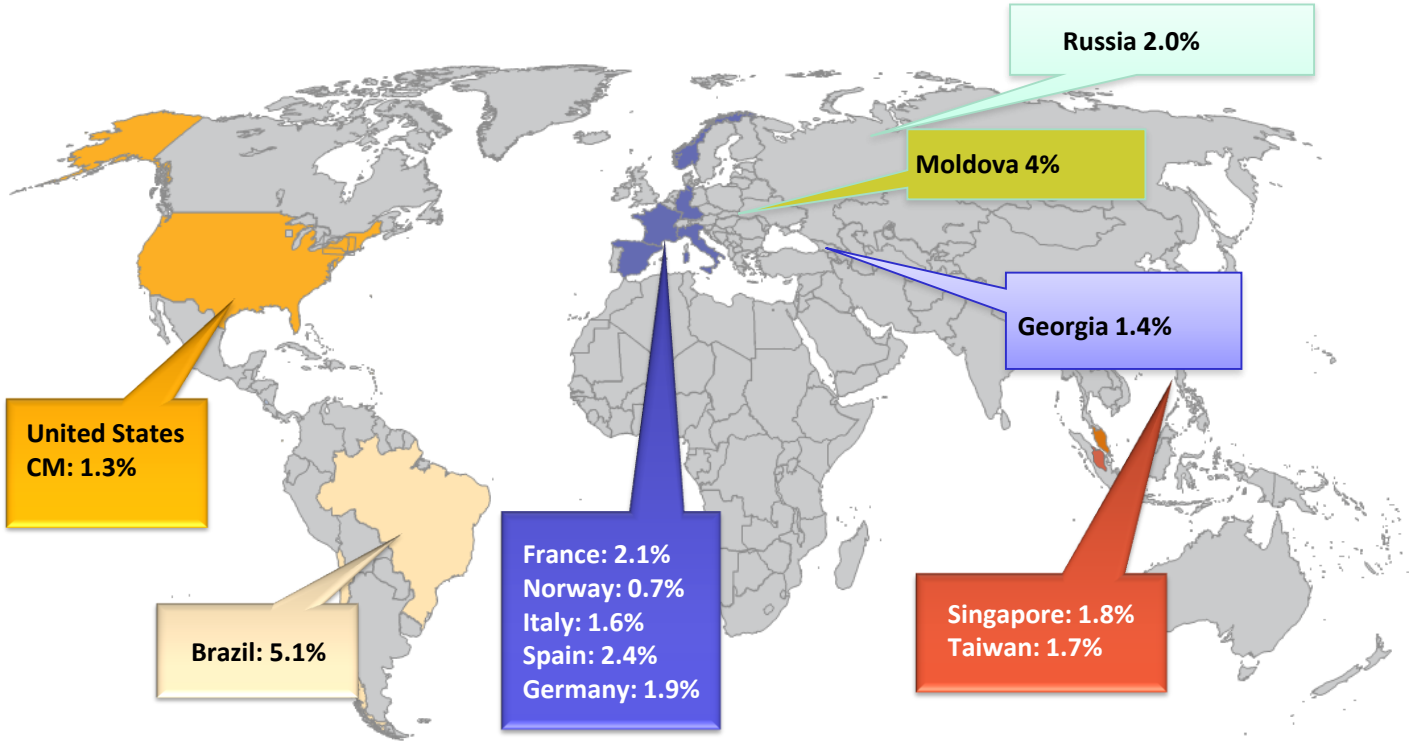
Young/middle-aged woman

… who has been suffering from severe, disabling migraines for years

… with a poor or progressively waning effect of acute treatments

… who never received a prophylactic treatment or, conversely received several treatment, but some/many/all were ineffective

Chronic Migraine: Global Prevalence



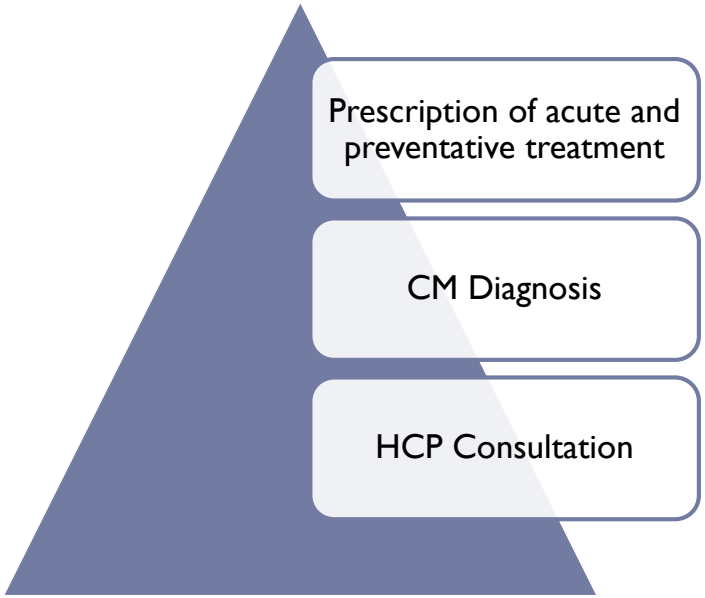
*Headache on ≥15 days/month

Ayzenberg et al. Cephalalgia 2012
Katsarava et al. Neurology 2009
Moldovanu et al. Cephalalgia 2007
Natoli et al. Cephalalgia 2010

Migraine is the **sixth highest cause of disability worldwide**, measured in years of life lost to disability

Global Burden of Disease 2013, Lancet 2015

The perfect world



The real world

56 (4.5%)

126 (10.0%)

512 (40.8%)

1254 patients

Respondents Classified as CM, MIDAS Grade ≥2, and Health Insurance Data N=1,254

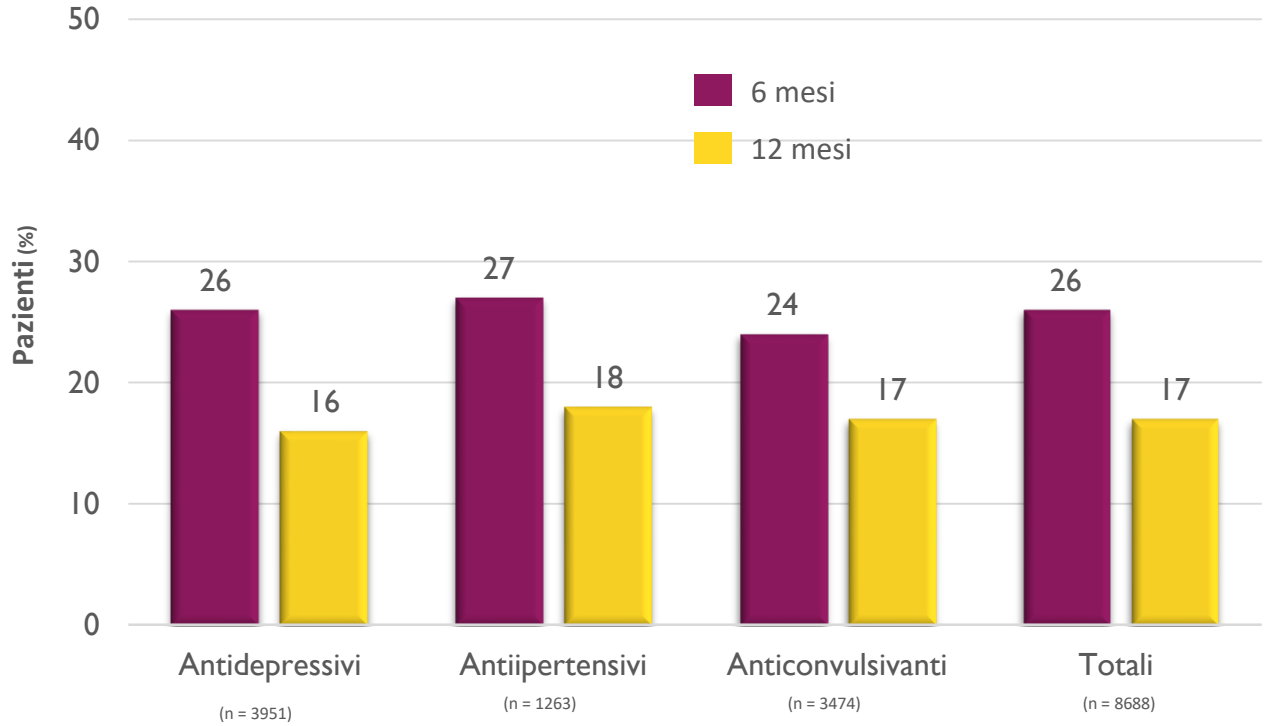
Dodick et al., Headache 2016

EFFECT OF PREVENTIVE DRUG: % of >50%-responders

Active Drug	References	Sample	% with outcome with active drug [placebo]
Sodium valproate	Pooled	405	43.0 [23.3]
Topiramate	Pooled	1422	49.6 [25.1]
Topiramate	Pooled	1145	42.2 [23.3]
Topiramate	Pooled	1086	22.3 [11.0]
Propranolol	Pooled	541	45.1 [22.3]
Metoprolol	Pooled	225	39.9 [19.4]
Lisinopril	Schrader et al., 2001	120	23.3 [0.0]
Candesartan	Tronvik et al., 2003	120	38.3 [3.3]

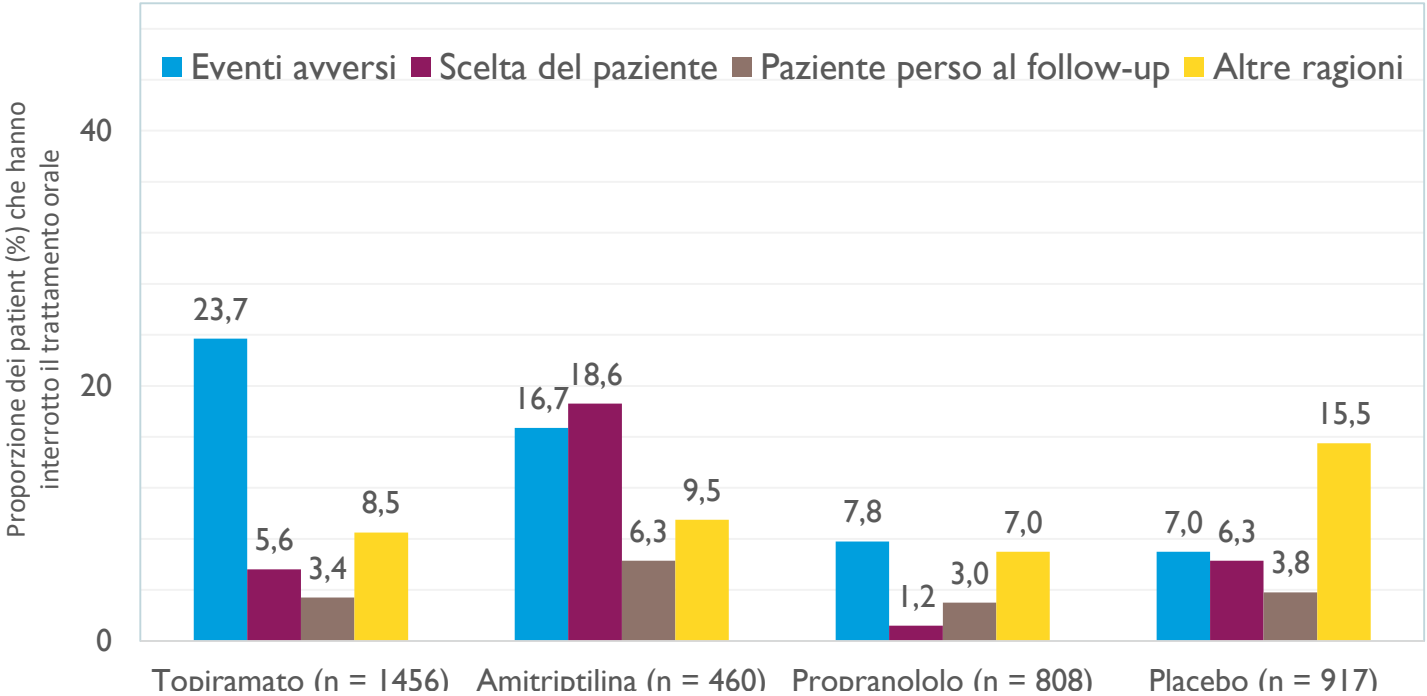
mod. da Shamliyan et al., J Gen Intern Med 2013

Aderenza alla terapia di profilassi
(proporzione di giorni coperti)



Adattato da Hepp et al. Cephalalgia 2015

Cosa causa l'interruzione della terapia?



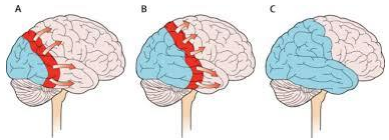
Adattata da Hepp et al. J Manag Care Pharm 2014

Migraine is a complex disorder characterized by recurring attacks, whose initiation depends on endogenous and exogenous factors

Migraine is a disturbance of sensory processing involving the meninges, cortex, thalamus, hypothalamus, brainstem nuclei and cranial pain pathways

Endogenous factors

Hyperexcitability of the cortex and the dysmodulated brain may contribute to initiation of migraine



Chawla, 2018

The hyperexcitable brain
An example of cortical spreading depression (CSD) originating in the visual cortex

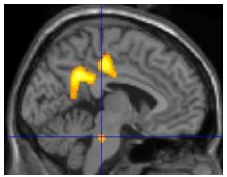


Image adapted from Levy et al, 2009.

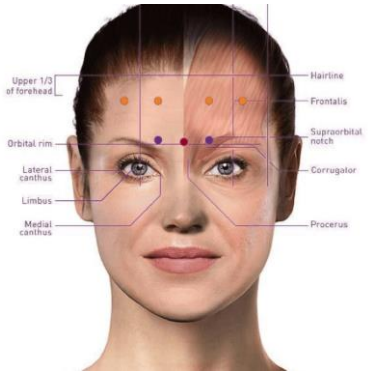
The dysmodulated brain
Brainstem activation

Exogenous factors

Peripheral stress, dietary products and environmental changes may also initiate migraine through activation of sensory afferents

Goadsby et al. N Engl J Med 2002;346:257–70 .Pietrobon. Neuroscientist 2005;11:373–86 - Goadsby. Headache 2005;45(Suppl. 1):S14–24 - Levy et al. Headache 2009;49:953–7.

Lessons from botox: is it targeting muscles?



	Motor
Mechanism of action	• OnabotulinumtoxinA blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals
Treatment benefit	• Muscle relaxation

Neural pathways involved in the transmission and modulation of cephalic pain

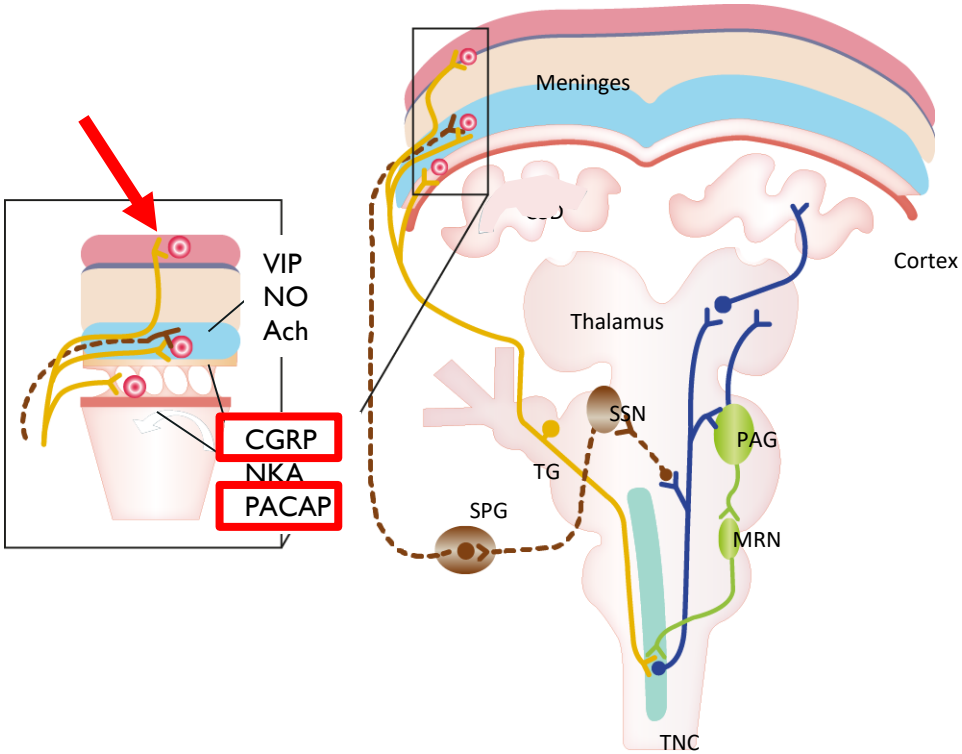


Figure adapted from Pietrobon 2005

Role of the trigeminovascular system activation in migraine pathophysiology

Activation of the trigeminovascular afferent fibres of the trigeminal ganglion

↓

Release of neurotransmitters from peripheral nerve terminals of trigeminovascular afferents

↓

Vasodilation of the meningeal vessels

↓

Plasma extravasation and mast cell degranulation leads to secretion of other pro-inflammatory substances in the dura (neurogenic inflammation)

↓

Activation of neurons in the trigeminal nucleus caudalis and in brain regions associated with pain perception

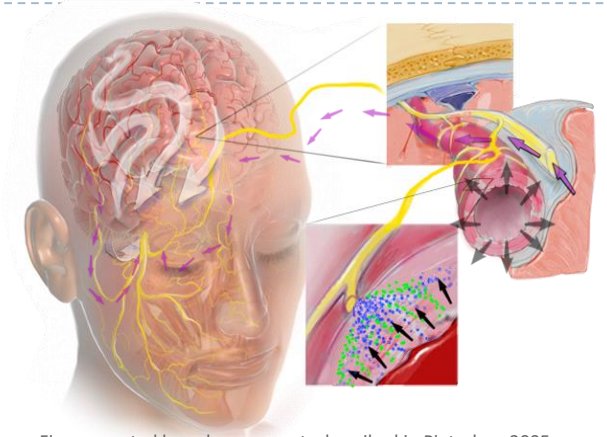
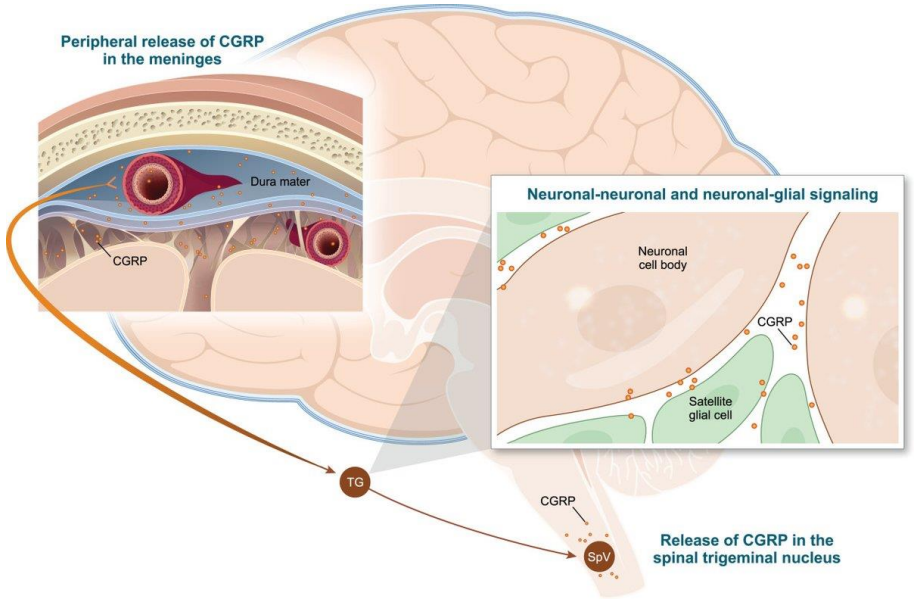


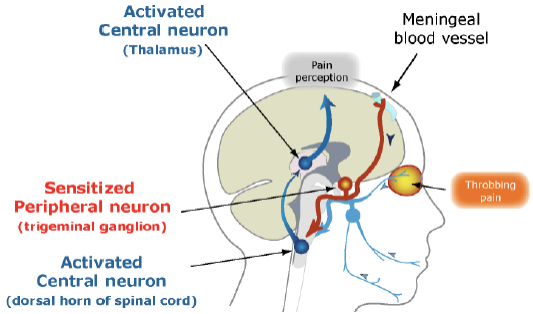
Figure created based on concepts described in Pietrobon 2005.

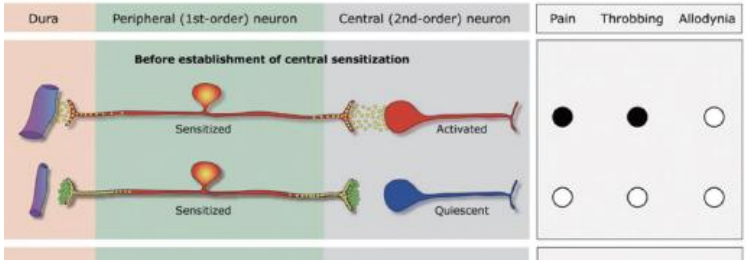
Moskowitz et al., Goadsby et al, Tassorelli et al., multiple publications

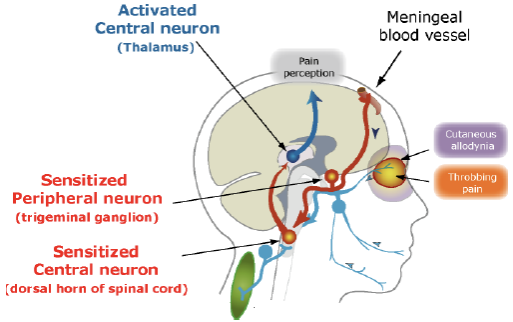
Neurovascular and neural pathways involved in the transmission and modulation of cephalic pain: the role of CGRP

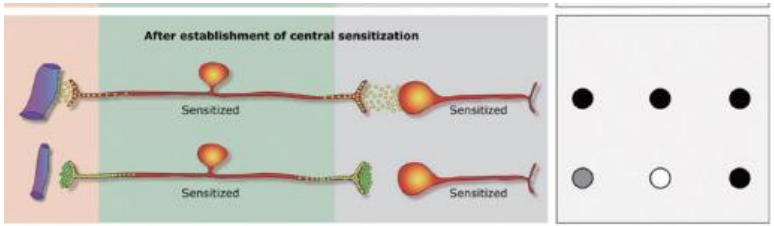


Peripheral and central sensitization as the underlying mechanisms of phenotypical changes in migraine

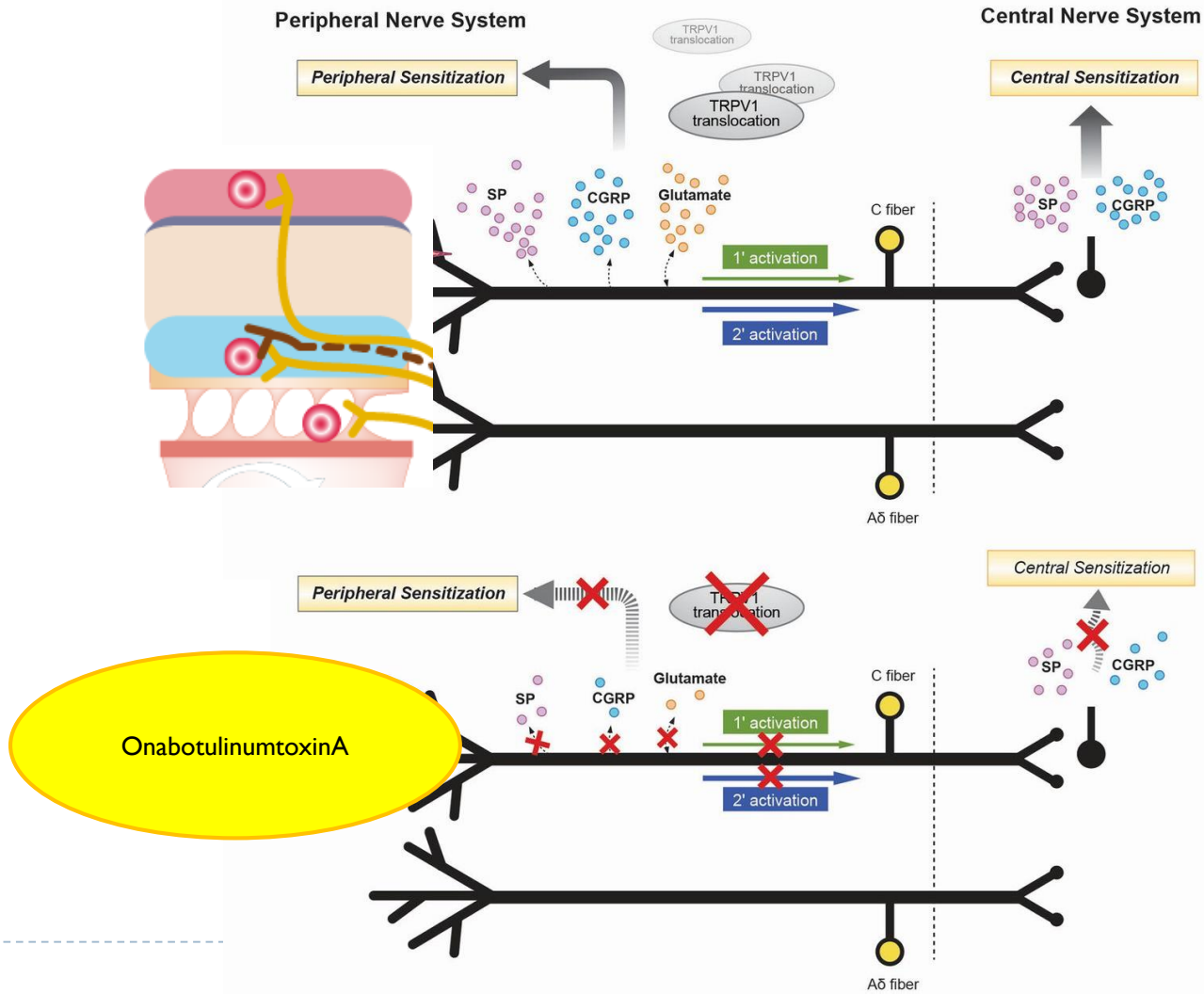




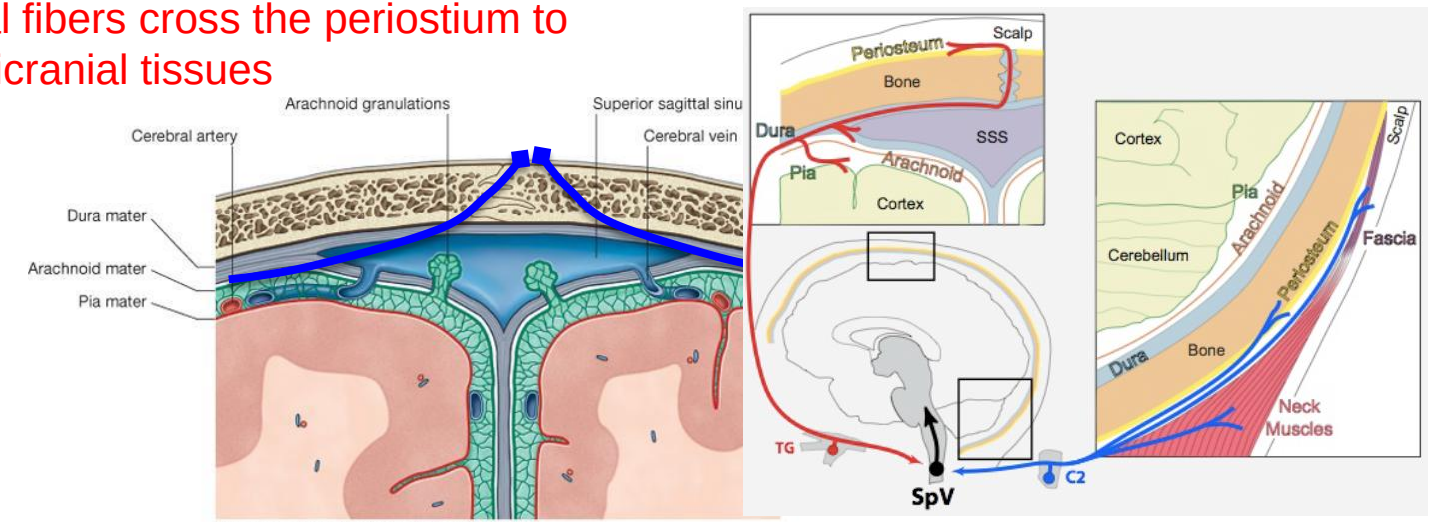




Burstein et al., 2004, 2011


Peripheral Nerve System
Central Nerve System
TRPV1 translocation
TRPV1 translocation
TRPV1 translocation
Peripheral Sensitization
Central Sensitization
SP
CGRP
Glutamate
C fiber
1' activation
2' activation
SP
CGRP
Aδ fiber
Peripheral Sensitization
Central Sensitization
OnabotulinumtoxinA
SP
CGRP
Glutamate
C fiber
1' activation
2' activation
SP
CGRP
Aδ fiber

Trigeminal fibers cross the periostium to reach pericranial tissues



Drake: Gray's Anatomy for Students, 2nd Edition.
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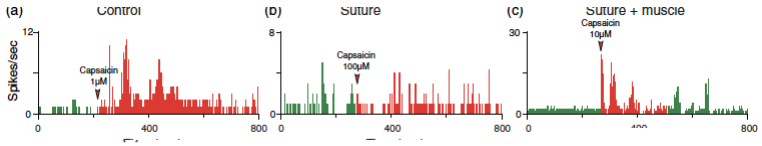
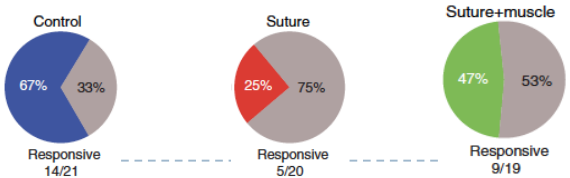
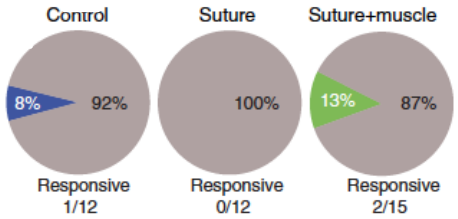
based on data fron Schueler et al., Pain 2013





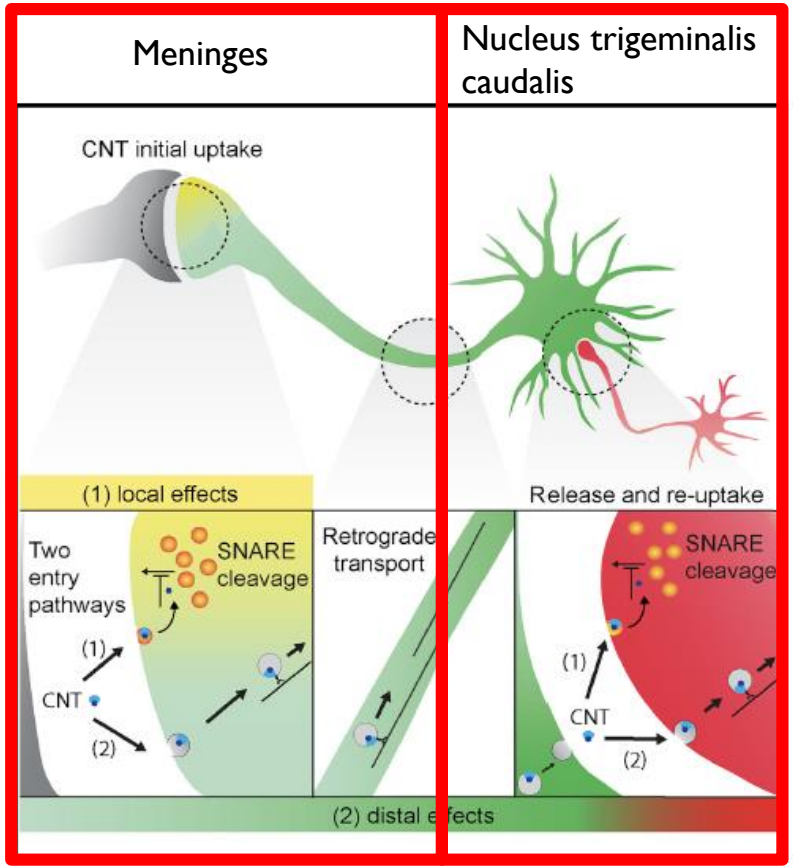
C fibers

Adelta fibers



Burstein et al., 2014 - Zung et al., 2016

Local and central effects of botulinum toxin



Bomba-Warzack et al., 2016

Inhibition of neurotransmitter release locally and distally (CGRP, substance P, glutamate, cytokine)

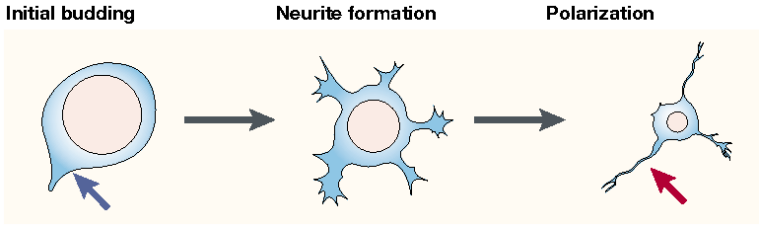
Inhibition of the surface expression of TRPV1 and TRPA1

Shimizu et al., 2012

Going beyond the periphery and SNAP25

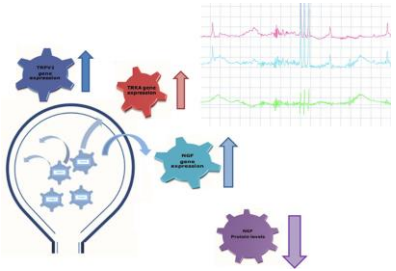
Induction of neuritogenesis

Jiang et al., 2014



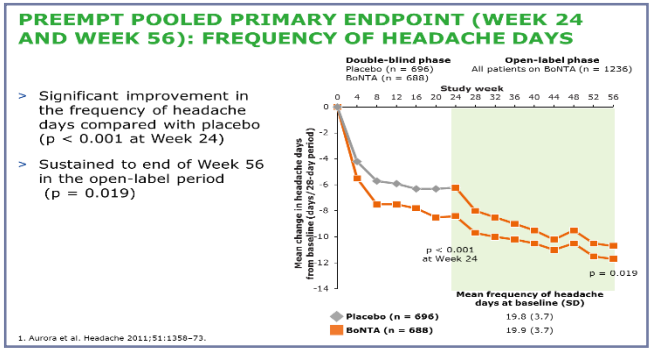
In vivo changes in gene expression

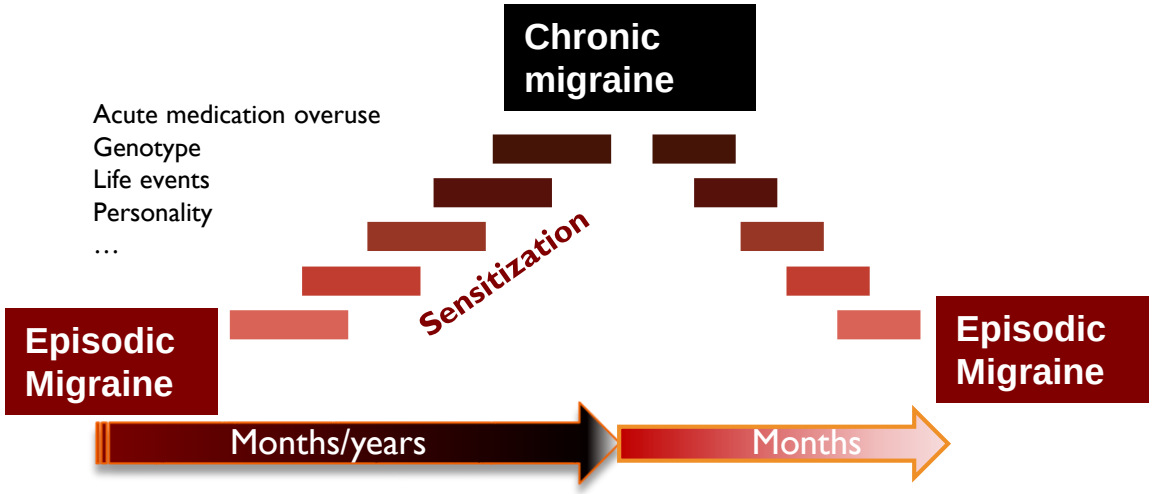
Zhang et al., 1993; Humm et al., 2000; Jung et al., 1997; Gómez-Pinilla et al., 2004; and Majewski, 2012; Lepiarczyk et al., 2015

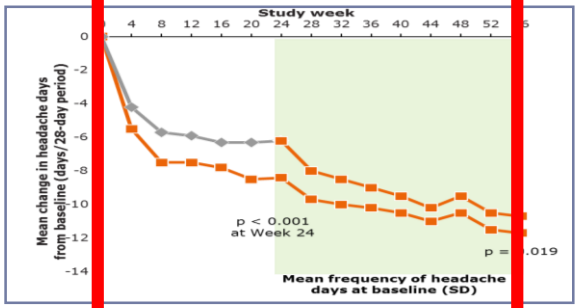


see also Matak & Lackovic *et al., 2015 for review*

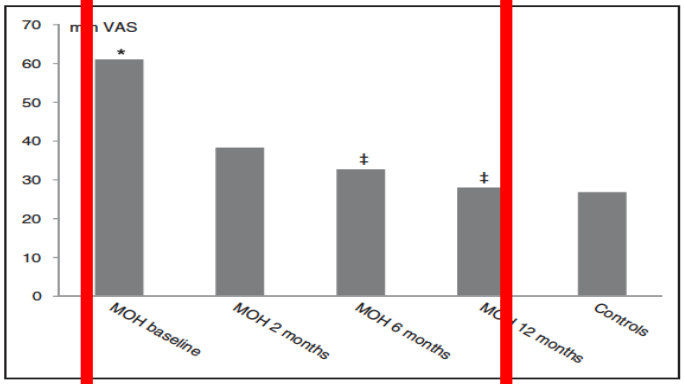
OnabotulinumtoxinA proved effective in Chronic Migraine, while findings in Episodic Migraine were controversial



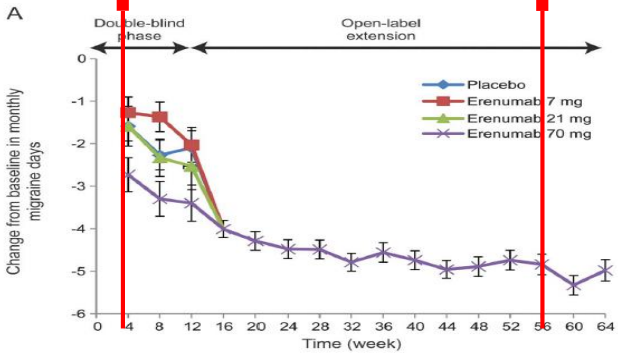




OnabotulinumtoxinA in PREEMPT studies
(Aurora et al., Headache 2011)

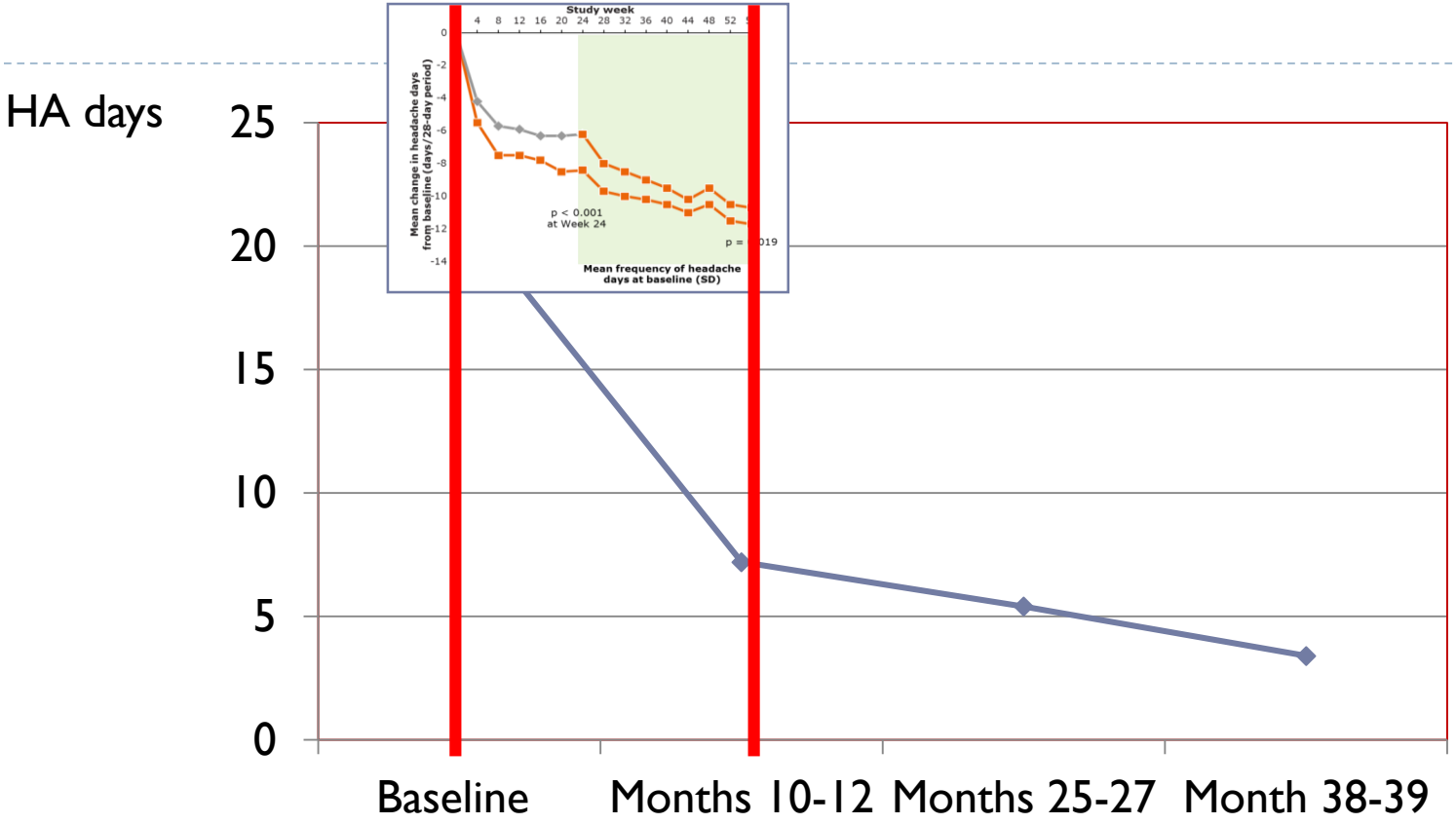


Cephalic supra-threshold pressure pain in subjects with MOH following detoxification
(Munksgaard et al., Cephalalgia 2013)



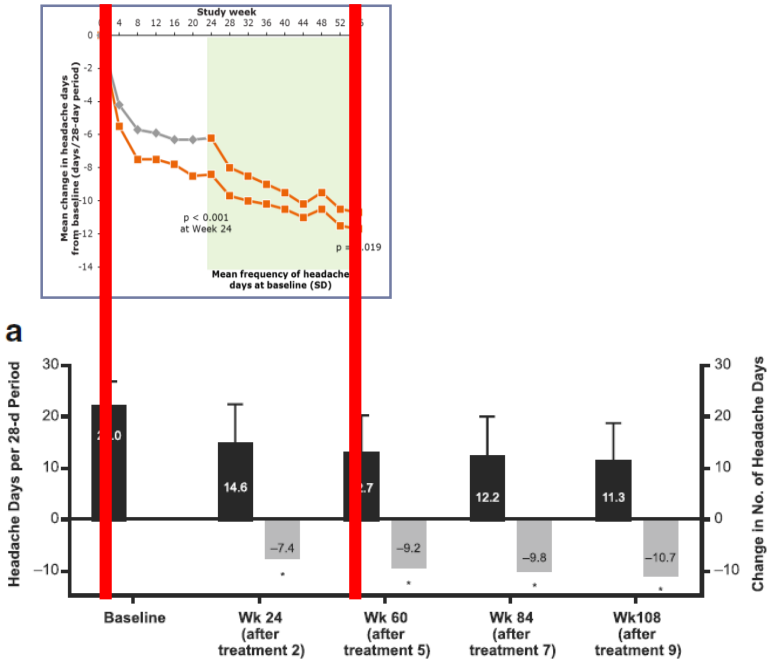
Reduction in monthly migraine days with erenumab in episodic migraine
(Ashina et al., Neurology 2017)

OnabotulinumtoxinA in Chronic Migraine - A 3-year Follow-up



Vikelis et al., J Headache & Pain, 2018

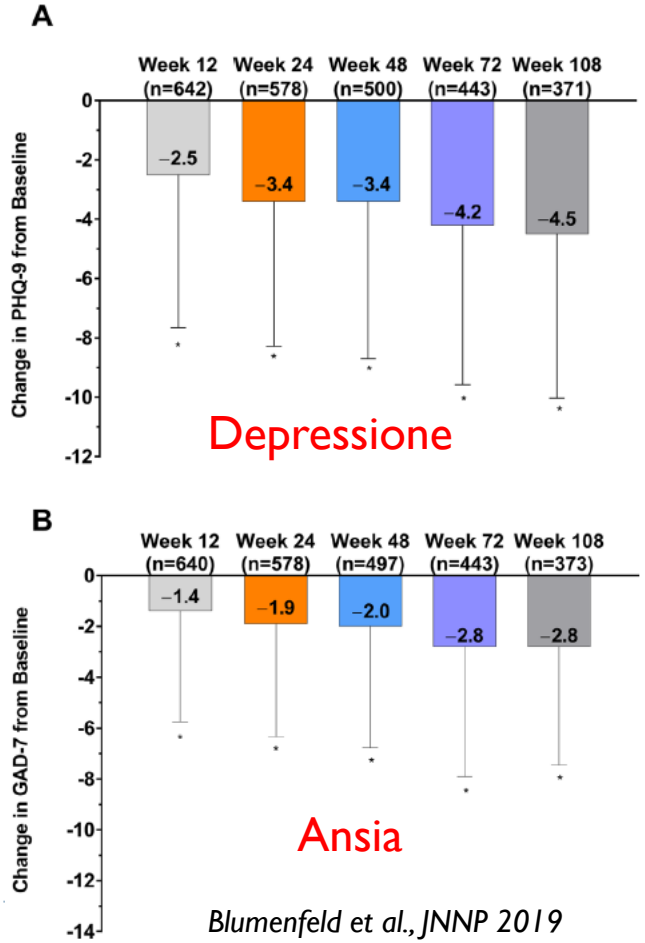
COMPEL study, n. 716 pts



Blumenfeld et al., J Headache & Pain, 2018

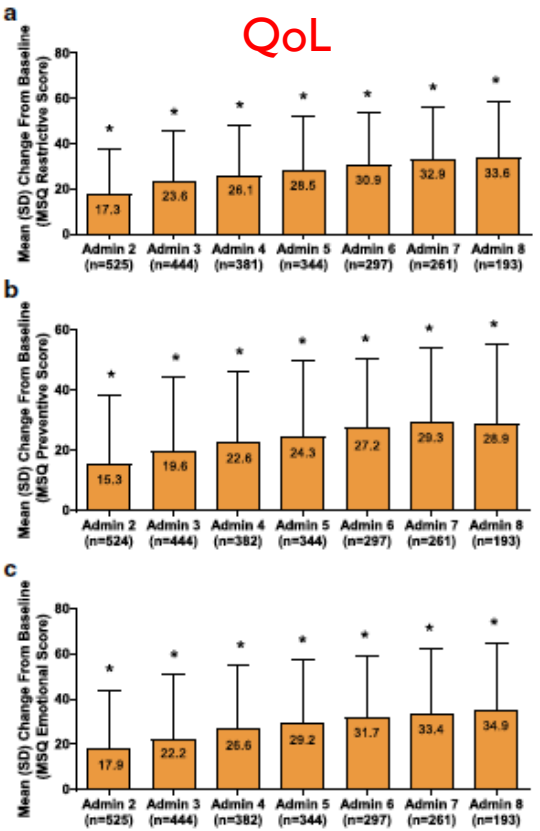
LONG-TERM REAL LIFE STUDIES

COMPEL



Blumenfeld et al., JNNP 2019

REPOSE



Ahmed et al., J Headache & Pain 2019

Possible clinical issues

Medication overuse: detox whenever possible

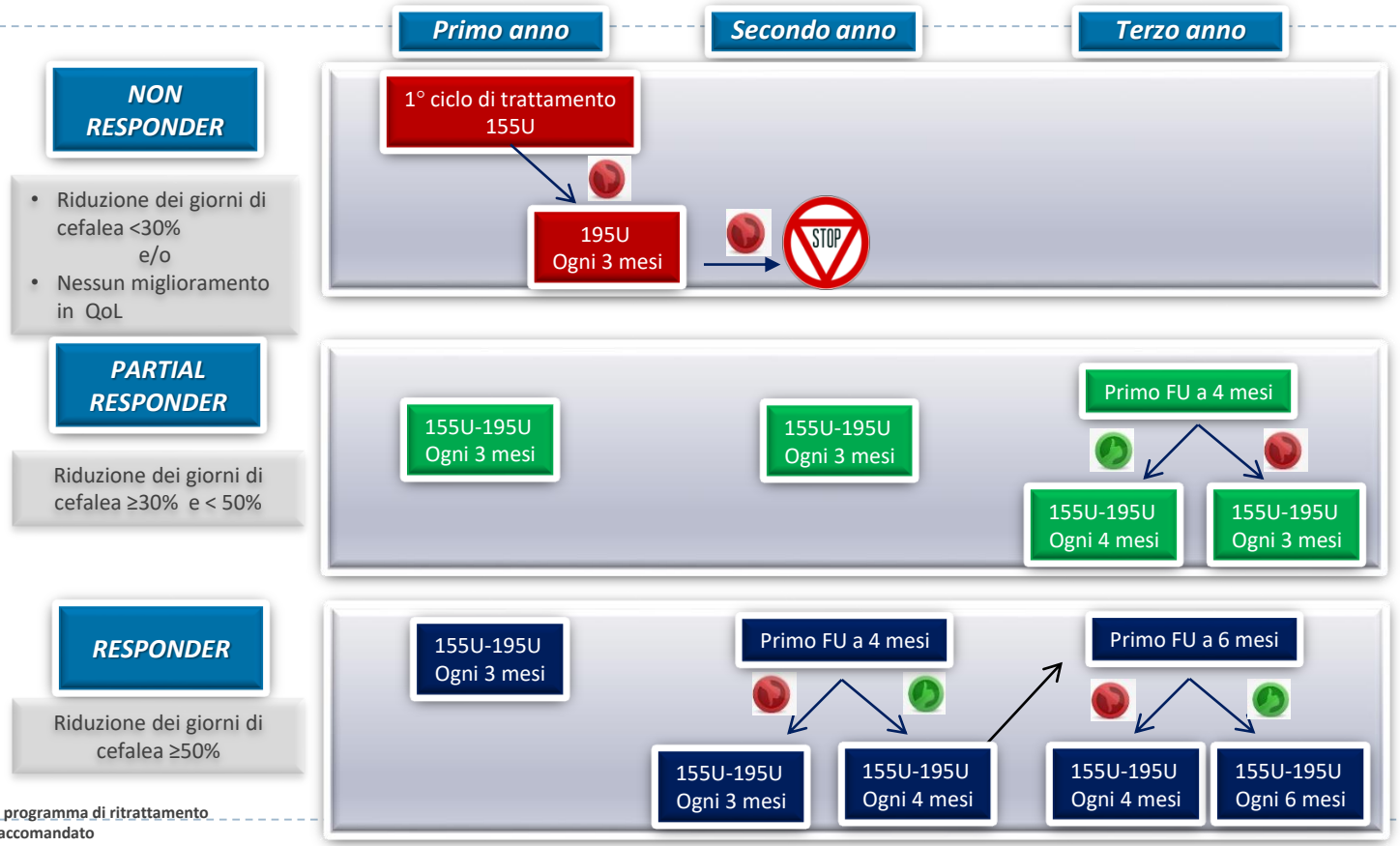
Non responders to the first cycle:
- try a total of 3 cycles
- increase dose from 155 to195 UI

Wearing off of the effect:
- increase dose from 155 to195 UI

Safety & tolerability: not an issue

How and when to stop?

Consensus Protocol
Steering Committee Italian Survey Project

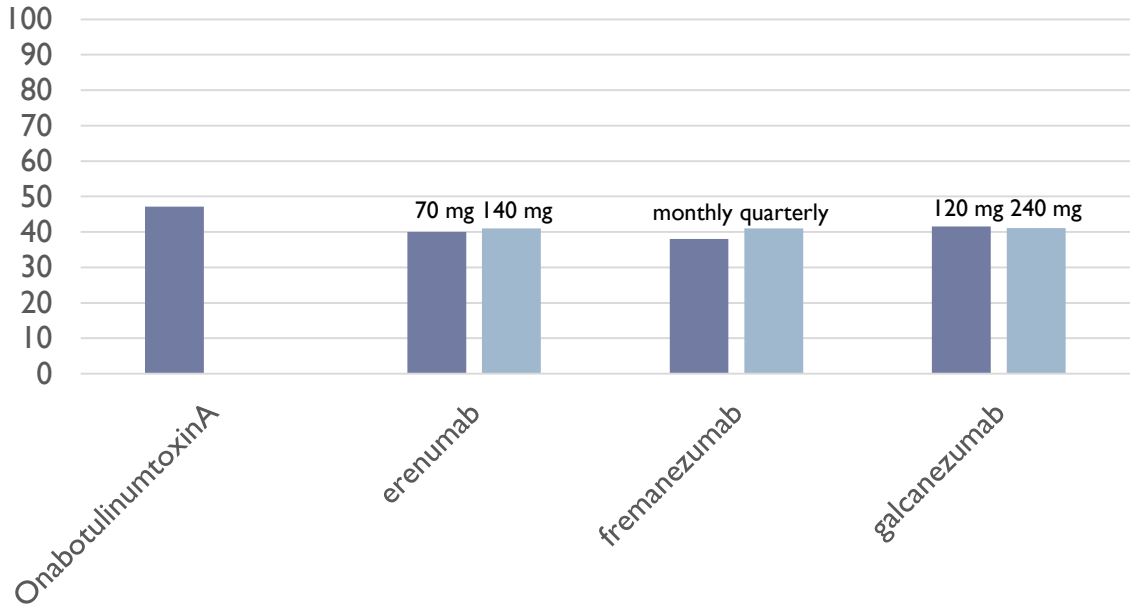


Il programma di ritrattamento raccomandato
è di ogni 12 settimane secondo RCP

Tassorelli C. et al., Expert Review of Neurotherapeutics, 2018

A solution for many, not for all

50% responders



To combine or not to combine?

Acknowledgements

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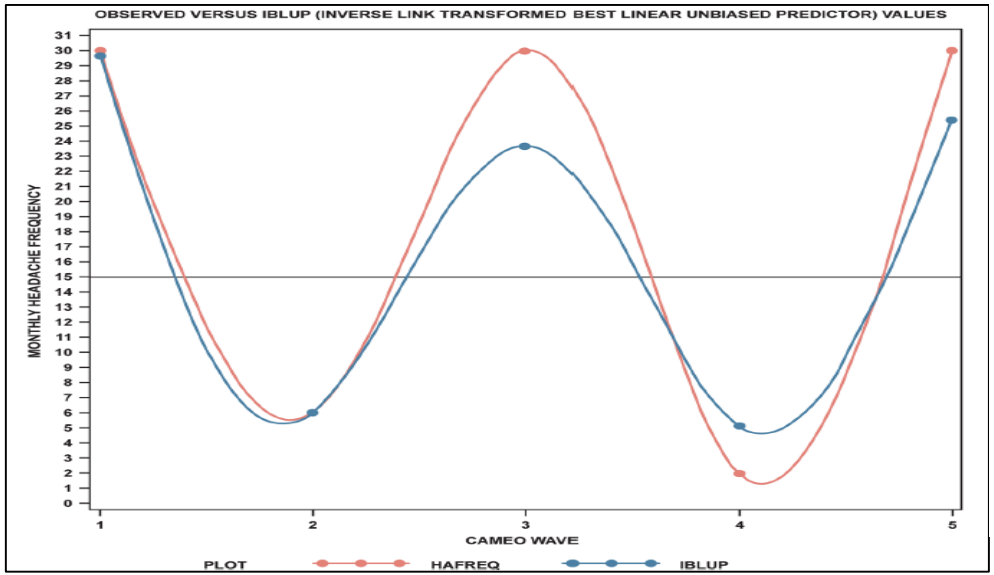
Chiara Demartini
Rosaria Greco
Anna Maria Zanaboni

Migraine is a condition with a dynamic pattern in many patients



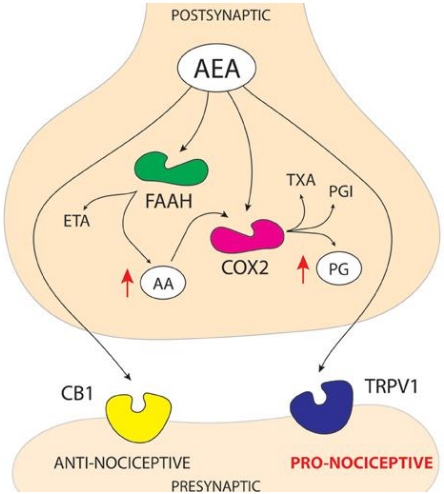
Over a 12-month period:

7.6% of episodic migraine sufferers meet at some criteria for chronic migraine

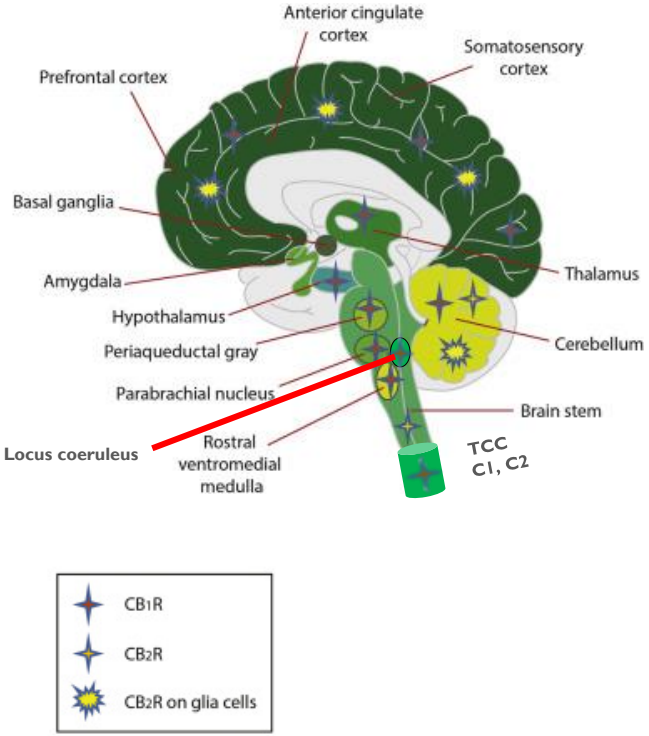
73.4% of chronic migraine sufferers no longer have a chronic pattern

Serrano et al., 2017

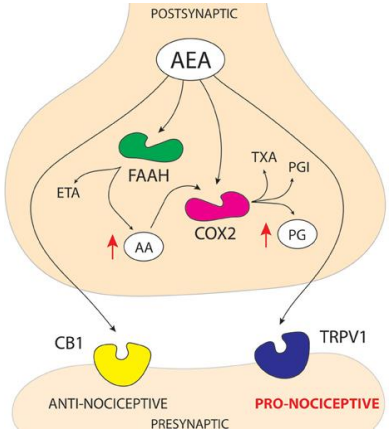
Dual-effect of endocannabinoid activation



Malek & Starowics, Br J Pharmacol 2018

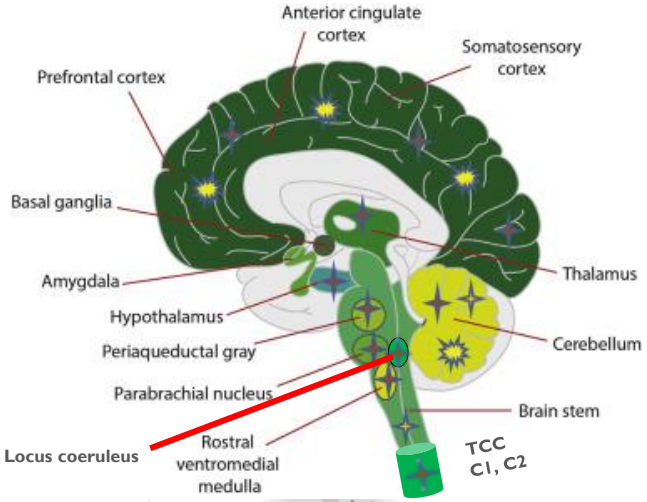


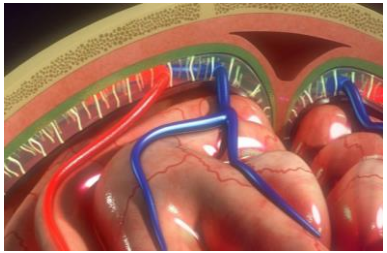
mod from Starowics & Finn, Adv. Pharmacol 2017

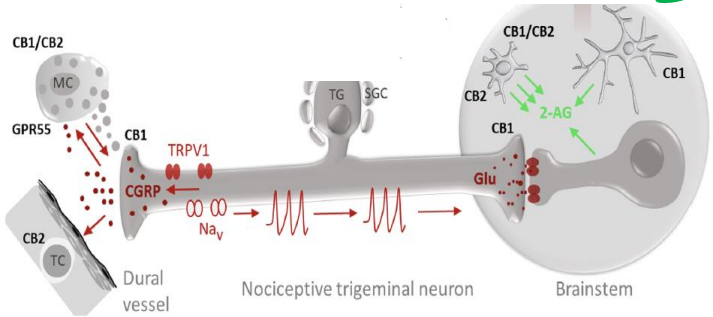


Modulation of the endocannabinoid pathway in animal models of migraine

Greco et al., 2010-2018

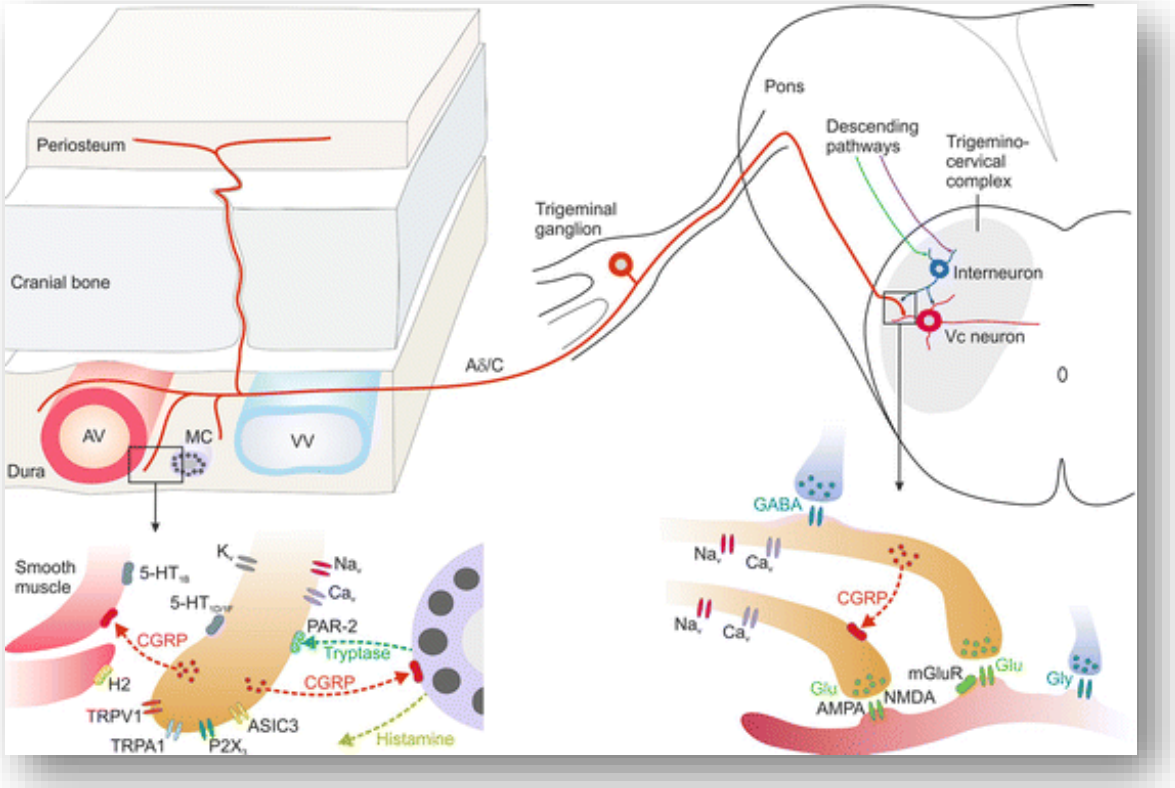






mod from Leimuranta et al. Front Pharmacol 2018

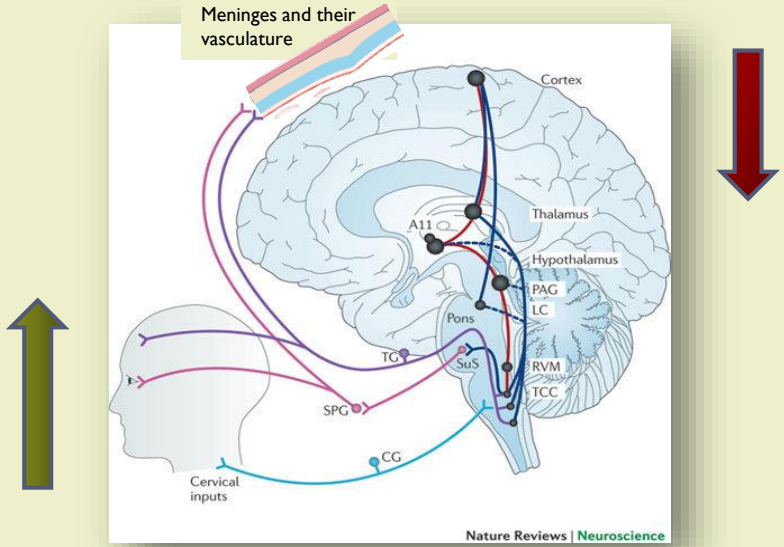
Anatomy of migraine: messengers involved



Bolay et al., 2015

Anatomy of migraine pain

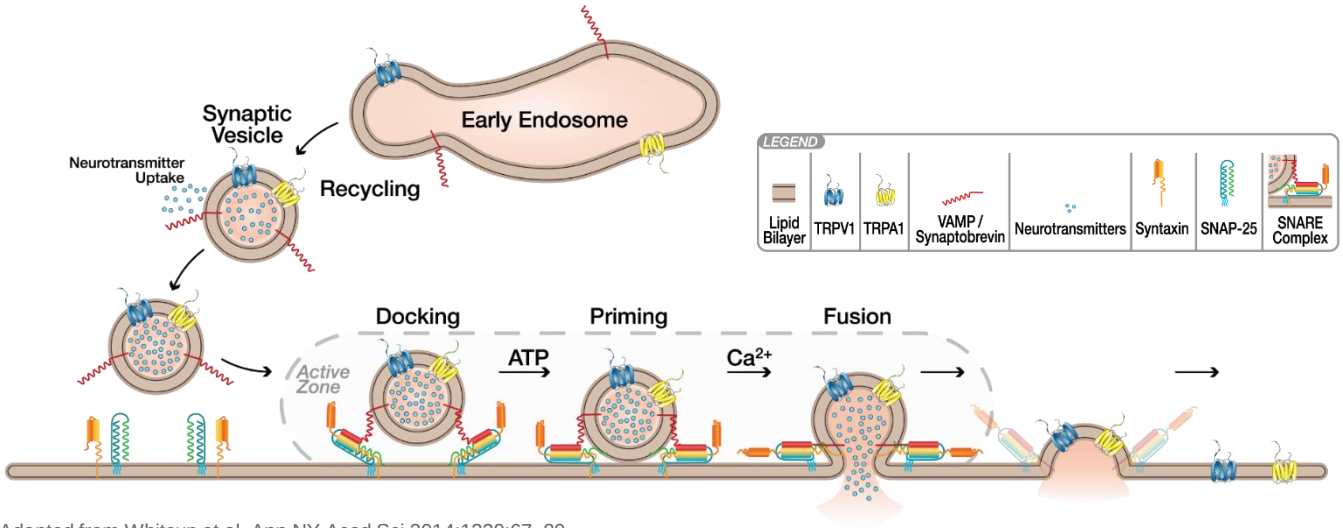
Pain-mediating and pain-controlling pathways in migraine



mod. from Akerman et al., 2011

SNARE mediated exocytosis: Neurotransmitter release and receptor insertion

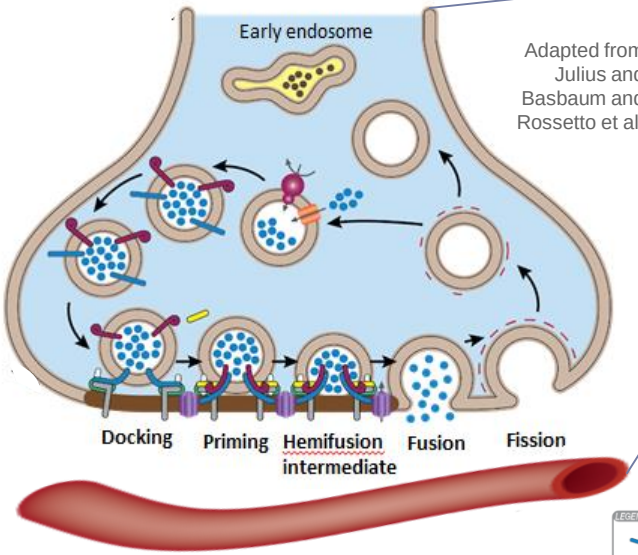
- Synaptic vesicles form a reserve pool at the nerve terminal and may be filled with neurotransmitters
- Most synaptic vesicles are decorated with proteins including receptors such as TRPV1 and TRPA1
- Synaptic vesicles dock adjacent to the nerve terminal and undergo fusion with the presynaptic membrane
- Successful fusion requires an interaction between VAMP/synaptobrevin with SNAP-25 and syntaxin, which together form the SNARE complex



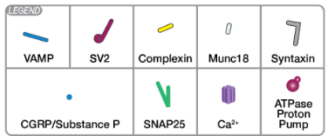
Adapted from Whitcup et al. Ann NY Acad Sci 2014;1329:67–80.

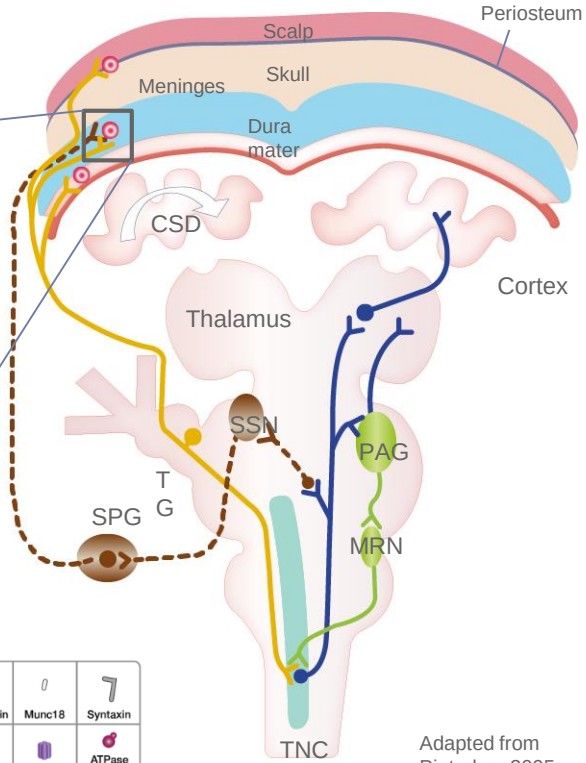
Pain signalling: neurotransmission at nerve terminals

Pain signalling is mediated by the release of neurotransmitters from synaptic vesicles in response to various stimuli



Adapted from Julius and Basbaum and Rossetto et al.



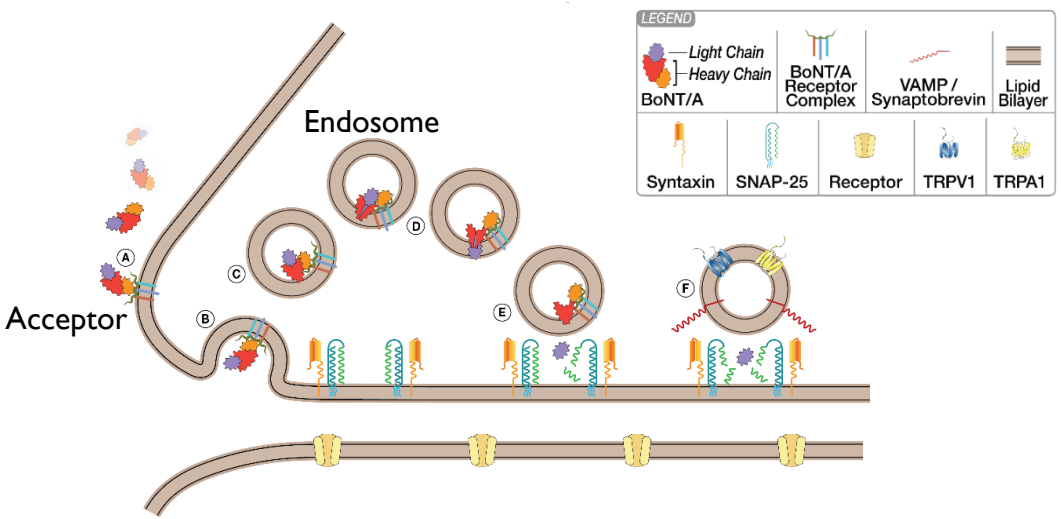


Adapted from Pietrobon 2005.

Julius and Basbaum. Nature. 2001;413:203–10. Rossetto et al. Nature Rev Microbiol 2014;12:535–49. Pietrobon. Neuroscientist 2005;11:373–86.

Onabotulinumtoxin A disrupts SNARE-mediated receptor and ion channel transfer to the presynaptic membrane

- Onabotulinumtoxin A inhibits SNARE-mediated synaptic vesicle trafficking through:
  - Inhibition of the release of neurotransmitter and neuropeptide-containing synaptic vesicles
  - **Disruption of cell surface expression of receptors and ion channels at the membrane of trigeminovascular endings in the meninges**



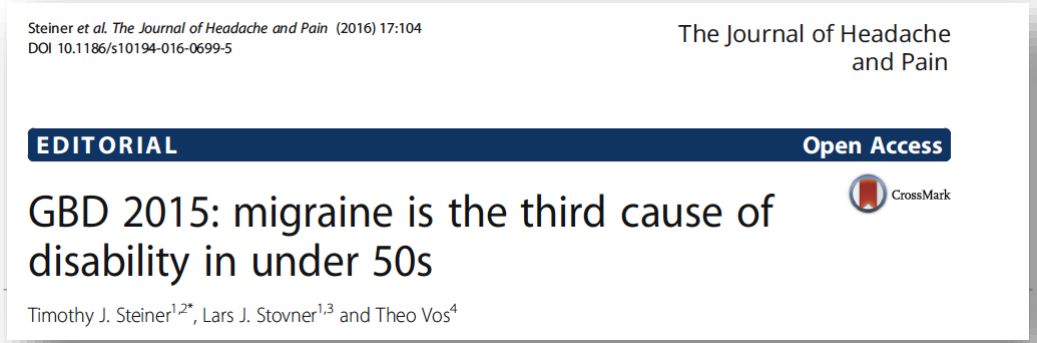
Adapted from Whitcup et al. Ann NY Acad Sci 2014;1329:67–80.

Migraine-related disability

DALYs	
Total neurological disorders	250.692.000
▸ Stroke	118.627.000
▸ Migraine	32.899.000
▸ Medication overuse headache	9.165.000
▸ Alzheimer's disease	23.779.000
▸ Parkinson's disease	2.059.000

DALY: sum of the number of years of life lost because of the disease

GBD 2015 Neurological Disorders Collaborator Group. The *Lancet Neurol* 2017;16:877–897



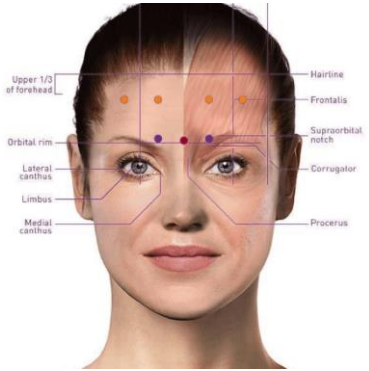
Steiner *et al. The Journal of Headache and Pain* (2016) 17:104
DOI 10.1186/s10194-016-0699-5

The Journal of Headache and Pain

EDITORIAL Open Access

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

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



- The antinociceptive effect of OnabotulinumtoxinA is distinct from its neuromuscular activity
- The biochemical effect of OnabotulinumtoxinA, cleavage of SNAP-25 to impair synaptic vesicle fusion and neurotransmitter release, is the same at both sensory and motor nerve terminals

	Motor	Sensory
Mechanism of action	• OnabotulinumtoxinA blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals	• OnabotulinumtoxinA blocks the release of neurotransmitters associated to the genesis of pain • OnabotulinumtoxinA reduces the cell surface expression of ion channels and sensory receptors
Treatment benefit	• Muscle relaxation	• Pain reduction • OnabotulinumtoxinA may also supress peripheral sensitisation, thereby possible inhibiting central sensitisation

Aoki. Headache 2003;43(Suppl. 1):S9–15ì - Whitcup et al. Ann NY Acad Sci 2014;1329:67–80.