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NOVEL PHARMACOLOGICAL APPROACHES IN MIGRAINE THERAPY

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NOVEL PHARMACOLOGICAL APPROACHES IN MIGRAINE THERAPY

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On September 19th and 20th, 2024, the University of Calabria, Rende (Cosenza) was venue of the congress "*Novel Pharmacological Approaches in Migraine Therapy*". The latter represented a collaborative scientific initiative of the University of Calabria (Cosenza), University Magna Graecia (Catanzaro), and Sant'Anna Institute (Crotone) under the Auspices of NEXT GENERATION EU (NGEU), the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project Mnesys (PE0000006), the Italian Society of Pharmacology (SIF), the Italian Society of Neuroscience (SINS), the Italian Society for the Study of Headache (SISC), the Italian Society of Neurological Rehabilitation (SIRN), and the Italian Society of Child and Adolescent Neuropsychiatry (SINPIA). The meeting was organized by Professors Antonio Leo and Damiana Scuteri and chaired by Professors Giacinto Bagetta, Maria Tiziana Corasaniti and Giovambattista De Sarro.

Migraine represents one of the most disabling forms of primary headache, with a severe social impact, rank as one of the leading causes of years lived with disability worldwide and therefore considered a very serious public health problem.

Migraine constitutes a substantial public health problem that mainly affects young and middle-aged adults. As widely reported, migraine is often associated to various comorbidities, including epilepsy, attention-deficit hyperactivity disorder, behavioral problems, obesity, atopic dermatitis, asthma, restless legs syndrome, and anemia that negatively impact the quality of life of patients, increasing further the use of health care and medication. Professor Paolo Martelletti (Rome) pointed at the need for training of young physicians in the clinical practice of migraine management. Particularly, Dr Angelo Pascarella (Catanzaro) described how migraine and epilepsy share several clinical features and have intertwined genetic and molecular underpinnings, which may contribute to common pathogenesis.

According to the International Classification of Headache Disorders (third edition) compiled by the International Headache Society, Professor Coppola (Salerno) reported that headache disorders are divided into primary and secondary headaches. Primary headaches represent idiopathic pain conditions such as migraine, tension-type headaches, and trigeminal autonomic cephalalgia (TAC). Secondary headaches result from a severe underlying disorder and are associated with high morbidity and mortality. This group includes conditions such as headaches attributed to a head injury, vascular disorder or infection or psychiatric disorder. In this field, Dr Belardo (Naples) underlined the effect of treatment with pentadecyl-2-oxazoline (PEA-OXA), a natural α-2 antagonist and histamine H3 partial agonist, on systemic pro-inflammatory state, allodynia, and affective disorders associated with social isolation. The most frequent types of primary headaches in the young population are migraine and tension-type headaches. In the context of these patholo-

gies, understanding endogenous and exogenous triggering factors aids the definition of different pathophysiological paradigms for the exercise of research.

Professor Philip Holland (London) explained that knowledge of the pathophysiology of migraine is crucial for identifying new therapies and discussed the importance of neurogenic inflammation and diffuse cortical spreading depression inducing activation of trigeminal neurons. Professor Gary Lawrence (Dublin) underlined the mechanism of action on SNARE gene products of botulinum neurotoxins to modulate CGRP release of identified nerve terminals in several forms of pain including neurogenic inflammation of migraine.

Professor Rossella Nappi (Pavia) described that sex steroids may influence the prevalence of migraine in both sexes. Female sex steroids may modulate different mediators and receptor systems in the pathogenesis of migraine through both genomic and non-genomic mechanisms at peripheral and neurovascular levels. Regarding the pathogenesis of migraine, Professor Stefania Ceruti (Milan) explained that activated glial cells and the linked neuroinflammation worsen the clinical scenario, leading to chronic migraine. Indeed, trigeminal glial cells are involved in the initiation and maintenance of pain in migraine leading to central sensitization. Professor Pierangelo Geppetti (Florence) also discussed the key role of transient receptor potential (TRP) channels in the context of migraine and the program to identify and develop innovative treatments targeting these channels.

Overall, this amount of data underscores the idea that basic research is fundamental both for identifying the pathophysiological features of migraine and to develop innovative therapies.

In the past, this clinical field has been characterized by lack of knowledge of the pathophysiology of the disease, leading to preventive approaches borrowed from drugs originally developed for other therapeutic indications, resulting in limited efficacy and in an unacceptable level of side effects causing poor adherence. Moreover, patients with ascertained primary headache disorders like migraine or tension-type headaches overuse drugs for their acute headaches, inadvertently amplifying the frequency and intensity of their headaches and their refractoriness. Consequently, a vicious cycle of further drug consumption and increased headache frequency develops, converting the treatment for their headache to the cause of the disease. Regarding this aspect, Professor Simona Sacco (L'Aquila) affirmed that medication-overuse headache (MOH) is a common neurologic disorder with an enormous disability that plays an important role in the transformation from episodic to chronic headache disorders.

More than 35 years of pharmacological research have established a sound, rational basis on which the currently available disease-modifying drugs have been developed.

Today, new pharmacological, non-pharmacological, and nutraceutical approaches are being used.

Professor Dimos-Dimitrios Mitsikostas (Athens) clarified many pharmacodynamic aspects of the Lasmiditan that acts as selective agonist of the 5-HT1F receptor, representing a promising mechanism-based approach for the treatment of migraine attacks and gained importance over the past few years.

Since 2018, two classes of drugs that counteract the actions of calcitonin gene-related peptide (CGRP), which plays a key role in migraine onset, became available: gepants (CGRP receptor antagonists) and monoclonal antibodies (mAbs) directed against CGRP or its receptor.

It is widely recognized that these drugs represent one of the most significant therapeutic achievements in the treatment of migraine. Due to their protein nature and high molecular weight, it has been proposed that they exert preventive effects by acting directly on the peripheral segment of the trigeminal-vascular system. Indeed, as Professor Marina De Tommaso (Bari) pointed out, thanks to their long half-lives, these molecules revolutionized the prophylactic treatment of this neurovascular disorder. Furthermore, as stated by Professor Alberto Chiarugi (Florence), these

drugs, by preventing chronic pain, remove not only migraine attacks but also all related symptoms, counteracting the awareness of discomfort. In particular, anti-CGRP antibodies seem to significantly impact brain functions of migraineurs, preventing not only migraine headache but also co-existing central, psychiatric symptoms and malaise.

Doctor Damiana Scuteri (Catanzaro) illustrated how the history of CGRP in migraine paves the route to success for key signaling pathways in the modulation of nociceptive facilitation. In particular, the real-world data presented about refractoriness, efficacy and safety point to the need for a clinical trial assessing efficacy and safety of onabotulinumtoxin A in combination with the newest anti-CGRP/R monoclonal antibodies and atogepant, as small molecule CGRP receptor antagonist, for the prevention of chronic migraine.

In this new scenario, however, several pathophysiological, therapeutic, and regulatory issues remain open. As fa as the latter topic is concerned, it is crucial to establish new appropriate pharmacovigilance patterns to detect adverse events of anti-CGRP monoclonals in the post-marketing experience, as stated by Doctor Francesca Bosco (Catanzaro).

Professor Stephen D. Silberstein (Philadelphia), introduced the endocannabinoid system and its potential involvement in the pathogenesis of migraine, suggesting cannabinoid-based therapy as an intriguing alternative for the treatment of migraine. According to Doctor Vincenzo Rania (Catanzaro) diamagnetotherapy, a non-pharmacological approach to manage migraine, could represent a non-invasive therapeutic method based on the repulsion mechanisms generated by the forces of high-intensity magnetic fields that can trigger cellular readjustment towards a positive physiological response, improving the quality of life of patients.

Professor Patrizia Popoli projected the picture of the efficacy and reliability of these drugs by addressing some of the uncertainties related to their use in clinical practice, such as their differential efficacy in migraine subtypes, predictors of outcome, switching from one molecule to another, adherence and persistence to long-term treatment, the persistence of effect after discontinuation, combined treatment with botulinum toxin or gepants, cost-effectiveness, and potential contraindications based on the known physiological effects of CGRP.

Furthermore, it is essential to establish serious and reliable networks for the treatment of headaches.

In this context, Professor Domenico Conforti (Rende, Cosenza) illustrated the ALCMEONE industrial research and development project, which aims at providing an innovative organizational and management model and an advanced technology platform of services to support the integrated clinical management of headache patients. The objectives of this project concern the integration of patient-centered healthcare pathways, fully supported by a service platform, assisting the patient in the self-recording of the disease and enabling the primary care level to manage most cases effectively and efficiently. Dr Rita Scarpelli (Catanzaro) carried out evaluations on the cost/benefit ratio of new treatments, illustrating the current data on prescriptions in the Calabria region.

In conclusion, this event involved academic researchers, pharmacologists, clinicians, and national and international leaders who provided postgraduate students, young researchers, and clinicians with their most up-to-date views.

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UNDERSTANDING THE PATHOPHYSIOLOGY OF MIGRAINE TO DEVELOP NEW THERAPIES: BENCH TO BEDSIDE

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OBJECTIVE: Migraine is a complex multi-symptom disorder that consists of several phases, namely the premonitory symptoms, aura (in up to 30% of cases), the headache phase and the postdrome. This diversity of symptoms across the attack duration suggests a key role for several physiological processes including the regulation of pain, cognition and arousal. To date, research has largely focused on the headache phase, with several new therapies translating from bench to bedside; however, there is an unmet need to develop novel therapies that target the diverse array of symptoms reported by patients.
METHODS: The abstract reviews key recent advances in bench to bedside translation for migraine, discusses novel therapeutics in the pipeline and potential future targets focused on intervening during the earliest premonitory symptoms.
RESULTS: Early studies highlighted a potential role for calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase activating polypeptide (PACAP) in migraine via its release in the extracranial circulation in patients and animals during migraine or experimental activation of the trigeminal nerve, respectively. Subsequently it was demonstrated that CGRP and PACAP could both trigger migraine-like attacks in between 55-57% of people with migraine. This has led to the development of several novel therapies targeting CGRP ligand or its canonical receptor, including monoclonal antibodies and small molecule antagonists. After this, a monoclonal antibody targeting the PACAP ligand has demonstrated superiority to placebo in reducing headache frequency in a phase II clinical trial. Building on the role of neuropeptide in migraine, CGRP was shown to activate the related Amylin 1 (AMY1) receptor and preclinical studies demonstrated sex-specific enhancement of light aversion (photophobia) following administration of the amylin agonist pramlintide, which was further able to trigger migraine-like attacks in 56% of people with migraine. Considering the key role of central neural circuits in migraine, the hypothalamus is considered a key regulator of homeostatic disruption in migraine (*e.g.*, abnormal fatigue and appetite dysregulation). The hypothalamus and periaqueductal gray (PAG) are abnormally activated during the earliest premonitory phase in migraine. Research to date has focused on several hypothalamic neuropeptides in migraine, including orexin, oxytocin and somatostatin, with the orexin system representing a potential key regulator of diminished arousal and pain in migraine.
CONCLUSIONS: The therapeutic toolbox available for migraine has benefited recently from translational bench to bedside research that has resulted in the development of new therapies targeting CGRP or its receptor, while those targeting PACAP and Amylin signaling remain at different stages of development. Novel targets at the bench include those targeting altered hypothalamic functioning in migraine, including orexin 1 receptor agonists, offering a future translational approach to target non-pain premonitory symptoms in migraine.

CANNABINOIDS AND MIGRAINE

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Cannabis sativa (*C. sativa*) is one of the world's oldest cultivated plants. It is called 'hemp' when used as a source of fiber and 'marijuana' when used as a drug for therapeutic or recreational purposes. Previously, it was believed that there were at least two species: *C. sativa L* (narrow leaves, branches apart, light green, and tall with few flowers) and *C. indica L* (wide broad leaves, branches close together, deep green, and short and bushy with dense flowers). Now we believe that there is just one species of *C. sativa L* with subgroups called cultivars. *C. sativa L* is the species and *sativa*, *indica*, and *ruderalis* are subspecies.
The chemical components in cannabis flowers consist of over 104 different plant cannabinoids including Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Other compounds include terpenes, flavonoids, steroids, non-cannabinoids, vitamins, and pigments. Classifications now consider the chemical content (chemotype/chemovars) of *C. sativa L*.
The search for the site of action of THC led to the discovery of 2 G protein-coupled receptors for THC, named cannabinoid receptor type-1 (CB1) and type-2 (CB2) and the endogenous cannabinoids lipids that engage cannabinoid receptors. The best-characterized endocannabinoids are arachidonoyl ethanolamide, known as anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). AEA is responsible for maintaining basal endocannabinoid tone and has a high selectivity for the CB1 receptor over the peripheral CB2 receptor AG is a full agonist for both CB1 and CB2.
THC, the constituent responsible for the mind-altering and intoxicating effects of *C. sativa*, acts on CB1 and CB2 receptors. CBD binds to other receptors and is devoid of the psychoactive effects associated with THC. In addition to its psychotropic properties, cannabis has analgesic, immunomodulatory, and anti-inflammatory effects. Cannabis is effective for the treatment chronic pain in adults. Anecdotal evidence suggests a role for cannabis in the treatment of headache and migraine.
The modulation of the endocannabinoid system, in the processing of nociceptive signals in the trigeminovascular system, may prove a well-tolerated and pharmacologically sound therapeutic option for migraine.

NEUROBIOLOGY AND THERAPEUTIC APPLICATION OF RECOMBINANT BOTULINUM NEUROTOXINS

G. W. Lawrence

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OBJECTIVE: OnabotulinumtoxinA injections reduce the frequency and severity of migraine attacks but the benefit varies between patients and its mechanism is unclear. This study examined the impact of different botulinum neurotoxins (BoNTs) on cellular process in sensory trigeminal ganglion neurons (TGNs) and utilized the information to develop novel toxin variants with enhanced anti-nociceptive activity.
METHODS: Novel synthetic BoNTs were created by recombinant genetic engineering, expressed in *Escherichia coli* and purified by affinity plus ion exchange chromatography. TGNs isolated from neonatal rodents were cultured and exposed to natural or synthetic BoNTs *in vitro*. CGRP release elicited by noxious stimuli was measured by ELISA. Inhibition of trigeminal nociceptive pain-indicative grooming was assessed after BoNT injection into the rat whisker pad followed by capsaicin or AITC injections at the same site on various days thereafter.
RESULTS: BoNT/A effectively intoxicated TGNs and inhibited CGRP exocytosis induced by K^+ depolarization or 20 nM capsa-

icin, but not by 1 mM capsaicin. Synthetic chimeras of BoNT/A and /E, BoNT/EA and LC/E-BoNT/A cleaved off a larger fragment of SNAP-25 and blocked CGRP release evoked by both low and high concentrations of capsaicin. A VAMP-cleaving BoNT/DA chimera inhibited AITC-evoked CGRP-release more effectively than any of the BoNTs that cut SNAP-25. Nerve growth factor (NGF) induced modest CGRP secretion and sensitized TGNs to capsaicin or AITC; both activities were prevented by BoNT/A, /EA, /DA or LC/E-BoNT/A. LC/E-BoNT/A produced a long-lasting suppression of capsaicin- and AITC-induced pain after injection into rat whisker pad.
CONCLUSIONS: BoNTs inhibit both NGF sensitization of nociceptors and their exocytosis of CGRP. Recombinant protein engineering can enhance the activity of BoNTs in TGNs. LC/E-BoNT/A is a promising therapeutic candidate.

GLIA ACTIVATION IN MIGRAINE PRECLINICAL SETTING

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OBJECTIVE: To provide an overview of the involvement of glia cells in the generation and maintenance of migraine and headache pain in preclinical models and to verify the feasibility of a clinical translation of available data so far.
METHODS: The contribution of glial cell populations located in both the central (*i.e.*, microglia, astrocytes) and in the peripheral (*i.e.*, satellite glial cells) nervous system to the various phases of a migraine attack have been analyzed, thanks to literature data and results from the laboratory. Focus has been put on possible differences between males and females.
RESULTS: Significant activation of glial cells has been observed in different animal models of migraine and headache pain. In the trigeminal ganglion, activated satellite glial cells promote nociceptor sensitization, that is also responsible for secondary orofacial migraine symptoms. Additionally, microglia contribute to the release of pro-inflammatory and pro-algogenic mediators that are in turn responsible for the sensitization of second order neurons in the spinal cord prevalently in male animals. On the other hand, reactive astrocytes are emerging as key players in both the ionic alterations leading to cortical spreading depression and in the alterations of the blood-brain barrier.
CONCLUSIONS: Although data are still not fully conclusive and generalizable, in several preclinical models of migraine and headache pain activation of glial cells has been clearly identified which drives neuroinflammatory processes. Due to the insensitivity of a percentage of migraineurs to currently available pharmacological treatments which mostly target neurons, it is worth studying new therapeutic or adjuvant glial-based approaches which might prove beneficial for patients.

MIGRAINE AND EPILEPSY: A DIAGNOSTIC CHALLENGE

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OBJECTIVE: Migraine and epilepsy are two common, chronic, disabling, paroxysmal neurological disorders. Research has highlighted the intricate relationship and overlap between them. They share several pathophysiological mechanisms and clinical features, complicating diagnosis and management. Additionally, antiseizure medications (ASMs) effectiveness for migraine suggests a therapeutic intersection.
METHODS: A comprehensive literature review was conducted to explore the complex relationship between migraine and epilepsy, focusing on comorbidity rates, neurophysiological and genetic mechanisms, clinical presentation and treatment approaches.
RESULTS: Migraine and epilepsy frequently coexist, with migraine prevalence in epilepsy patients ranging from 8.4% to 23%, while the reverse is noted at 1% to 17%. Both conditions share cortical hyperexcitability as the common pathophysiological mechanism. Genetic studies have identified shared variants, like CACNA1A, linked to both familial hemiplegic migraine and some epilepsy syndromes. Clinically, both disorders can manifest with overlapping symptoms, including visual and sensory disturbances, complicating the diagnosis. The ICHD-3 includes peri-ictal headaches, such as ictal migraine, migraine-induced seizures, and postictal headaches. Additionally, certain epilepsy syndromes, such as occipital childhood epilepsy, are strongly associated with migraine. ASMs, such as valproic acid, topiramate, lamotrigine and perampanel, may be effective in preventing migraines, suggesting a shared pathophysiological pathway.
CONCLUSIONS: Understanding the relationship between migraine and epilepsy presents significant challenges. Early recognition of comorbidity is crucial for appropriate management, as tailored treatment strategies may improve outcomes. Ongoing research is needed to further elucidate this relationship.

CLASSIFICATION OF HEADACHES IN DEVELOPMENTAL AGE: DIAGNOSIS AND TREATMENT

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OBJECTIVE: Disorders affecting the nervous system are diverse and include several conditions, which may cause long-life disability. Among them, migraine is the third most prevalent medical disorder, associated with highest age-standardized disability-adjusted life-years (DALY) rates. Specifically, migraine ranks as the leading cause of neurological disability among children and adolescents between the ages of 5 and 19 years. This manuscript aims to review the state of the art of pediatric migraine, exploring its diagnosis and management, with particular attention to the multidimensional burden on patients' quality of life.
According to the International Headache Classification (third edition) edited by the International Headache Society, headache disorders are divided into primary and secondary headaches. Primary headaches represent idiopathic pain conditions, such as migraine, tension-type headache and trigeminal autonomic cephalalgias (TACs). Secondary headaches arise from serious underlying pathology and are associated with high morbidity and mortality. In this group, there are conditions, such as headache attributed to head trauma or vascular disorder, or infection or psychiatric disorder. In the developmental age, primary

headaches are frequent, interesting about 60% of children and adolescents, especially females. The most type of primary headaches in the young population are migraine and tension-type headache, with a subtle difference between sexes. In fact, while migraine with aura is significantly associated with the female gender, migraine without aura is more typical of males. Other gender differences regard pain location, and associated symptoms. In girls, pain shows more often a frontal, temporal or occipital location; in boys pain tends to be located at the vertex of the head. While in female's photophobia, nausea, and light-headed feeling are more common, in males there is more often nausea, vomiting, confusion, or difficult concentration. In addition, girls also show a higher frequency of migraine attacks and a higher rate of chronicity.
Pediatric migraine is associated with significant disability, that impacts notably on quality of life. Children and adolescents with migraines exhibit often emotional and psychological disorders, such as anxiety and depression, isolation, and loneliness. Frequent migraine attacks may lead to regular absences from school for a child, resulting in learning gaps and challenges in keeping up with academic work. Concentration difficulties, sleep disorders and cognitive impairment are often present in these patients.
Furthermore, the presence of comorbidities complicates the clinical picture. Children and adolescents with migraine are more likely than the general population to have medical conditions, including epilepsy, attention-deficit hyperactivity disorder, behavioral problems, obesity, atopic dermatitis, asthma, restless legs syndrome, and anemia.
In this context of multidimensional disease burden, the early treatment and management of primary headache seems important and necessary. In fact, the main objective of migraine treatment is the improvement not only of headache parameters but also of function at home, in school and socially, with a notable improvement of health-related quality of life. Early and effective treatment for migraine allows patients to develop healthy habits and coping strategies that are useful throughout their lives for managing their condition. Besides reducing disability and improving short-term outcomes, optimal migraine treatment may also decrease the risk of disease progression and enhance self-efficacy and self-management. The pharmacological intervention is designed to acute treatment. First-line drug for acute migraine in the pediatric population involves early treatment with a non-steroidal anti-inflammatory drug (NSAID), especially ibuprofen. For pediatric patients who do not achieve success with an NSAID, the use or addition of a triptan should be considered.
CONCLUSIONS: Primary headache, especially migraine, is a frequent condition that occurs in pediatric population, affecting notably the well-being of these patients. Early diagnosis and treatment of this condition has a significant impact on short-term and long-term outcomes, which cannot be understated.

DITANS AND 5-HT1F RECEPTOR IN MIGRAINE

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OBJECTIVE: 5-Hydroxytryptamine exerts its effects through several G-coupled receptors. 5-HT1B and 5-HT1D receptors are targets for the first disease-specific and mechanism-based drugs for the symptomatic treatment of migraine, the so-called triptans. Recently, another migraine-specific and mechanism-based class of drugs has been approved for the symptomatic treatment of migraine, the so-called ditans, which are selective agonists at 5-HT1F receptors. This article aims to present a detailed and comprehensive review of all developments related, both scientifically and clinically.
METHODS: A PubMed search with key words 'migraine', '5-hydroxytriptamine', '1F receptor' has been performed.
RESULTS: Four were the main conclusions after the analytical review of all relevant articles in the literature: 1. The 5-HT1F receptor is expressed by cells within the central nervous system (CNS) and by the trigeminal neurons, but not in vascular smooth muscle, suggesting that ditans modulates neurotransmission without vasoactive properties; 2. Animal studies performed in different laboratories have shown that selective 5-HT1F agonists inhibit neurotransmission from an activated trigeminovascular system; 3. In a clinical level, long-term clinical trials with two different ditans have provided good evidence that lasmiditan that cross the blood–brain barrier (BBB) tageting peripheral and central located 5-T1F receptors, is effective and safe in the symptomatic treatment of migraine; 4. Dizziness is the most common adverse event of lasmiditan and people should not drive for 8 h after taking lasmiditan.
CONCLUSIONS: Ditans are effective medicines for the symptomatic treatment of migraine without vascular adverse effects. However, development of novel ditans that do not cross the BBB is expected to result in better tolerability and improved clinical use.

Anti-CGRP ANTIBODIES COUNTERACT INTEROCEPTIVE AWARENESS OF MALAISE

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OBJECTIVE: Dysfunctional processing of interoceptive cues has a key role in disease pathogenesis. CGRP regulates interoceptive information and emotional states encoded by neural pathways projecting to the amygdala from lateral parabrachial nucleus and thalamus. Here, we investigated whether anti-CGRP mAbs modulate interoception and malaise sensations.
METHODS: Rats were exposed for different times to anti-CGRP antibodies at 100 mg/kg s.c, and Western blotting adopted to investigate pharmacokinetics of anti-CGRP antibodies upon transcardial perfusion. Gene array was adopted to evaluate the impact of fremanezumab on gene expression profiles in trigeminal ganglion and different brain regions. Conditioned taste aversion was used as a model of aversive memory and awareness of malaise. Lastly, exposure to cycles of cisplatin allowed to evaluate the impact of anti-CGRP mAbs on chemotherapy-induced anorexia and weigh loss.
RESULTS: We report that systemically administered anti-CGRP mAbs reach the rat brain cortex and hypothalamus at concentrations in keeping with those reported in the literature for IgG and about one order of magnitude lower than those present in the skin and gut. Accordingly, subcutaneous fremanezumab alters transcriptional homeostasis of the trigeminal ganglion as well as

that of brain cortex, hypothalamus and amygdala. Interestingly, Gene Ontology enrichment analysis demonstrated that, among the tissue biomarkers evaluated, those showing upregulation were exclusively related to the nervous system, highly represented in the hypothalamus and included the amygdala. We also found that both fremanezumab and galcanezumab counteracted conditioned taste aversion, a learning process sustained by CGRP release in the amygdala. Finally, both antibodies reduced anorexia and weight loss in rats exposed to two cycles of cisplatin exposure.
CONCLUSIONS: Data indicate that anti-CGRP mAbs modulate interoception and sensation of malaise, and disclose the translational potential of these biologics to treatment of mental, eating and oncological disorders.

EXPLOITATION OF DISEASE MODIFYING PROPERTIES OF anti-CGRP/R mAbs

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OBJECTIVE: Targeted therapies acting on calcitonin gene-related peptides (CGRP) have recently changed the scenario of migraine therapy. However, it is not clear how drugs acting in the periphery at vascular and trigeminal nociceptive afferents might alter the complex pathophysiologic basis of migraine. Brain functional analysis methods could be helpful in clarifying potential disease-modifying properties of anti-CGRP therapies.
METHODS: Functional magnetic resonance imaging (FMRI), electroencephalogram (EEG), evoked potentials and trigeminal reflex studies in migraine patients treated with anti-CGRP therapies, mainly monoclonal antibodies, were reviewed.
RESULTS: FMRI, EEG, event-related responses and trigeminal reflexes showed strong inhibition of cortical areas responsible for pain processing and modulation of the occipital cortex as a potential trigger of cortical spreading depression phenomena in migraine patients.
CONCLUSIONS: Effective inhibition of nociception at the peripheral level could modulate the cortical areas that process pain signals and cause a general resetting of cortical excitability abnormalities that predispose to migraine attacks.

REAL WORLD EVIDENCE IN FAVOR OF anti-CGRP/R mAbs AND BEYOND

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OBJECTIVE: Chronic migraine is a neurovascular disorder that represents the second cause of disability and of lost years of healthy life. The novel age of preventative migraine treatment was opened by monoclonal antibodies (mAbs) targeting the pathway of the calcitonin-gene related peptide (CGRP), a game-changing approach for migraine pharmacology. However, some 40 % of patients still belong to the non-responder segment. Therefore, the present study has the purposes to: 1. Identify the involvement of genetic variants occurring along the CGRP signaling in refractoriness; 2. Determine the efficacy of anti-CGRP mAbs in resistant chronic migraine through pharmaco-epidemiological analysis; 3. Assess the safety of onabotulinumtoxin A for combined treatment in resistant, chronic migraine; 4. Propose a clinical study to demonstrate efficacy and safety of anti-CGRP/R mAbs in combination with onabotulinumtoxin A in refractory, chronic migraine.
METHODS: The process of identification and selection of the studies included in the analysis has followed the most updated PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) criteria for systematic reviews and meta-analyses and the guidance from the Human Genome Epidemiology (HuGE) Network for reporting gene-disease associations. The pharmaco-epidemiological analysis was conducted on a wide sample of 298,000 inhabitants, 213,000 under 60 years of age most at risk for chronic migraine. The clinical trial design followed the SPIRIT and the CONSORT statements. Patients to be enrolled must be affected by chronic migraine refractory to the most common preventative therapies. The HuGE risk-of-bias score was used for genetic association studies. The risk of bias was assessed following the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for the evaluation of nonrandomized studies of the effects of intervention (NRSI) for real-world. Heterogeneity between and across studies and small sample size was calculated. A prespecified statistical analysis plan was established. Pooled data of real-world evidence, together with pharmaco-epidemiological analysis in the local Italian setting were gathered. The results were statistically evaluated for differences using $\chi 2$ test considering $p < 0.05$ significant.
RESULTS: The polymorphisms rs3781719 (T > C) of the CALC A gene encoding CGRP and rs7590387 of the gene encoding the receptor activity-modifying protein (RAMP) 1 (C > G) were identified. According to results, the use of onabotulinumtoxin A was decreased in favor of anti-CGRP/R mAbs over the period of 2020-2022. Only erenumab, galcanezumab and fremanezumab were prescribed. No prescription of eptinezumab was recorded. The early diagnosis of migraine improved therapeutic outcomes with mAbs, that reduced monthly headache days (MHDs), monthlu migraine days (MMDs) and numeric rating scale (NRS) score for intensity. Incidentally, also patients arriving to clinical observation aged over 50 were detected. Pooled analysis demonstrated that 60-70% of patients treated with the combination therapy of anti-CGRP/R mAb and onabotulinumtoxin A experienced an improvement in mean MHDs at 30 days and MMDs at 30 days. Furthermore, onabotulinumtoxin A resulted safer than oral topiramate, supporting combination therapy.
CONCLUSIONS: Data about refractoriness, efficacy and safety point to the need for a clinical trial assessing the efficacy (on the primary endpoint of the mean change in MMDs from the baseline phase after 1, 3, 6, 9 and 12 months) and safety of onabotulinumtoxin A in combination with the newest treatment options, also including atogepant as small molecule CGRP receptor antagonist for the prevention of chronic migraine. The synergic/additive mechanism of action to rescue difficult-to-treat patients could rely on inhibition of CGRP release from thin unmyelinated C fibers dural nociceptors and prevention of CGRP action.

PUBLIC HEALTH ISSUES IN CURRENT MIGRAINE MANAGEMENT

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OBJECTIVE: According to the most recent estimates of Global Burden of Disease Study 2021 (GBD 2021), primary headache dis-

orders are the most prevalent neurological disorders. Considering that headache disorders are responsible for approximately 5.5% of all-cause disability (around 8% among young adults), it becomes evident that reducing disability associated with headache disorders might therefore be a relevant driver for enhancing population health at global level and thus ensure the achievement of the goals of Sustainable Development Goal 3 - Ensuring healthy lives and promoting well-being for all at all ages, a United Nations project.
METHODS: Policy initiatives aimed to set the stage for future concrete actions aimed to tackle headache disability as main driver for improving global health. Six specific domains of possible interventions have been identified: 1. Targeting chronic headaches; 2. Reducing the overuse of acute pain-relieving medications; 3. Promoting the education of healthcare professionals; 4. Granting access to sustainable costs for preventive medication in Western Countries and at least acute medication in Low-Medium-Income Countries (LMIC); 5. Implementing training and educational opportunities for healthcare professionals in LMIC; 6. Building a global alliance against headache disorders.
RESULTS: The immediate results can be resumed here: 1. The Global Campaign against Headache - Lifting the Burden pointed out that there are unmet needs in chronic headaches recognition and management; 2. Recognizing and treating the overuse of medications early is of relevance as medication overuse is both a cause and an effect of clinical worsening, which leads to higher health resources consumption, and is a strong driver of increased disease cost and patients' disability. 3. It is crucial to identify the educational activities that are important to provide the practical knowledge and skills needed to treat the most common primary headaches, which in many cases could be done firstly at the pharmacy level. This specifically includes training how to treat tension-type headache, and common migraine without aura at low frequency at primary-care level. 4. Ensuring access to novel preventive medications (CGRP – MoAbs, Gepants, Ditans) as an economically sustainable tool in Western Countries and granting at least appropriate acute and low-cost acute medications for migraine (paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), triptans) in LMIC is the only viable way to reach the large amount of people who globally needs headache care, *i.e.*, 35% of the all-age population. 5. Training is the first step toward reaching SDG 3 as, particularly in LMIC, presenting a dramatic shortage of clinicians with specific skills in diagnosing and management of headache disorders. An ongoing online tool tailored for the needs and resources of LMIC is being launched in 2023 (freely available for LMIC healthcare professionals as per World Bank rules – based on Gross National Incomes – at https://www.unitelmasapienza.it/en/training-course-in-headaches-lmic/). 6. The world's leading scientific journal, The Journal of Headache and Pain, now offers scientific and educational knowledge globally, covering the world communities through its affiliated societies, European Headache Federation (EHF), Lifting The Burden (LTB) and Asian Regional Consortium for Headache (ARCH).
CONCLUSIONS: To conclude making headache care sustainable across the globe is an achievable objective which will require multi-stakeholder collaborations across all sectors of different societies, and which will directly improve health and productivity of populations, particularly young adult women worldwide

CALABRIA REGIONAL NETWORK FOR CHRONIC MIGRAINE CARE: THE ROLE OF INNOVATIVE MANAGEMENT MODELS AND ADVANCED DIGITAL SERVICES

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OBJECTIVE: The aim of the Calabrian Headache Network is to apply in the clinical practice innovative management models and advanced digital services for the effective and efficient management of patients with chronic migraine. This research provides an overview of the network's stepped care model, which aims to manage migraines and medication overuse headaches through a multidisciplinary approach.
METHODS: Inadequate communication and awareness among patients and healthcare professionals regarding migraines lead to delays in diagnosis and inappropriate referrals. To address these issues, the Calabrian Headache Network implements a stepped care model consisting of four levels of care. General practitioners and community pharmacies manage the first level, outpatient neurologists handle the second level, hub-and-spoke headache centers manage the third level, and the Regional Headache Centre serves as the fourth level for complex cases. For the achievement of the intended goal, the deployment of a platform of digital services to support the integrated clinical management of migraine patients is fundamental. The platform is capable of delivering digital services that provide accurate decision support to healthcare professionals and effective empowerment to patients, improving the appropriateness and efficiency of the healthcare services provided.
RESULTS: The Calabrian Headache Network is currently undergoing a piloting activity involving healthcare providers and enrolled patients. The expected results allow to encourage timely and accurate diagnoses, improve the effectiveness of therapeutic treatments and make integrated care pathways more appropriate than those currently adopted.
CONCLUSIONS: In terms of impact on the healthcare regional system, the project is able to reduce emergency room admissions and inappropriate hospitalizations, strongly limit the phenomena of health care migration, induce efficient use of health care resources.

Anti-CALCITONIN GENE-RELATED PEPTIDE (CGRP) MONOCLONAL ANTIBODIES (mAbs) FOR THE PREVENTIVE TREATMENT OF MIGRAINE: ANALYSIS OF EXPENDITURE AND PHARMACOUTILIZATION DATA IN THE CALABRIA REGION

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OBJECTIVE: Migraine is a recurring form of headache. It has been classified as the second most disabling and the third most frequent pathology. Galcanezumab, Fremanezumab, Eptinezumab and Erenumab, are new-generation monoclonal-antibodies approved for the prophylaxis of episodic and/or chronic

migraine, which act by binding soluble CGRP (Eptinezumab, Galcanezumab, Fremanezumab) or the receptor (CGRP-R; Erenumab). In fact, it has been shown that the levels of this peptide, widely distributed in the central and peripheral nervous system, increase significantly during spontaneous migraine attacks and decrease, on the other hand, following the administration of triptans, leading to a marked symptomatic improvement. The objective was to evaluate the treatments and pharmaceutical expenditure in 2023 associated with their use in the Calabria region.
METHODS: The data was extracted and processed in 2023 using the company's software for spending data and the data of the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) Registry for pharmacoutilization.
RESULTS: The analysis revealed that in 2023, there was a 37% increase in Anti-CGRP-mAbs spending compared to the previous year with an expense equal to 1.033.539,50 euro. In all three years, greater consumption was recorded for the Aimovig 140 mg pen (Erenumab) and Emgality 120mg pen (Galcanezumab) as compared to the other drugs. Most started treatments concerns women, with an average age for both males and females of 46 years, a maximum age of 60 years and a minimum age of 29 years. The number of treatments started in 2023 is 380 with 1658 prescriptions,1250 revaluations and 27 closed treatments.
CONCLUSIONS: Despite the high cost, anti-CGRP mAbs have demonstrated high efficacy associated with rapid onset of action and high levels of safety and tolerability. Given equal efficacy and safety, clinicians should prescribe them also considering an adequate patient selection, with the aim of guaranteeing the best possible treatment while minimizing the impact on the National Health Service resources.

PATTERNS OF ACTIVE PHARMACOVIGILANCE OF NOVEL THERAPIES

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OBJECTIVE: Pharmacovigilance practices are essential for the rational use of drugs, especially in the field of biologic drugs. Considering the limitations of pre-marketing studies, the risks associated with the characteristics of biological drugs, and the chronic use of most of these drugs, intensive and continuous pharmacovigilance activities are necessary.
METHODS: A literature search was conducted to identify clinical trials and real-world studies that reported findings on adverse effects caused by treatment with anti-CGRP monoclonal antibodies.
RESULTS: Several clinical trials have tested and demonstrated the therapeutic efficacy of fremanezumab in reducing the number of migraine days and the acute use of other drugs, and they have evaluated the occurrence of adverse events. The most common adverse events involved the injection site, and the percentage of patients discontinuing treatment due to adverse events was similar in each treatment group (less than 2%). Evidence from real-world studies also confirmed clinical trial results. In recent years through real-world studies, some new adverse effects for fremanezumab, erenumab, galcanezumab, eptinezumab, have been observed that were not yet listed in the package inserts of these monoclonal antibodies, such as menstrual disorders, Raynaud's phenomenon, weight gain, throat constriction, and oral paresthesia.
CONCLUSIONS: Data obtained on efficacy and safety from clinical and real-life studies on anti-CGRP antibodies are comparable. However, the observation must be extended to other less-represented population segments. Implementing supervisory activities is necessary post-marketing to better characterize the tolerability profile of biosimilars. In this context, a practical and rational use of biosimilars plays an important role in the financial sustainability of regional health service systems.

INDEPENDENT ASSESSMENT OF NOVEL THERAPIES FOR EFFICACY AND AFFORDABILITY

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OBJECTIVE: Migraine is a debilitating neurological condition. With the advent of new drugs (*i.e.*, monoclonal antibodies targeting CGRP or its receptor) a new therapeutic opportunity became available to patients. The mechanisms leading to the approval and evaluation of new drugs, with a specific mention of what can be considered 'therapeutically relevant' in the treatment of migraine, are briefly described.
METHODS: The process of drug assessment and evaluation involves two different steps. The regulatory step deals with the evaluation of the benefit/risk ratio and is taken at European level by the European Medicine Agency (EMA). According to this evaluation, marketing authorization can be granted on a European level. The second step is taken independently in every single European Country and concerns the evaluation of the comparative efficacy and safety of the new drug with respect to the already existing therapeutic alternatives. Because of such evaluation, each Country takes a decision on the reimbursement and pricing of the new drug.
CONCLUSIONS: The Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) has also established some specific criteria to evaluate if a drug can be considered as 'innovative'. Under the point of view of the public health, innovativeness does not necessarily imply a novelty of the target or a technological innovation, but it is strictly dependent on the improvement in the level of cure, *i.e.*, to be considered innovative the new drug must show a clear added therapeutic value over existing alternatives. In case of migraine, a new drug can be considered as 'superior' to the existing alternatives (thus potentially obtaining a higher price) when it reduces number and duration of episodes, but to be defined truly innovative (thus obtaining several additional benefits) it must demonstrate a significant therapeutic advantage in terms of reduced disability and/or increased quality of life.

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SPINAL AND SUPRASPINAL CHARACTERIZATION OF AN INFLAMMATORY CFA-INDUCED MODEL OF VULVODYNIA

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OBJECTIVE: Vulvodynia is a gynecological disease characterized by chronic pain in the vulva and tissues surrounding access to the vagina. The chronic vulvar pain that characterizes the disorder is typically associated with severe burning, dyspareunia (pain during sexual intercourse) and redness. Factors such as genetic predisposition, hormonal imbalances, pelvic floor dysfunction, and immune system dysregulation have been suggested to play a role in its establishment, rising the need of further mechanistic understanding and search for new therapeutical targets.
METHODS: In this study we used female C57BL/6J mice in which vulvodynia was induced by one injection of Complete Freund Adjuvant for up to four weeks. During these 28 days behavioral, electrophysiological and immunohistochemical analysis were performed. We employed pharmacological interventions using GABApentin, amitriptyline, and PeaPol, a combination of palmitoylethanolamide and polydatin.
RESULTS: All three drugs showed efficacy in alleviating tactile allodynia and depressive-like behavior. Concurrently, we also observed a normalization of the altered neuronal firing and a reduction of microglia hypertrophic phenotypes.
CONCLUSIONS: Our results suggest a role for microglia in neuroinflammatory phenomena surrounding spinal neuronal overexcitability in vestibulodynia, emerging as a novel therapeutic target. Treatment with PEAPol improved not only evoked pain, but also spontaneous pain, promoting mice well-being, as observed in nesting behavior. Finally, for the first time in CFA-induced vestibulodynia model, we showed the development of depressive-like symptoms, often present also in patients, reinforcing the translational value of the study.

N-PALMITOYLETHANOLAMIDE-OXAZOLINE (PEA-Oxa) REDUCES SEIZURE SEVERITY AND RELATED NEUROPSYCHIATRIC-LIKE COMORBIDITIES IN THE PENTYLENETETRAZOL KINDLING MODEL

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OBJECTIVE: Antiseizure medications (ASMs) are the first-line drugs to treat epilepsy. Given the significant adverse reactions of ASMs, the search for safer molecules is shifting towards bioactive compounds such as N-acylethanolamines. N-palmitoylethanolamide-oxazoline (PEA-Oxa) has attracted considerable interest due to its neuroprotective and anti-neuroinflammatory properties. This work aimed to study the effects of different doses of PEA-Oxa in Pentylenetetrazol (PTZ)-induced kindling, and its effects in modulating neuroinflammation.
METHODS: A sub-convulsant PTZ dose (30 mg/kg i.p.) was administered to C57/BL6J (B6) mice every other day up to kindling development. PTZ-kindled B6 mice received chronic PEA-Oxa treatment at different doses. All groups were subjected to several behavioral tests (passive avoidance, novel object recognition test, three-chamber tests, elevated plus maze, and forced swimming test) for assessing neuropsychiatric-like deficits. Finally, different neuroinflammatory markers were evaluated.
RESULTS: PTZ-kindled B6 mice showed an increased seizure severity score and reduced behavioral performance, such as cognitive impairment, sociability, and anxiety. PEA-Oxa treatment reduced the seizure severity score and rescue behavioral performance in B6 mice. We also revealed that PEA-Oxa has anti-inflammatory effects by reducing several neuroinflammatory markers dose-dependently.
CONCLUSIONS: The present data supports the beneficial effects of PEA-Oxa supplementation against seizure and related neuropsychiatric comorbidities in the PTZ-Kindling model. Further experiments are needed to clarify the mechanisms by which PEA-Oxa exerts beneficial effects in PTZ-induced kindling.

PUDENDAL NERVE CONSTRICTIONS (PNC) AS A NEW ANIMAL MODEL OF VULVODYNIA

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OBJECTIVE: Vulvodynia is a gynecological condition characterized by persistent discomfort in the vulvar region. This enduring vulvar pain is often accompanied by intense burning sensations, dyspareunia (pain during intercourse), and erythema (redness). Current *in vivo* experimental models of vulvodynia, such as CFA-induced vulvodynia, only partially represent the entire affected population. Pudendal nerve entrapment is one of the most common causes identified to date. Therefore, in our study, we developed a novel *in vivo* model of vulvodynia by inducing constriction of the pudendal nerve.
METHODS: Female C57BL/6J mice, via surgical procedures, has been tied monolateral the pudendal nerve using surgical silk thread. The vulvar mechanical allodynia (Von Frey test) and the general welfare (Nesting test) were measured from week 1 to 3 post pudendal nerve constrictions (PNC), during these weeks the animals were orally treated with Gabapentin and Amitriptyline. From 21st day immunofluorescence and electrophysiology analysis were performed.
RESULTS: Surgery reduced the vulvar withdrawal threshold in mice from 1 to 3 weeks post-PNC induction, with treatment reducing allodynia by week 3. Nesting behavior worsened after PNC but improved with treatment. At 2 weeks, the tail suspension test revealed depressive-like behavior, which was alleviated by drugs at 3 weeks. By 21 days, reactive microglia increased in the ipsilateral spinal cord, and both ongoing and evoked nociceptive neuron activity also rose.
CONCLUSIONS: In conclusion, future behavioral and immunofluorescence studies will be conducted to further characterize this new model but, to date, our findings underscore the utility of the PNC model in elucidating the mechanisms of vulvodynia disease and highlight its potential as a valuable tool for future preclinical research and drug discovery efforts.

POOLED ANALYSIS DEMONSTRATED EFFICACY OF THE TREATMENT OF COMBINATION OF ANTI-CGRP(R) mAbs AND ONABOTULINUMTOXIN A IN CHRONIC MIGRAINE

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OBJECTIVE: Chronic migraine is a neurovascular disorder, that remarkably impairs the patients' quality of life, especially in refractory 40% cases despite the novel monoclonal antibodies (mAbs) directed towards the signaling of the calcitonin gene-related peptide (CGRP). Onabotulinumtoxin A was demonstrated to be effective and safer than topiramate. Therefore, the objectives of this study were to: 1) assess the real-world evidence of efficacy of anti-CGRP mAbs in resistant chronic migraine; 2) design a clinical trial to assess efficacy and safety of combination therapy in refractory chronic migraine.
METHODS: The retrospective phase included a wide sample of 298,000 inhabitants, 213,000 under 60 years of age. The clinical trial to evaluate efficacy and safety of the combination treatment followed SPIRIT and CONSORT statements to recruit patients suffering from chronic migraine and refractory to the most common preventative treatments. The results were statistically evaluated for differences using $\chi 2$ test considering $p < 0.05$ significant and a prespecified statistical analysis plan for the combination therapy clinical trial was set.
RESULTS: Pooled analysis demonstrated that treatment of combination of anti-CGRP(R) mAbs and onabotulinumtoxin A provides ≥50% reduction of monthly headache days (MHDs) in up to 58.8% of patients *vs*. onabotulinumtoxin A alone. According to results, early diagnosis of migraine improves therapeutic outcomes with mAbs, that reduced MHDs, MMDs and NRS score. Interestingly, also patients arriving to clinical observation aged over 50 were detected. The outcome measures of the trial will include reduction of monthly migraine days (MMDs) after 1, 3 and 6 months of treatment with mAbs and of pain intensity assessed by the numeric rating scale (NRS) after 6 months of treatment.
CONCLUSIONS: The synergic/additive mechanism of the combination may be due to inhibition of CGRP release from thin unmyelinated C fibers dural nociceptors and prevention of CGRP action.

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