Combining preventive drugs: When enough is not enough

L. Grazzi
Unita’ di Neuroalgologia, Centro Cefalee
Fondazione IRCCS Istituto Neurologico «C.Besta», Milano

Disclosure: L. Grazzi has received consultancy and advisory fees from: Allergan SpA; Electrocore LLC; EliLilly; Novartis AG

Moreover Collaborator for RCTs sponsored by: EliLilly; Novartis; TEVA Pharm Ind
Preventive therapy for migraine

Prior to 2017, there were no preventive medications designed specifically for migraine prophylaxis in our lifetime

1. Low specificity
2. Low response rate
3. Slow onset of efficacy
4. No efficacy at long term
5. Side effects
6. No efficacy in all migraine forms

After 2017, the MABs preventive therapy “...”

Is it enough or we have to find more solution for problematic patients...

- Combining different therapies to improve clinical results
- Which the “best combination”

1. MABs plus traditional therapies  
   see real life studies

2. MABs plus Onabotulinumtoxin A  
   see clinical preliminary experiences

3. MABs plus Gepants  
   see clinical preliminary experiences

4. MABs plus non-pharmacologic approaches  
   see different studies
COMBINING DRUGS…..

**Dual Therapy with antiCGRP monoclonal antibodies and botulinum toxin for migraine prevention: is there a rationale**

*Pellesi, Do, Ashina et al. Cephalalgia*, 2020. One of the first clinical evidence to support a rationale for dual therapy with anti-CGRP and botox

**Combined onabotulinumtoxin A /Atogepant treatment blocks activation/sensitization of high-threshold and wide dynamic range neurons**

*Melo-Carrillo, Strassman, Schain et al, Cephalalgia, 2020.* A scientific demonstration of a possible combined effect between Onabotulinumtoxin A & Atogepant that can reduce migraine (Adelta & C blockade)

**Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy**

*Mullin, Kudrow, et al. Neurology, 2020.* Rimegepant 75 mg may be effective for acute treatment during concomitant erenumab preventive administration
COMBINING DRUGS …..

Erenumab and Onabotulinumtoxin A combination therapy for the prevention of intractable Chronic Migraine without aura: A retrospective analysis.

*Armanious, Khalil et al, Journal of Pain and palliative Care Pharmacotherapy, 2021.* Seventy-eight pts treated with Ere plus Onab:
- enhanced effect on the modulation of CGRP release from peripheral unmyelinated C fibers and blocking CGRP receptors in the myelinated Adelta fibers

Real-world evidence for control of Chronic Migraine patients receiving CGRP monoclonal antibody therapy added to Onabotulinumtoxin A: A retrospective Chart review.

*Blumenfeld, Frishberg et al, Pain Ther, 2021.* The combination is well tolerated and effective

Improvements in pain, medication use and quality of life in OnabotulinumtoxinA-resistant chronic migraine patients following erenumab treatment – real world outcomes

*J Talbot, et al. Journal of Headache and Pain, 2021.* Outcomes of 9 months of erenumab treatment in a cohort of patients with difficult-to-control chronic migraine, all of whom had prior unsatisfactory response to onabotulinumtoxinA. Improvements in pain, medication use and quality of life in onabotulinumtoxinA-resistant chronic migraine patients following erenumab treatment
Combination Therapy in migraine: asset or issue?


The combination of different therapies to improve the clinical results: major concerns

Safety: see at chronic diseases and comorbidities and drugs interactions

Effectiveness: the clinical data have to confirm an increase in benefit

Costs: resources consuming…cost-effectiveness

Different strategies from adding drugs can be adopted to improve clinical results due to innovative drugs: “Combining” can be a perfect strategy, but not enough if limited to drugs…
Head Pain & Migraine: Complex disease where biological, social and psychological aspects are strictly connected

Central sensitization and the biopsychosocial approach to understanding pain

L Adams, D Turk
J Appl Behav Res. 2018; 23: e12125

Acceptance and Chronic Pain

L McCracken, KE Vowles
Current pain and Headache Report, 2006;10(2)

Changes after multidisciplinary pain treatment in Patient pain beliefs and coping are associated with concurrent changes in pain functioning

M Jensen, J Turner, J Romano
Pain, 2007; 131: 91
Behavioral approach for a biobehavioral disorder

Migraine and other kinds of headache are **bio-behavioral disorders**, more than a painful condition residing in receptor physiology and more aptly recognized as a condition wherein physiology, cognition and behavior are intermingled.

Consequently a simple pharmacological approach can be inadequate:

*Saper, Hamel, Lake, Cephalalgia, 2005*

*Lake, Headache, 2008*

*Saper, CNS Drug, 2013*

Primary headaches can be best understood and managed from a biopsychosocial perspective (*Andrasik, 2009*)
Which are the most important aspects of a biopsychosocial intervention?

* Proper diagnosis

* Patient education

* Multidimensional assessment & functional diagnosis (MIDAS; HIT6; PCS; MSQoL)

* Strategic intervention including different approaches according to the assessment and patients needs: *drugs and more*…

* Changes monitoring

* Follow up (*Lake, Headache, 2006*)
Behavioral and Pharmacologic Treatment of Transformed Migraine With Analgesic Overuse: Outcome at 3 Years
Licia Grazzi, MD, Frank Andrasik, PhD, Domenico D'Antico, MD; Massimo Leone, MD, Susan A. Uthai, MD, Steven J. Kamo, PhD; Graziano Bussone, MD

Objectives.—To determine whether combined treatment using medication and biofeedback would be more effective than drug treatment alone for treating transformed migraine complicated by analgesic overuse.
Background.—Headaches that are chronic, daily, and aggravated by medication overuse are particularly difficult to treat.
Methods.—Sixty-one consecutive patients with transformed migraine and analgesic overuse were treated with liquidation pharmacologic therapy alone or with intermittent pharmacologic therapy combined with biofeedback-assisted relaxation. All patients were followed prospectively for 3 years.
Results.—Both treatment groups exhibited lower levels of improvement immediately following treatment and for 1 year thereafter. At year 3, participants receiving combined treatment showed greater sustained improvement in their transformed migraines compared with those receiving drug treatment alone (P < .05). In addition, a greater number of patients assigned to pharmacologically treatment alone relapsed (i.e., transformed migraine improved for 3 months but relapsed), compared with those assigned to combined treatment (P = .04). These results suggest that a combination of pharmacologic and behavioral treatment is more effective than long-term therapy alone in the long-term management of transformed migraines with analgesic overuse.
Conclusions.—These findings, as well as evidence from other forms of behavioral and cognitive-behavioral treatment, is encouraging.

Keywords: drug-induced headache, transformed migraine, pharmacologic treatment, biofeedback-assisted relaxation treatment, long-term follow-up

Abbreviations: CTH chronic daily headache, MMPI Minnesota Multiphasic Personality Inventory, STAI State-Trait Anxiety Inventory

Vox Clamantis
Acceptance and Commitment Therapy (ACT) vs Erenumab for High Frequency Episodic Migraine Without Aura:
Time to Take the Gloves Off!
Licia Grazzi; Paul Rizzoli
(Headache 2020;60:804-806)

Received: 6 July 2020 HEADACHE RESEARCH SUBMISSIONS
Acceptance and commitment therapy for high frequency episodic migraine without aura:
Findings from a randomized pilot investigation
Licia Grazzi MD | Frank Andrasik PhD | Paul Rizzoli MD | Carolyn Bernstein MD, Emanuela Sansone MSc | Alberto Raggi PsyD PhD
| Accepted: 25 March 2021 DOI: 10.1111/head.14139
The MIND-CM study: We aim to assess whether adding on Mindfulness is also associated to a superior improvement of neuroimaging pattern, controlling for prescribed neuromodulators or antidepressants in Chronic Migraine with Medication Overuse.

MIND-CM: Trend Drugs/3-6M

53.5 [30.7-76.4]
25.4 [13.4-37.4]
P = .026

MIND-CM: Trend frequency/3-6M

39.5 [27.6-51.4]
23 [12.6-33.4]
P = .011

P-value for tend <.001 in both groups
At 6M pts in MIND had 5.5 headaches less per month

P-value for tend <.001 in both groups
At 6M pts in MIND consumed 9.4 drugs less per month
Functional MRI studies evidenced:

- abnormalities in specific cerebral area of subjects affected by overuse: prefrontal cortex, amygdala, hippocampus, nucleus accumbens (Nava, 2004)

- evidence of normalization among MOH patients, of different brain areas (e.g. primary somatosensory cortex) after withdrawal

- these same areas are more activated after mindfulness sessions in normal subjects (Zeidan et al., 2011; Borsook, 2016)

- Cognitive Behavioral Therapy: evaluation of changes in brain activation and resting-state connectivity after 8 weeks of CBT in youth with migraine; it seems to alter brain functioning in areas that control emotion and pain, which are different from those affected by pill-taking (Nahman-Averbuch, et al. Headache, 2020)

- Changes in Conditioned Pain Modulation (Wells et a, JAMANeurol, 2020)
Moreover, fMRI studies reported that during pain, mindfulness practitioners had:

- Reduced activation in specific cerebral areas: amygdala, hippocampus, emotional/evaluative regions of prefrontal cortex
- Increased activation in the anterior & mid-cingulate cortex, thalamus and insula (Grant et al, 2011; Salomon et al, 2011; Davidson, 2012)

**Insula** as Cortical Hub that:

* Processes many of the complex sensory, emotional aspects associated to migraine condition
* Integrates many of the dynamic processes involved in migraine 

*(Borsook, 2016)*
Erenumab: clinical indexes, and more…

Neurophysiological and biomolecular effects of erenumab in chronic migraine: An open label study

Roberto De Icco, Giuseppe Famingo, Rosaria Greco, Sara Bottiroli, Chiara Demartini, Anna Maria Zanaboni, Marta Allena, Elena Guaschino, Daniele Martinelli, Alessia Putorti, Valentina Grillo, Grazia Sances and Cristina Tassorelli

The RESET BRAIN study
A RandomizEd double-blind cross-over Study to assess Erenumab effecT on BRAIN networks function and structure in comparison to placebo in episodic migraine patients

Skorobogatykh et al.

The Journal of Headache and Pain REVIEW ARTICLE

Functional connectivity studies in migraine: what have we learned?

Biomarkers
preliminary evidence of improvement in inflammatory patterns and/or catecholamines (in MOH patients).

Grazzi et al, Neurol Sci. 2018

Functional MRI of migraine
Todd J Schwedt, Chia-Chun Chiang, et al.
Lancet Neurol 2015; 14: 81–91

Migraine as a Cortical Brain Disorder
Piero Barbanti, MD, PhD; Filippo Brighina, MD; Gabriella Egeo, MD, PhD; Vincenzo Di Stefano, MD; Marcello Silvestro, MD; Antonio Russo, MD, PhD
HEADACHE CURR, oct 2020
Final Considerations

✓ Migraine is a complex clinical condition where biologic and emotional aspects are strictly connected

✓ The history of migraine treatment is changing with MABs! Expectation is high: MABs will change dramatically the life of our patients

✓ Combining drugs: possible, but not the only choice: behavioral approaches can improve efficacy of drugs, alleviate pain, enhance consciousness of patients about their symptoms and the correct use of drugs during the therapeutic program

✓ A flexible and integrate approach: to decrease social costs and to use resources appropriately (Kabbouche et al, Headache, 2005; Soee et al, Cephalalgia, 2013; Grazzi et al, Neurol Sci, 2013; Westergaard et al, Cephal, 2014)
Conclusion: The «Enough»…. is enough

Domenico D’Amico
Massimo Leone
Alberto Proietti
Susanna Usai

Frank Andrasik
Carolyn Bernstein
Paul Rizzoli

GRAZIE!!