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AL001

Overuse of analgesics can affect the fertility biomarker Anti-Müllerian hormone in females. A translational study

L. Carlsen
Rigshospitalet Glostrup, Neurology Department, Glostrup, Denmark
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Objective: Over-the-counter analgesics (OTC) have been associated with disrupted male endocrinology, while effects on female endocrinology remains nearly unknown. The aim was to understand the effect of long-term analgesic exposure in females with medication overuse headache (MOH) on Anti-Müllerian Hormone (AMH), a surrogate measure of female fertility.
Methods: Using a translational approach, an observational prospective clinical study was conducted to determine AMH-levels in females with MOH, in combination with pre-clinical investigation of primary granulosa cells (GC) to understand the effects of analgesics on GC-function.
Results: We included 21 females (mean-age 30.0 years; SD (7.3)) for AMH-measurement. AMH increased by 21% from baseline (mean 20.1 pmol/L; SD (8.7)) after withdrawal of analgesics ((mean 24.3pmol/L; SD (12.0)); p=0.0023). Exposing primary GCs to analgesics (acetaminophen (100 and 200 µM, n = 9–10) and ibuprofen (150 and 200 µM, n = 12–13)) did not reduce AMH-levels. In contrast, *de novo* DNA synthesis in GCs (n=6) exposed to acetaminophen was reduced with 78% (p=0.0036) compared to controls, suggesting that cellular proliferation was restricted.
Conclusion: Frequent use of OTC was associated with repressed AMH-levels likely through disruption of GC proliferation. Further research is crucial to investigate a potential effect of analgesics on adult female reproductive endocrinology.

AL002

Sex differences in RAMP1/RAMP2 expression in the human middle meningeal artery match functional response to CGRP

T. de Vries, D. Schutter[1], R. Dammers[2], A. Vincent[2], A. H. J. Danser[1], A. Maassen van den Brink[1]
[1]Erasmus MC University Medical Center, Internal Medicine, Division of Pharmacology and Vascular Medicine, Rotterdam, Netherlands; [2]Erasmus MC University Medical Center, Neurosurgery, Rotterdam, Netherlands
Correspondence: T. de Vries
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Objective: CGRP induces vasodilation after binding to the CGRP receptor (CLR-RAMP1), but can activate the adrenomedullin receptor (CLR-RAMP2) as well. Previously, age-dependent sex differences were observed for CGRP-induced relaxation of human middle meningeal arteries1. In addition, RAMP1 and RAMP2 mRNA expression was highly variable between patients2. The current study aims to investigate whether RAMP1 and RAMP2 expression differs between men and women and varies throughout life.
Methods: RNA was isolated from homogenized human middle meningeal arteries (14 F, 12 M, age 51±3 years) and qPCR was performed for RAMP1 and RAMP2 mRNA expression. The ratio between RAMP1 and RAMP2 expression with increasing age was investigated for men and women separately.
Results: The RAMP1/RAMP2 ratio significantly decreases with age in men, while a positive trend can be observed for women. These findings match the pattern of maximum relaxation to CGRP as observed in a previous study1, with a significant decrease with age in men and a trend for increased maximum relaxation with age in women.
Conclusion: The current study suggests that the maximum effect of CGRP-induced relaxation of human middle meningeal arteries matches the ratio of RAMP1/RAMP2 expression, and changes in a sex-dependent manner with increasing age. Interestingly, migraine is generally most prevalent in pre-menopausal women. Here, these young women show a relatively high RAMP2 and low RAMP1 expression, suggesting predominance of the adrenomedullin receptor over the canonical CGRP receptor in this population. Possibly, increased exposure of CGRP in young women results in downregulation of RAMP1. Future research should investigate whether RAMP1 and RAMP2 expression is altered in migraine patients.

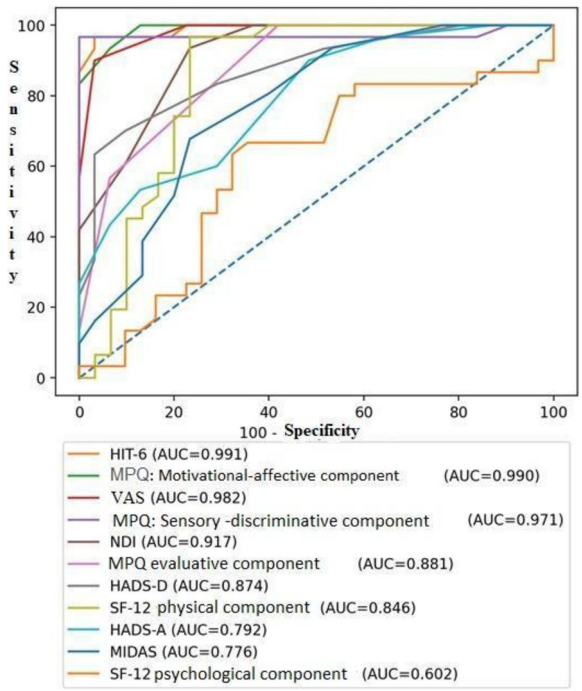

Fig. 1 (Abstract P037). See text for description

Questionnaire/Scale	AUC (95% CI)	SE AUC	p	Se	Sp	Optimal cut-off point
MIDAS	0,775 (0,658-0,893)	0,0599	<0,001	76,67	67,74	<20,0
HIT-6	0,990 (0,966-1,000)	0,0126	<0,001	96,67	96,77	≥63,0
NDI	0,917 (0,844-0,991)	0,0374	<0,001	76,67	93,55	<16,0
VAS	0,981 (0,947-1,000)	0,0178	<0,001	90	96,77	≥7,0
HADS-A	0,791 (0,677-0,906)	0,0584	<0,001	90	51,61	≥7,0
HADS-D	0,8742 (0,783-0,965)	0,0464	<0,001	70	90,32	≥6,0
SF-12 psychological component	0,602 (0,460-0,745)	0,0727	0,016	66,67	64,52	≥38,4
SF-12 physical component	0,846 (0,747-0,945)	0,0506	<0,001	76,67	96,77	<38,8
MPQ evaluative component	0,881 (0,793-0,970)	0,0452	<0,001	100	58,06	≥3,0
MPQ motivational-affective component	0,990 (0,965-1,000)	0,0129	<0,001	100	87,1	≥8,0
MPQ sensory-discriminative component	0,971 (0,927-1,000)	0,0224	<0,001	96,67	100	≥23,0

Fig. 2 (Abstract P037). See text for description

Questionnaire/Scale	Odds ratio	95% CI	p
MIDAS	6,88	2,23 - 21,33	<0,001
HIT-6	871,31	51,94 - 14617,87	<0,001
NDI	47,46	9,03 - 252,14	<0,001
BAIII	270,42	26,58 - 2751,77	<0,001
HADS-A	9,58	2,41 - 38,47	<0,001
HADS-D	21,75	5,26 - 90,02	<0,001
SF-12 psychological component	3,63	1,26 - 10,49	0,02
SF-12 physical component	98,49	11,36 - 862,64	<0,001
MPQ evaluative component	83,5	4,69 - 1490,87	<0,001
MPQ motivational-affective component	372,7	19,19 - 7243,32	<0,001
MPQ sensory-discriminative component	1239	48,54 - 31628,77	<0,001

Fig. 3 (Abstract P037). See text for description

P038

Primary laugh-induced headache: case report

M. Moncyte[1], A. Dapkutė[2], K. Ryliškienė[2,1]
[1]Kardiolitos klinikos, Center of Neurology, Vilnius, Lithuania; [2]Vilnius University, Center of Neurology, Vilnius, Lithuania
Correspondence: A. Dapkutė
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Objective: Laugh and other Valsalva maneuver-induced headaches are often secondary to structural brain abnormalities. However, primary laugh-induced headache is rare and poorly described. Here we present a case of a primary laugh-induced headache not provoked by other Valsalva maneuvers.
Methods: Case report.
Results: A 21-year-old male presented with a history of typical headaches since the age of 11–12, with increased frequency over the last 3 years due to lifestyle cahnges (e.g. singing along to loud music), from once per year to once per month. Attacks occurred after vigorous laughter or yelling, featuring sudden headaches of moderate to severe intensity lasting less than 3 seconds, localized in the frontal area. On some days, he experienced up to 10 bouts per day, accompanied by a sense of pressure in the head and painful eye movements throughout the day. He did not experience any associated autonomic symptoms, and no other Valsalva maneuvers could provoke such headaches.
The patient also reported a distinct type of headache after increased physical activity, specifically prolonged jogging. This headache was of low intensity, pressing in nature, dispersed throughout the head, lasting up to 1 hour, associated with bilateral ear congestion, and improved after cessation of physical activity
Neurological and cardiological examinations, including vital signs, were unremarkable. Carotid and vertebral duplex ultrasound results were normal. Brain MRI detected no structural brain abnormalities but reported thickened mucous membranes of the maxillary sinuses and ethmoidal cells. An otolaryngologist diagnosed chronic rhinitis and concluded that the headaches were unlikely to be associated with these findings. The patient was diagnosed with primary laugh-induced and primary exercise headaches.

Conclusion: This case illustrates an occurrence of two rare types of primary headaches: primary laugh-induced headache in combination with primary exercise headache, with no detected structural brain abnormalities.
The patient gave their explicit informed consent to publish their information in an open access journal.

P039

Targeting pain of burning mouth syndrome: onabotulinum toxin A injection as a promising symptomatic treatment

L. Barbosa[1,2], A. Costa[1,3]
[1]Unidade Local de Saúde de São João, Neurology, Porto, Portugal; [2]Unidade Local de Saúde do Tâmega e Sousa, Neurology, Penafiel, Portugal; [3]Faculty of Medicine, University of Porto, Clinical Neurosciences and Mental Health, Porto, Portugal
Correspondence: A. Costa
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Objective: Burning mouth syndrome (BMS) is a craniofacial pain disorder often resistant to pharmacological treatments. Recent advances in neuropathic pain management exhibited promising analgesic effects with onabotulinum toxin A (BoNT-A) injections. We present two BMS cases treated with BoNT-A following a pain management protocol, reporting positive outcomes.
Methods: We administered intradermal BoNT-A injections as monotherapy to two patients with BMS (injection details in image 1). An anesthetic spray was used to minimize discomfort during the technique. The procedure was repeated every three months.
Results: Patient 1 (P1) is a 48-year-old woman with idiopathic BMS since 2020. Previous treatments with gabapentin and topical clonazepam were ineffective and caused significant side effects. BoNT-A injections began in June 2022, at which time she reported persistent pain with an intensity of 7/10.
Patient 2 (P2) is a 39-year-old woman with secondary BMS due to scleroderma since 2012. Treatments with carbamazepine, pregabalin, and topical clonazepam provided no relief and had side effects. BoNT-A treatment started in November 2023, with baseline persistent pain severity of 6/10.
At 15-day follow-up, both patients reported significant pain relief (P1: 1/10; P2: 4/10), no daily life restrictions due to BMS, and no need for additional analgesics or topical anesthetics. Both patients found the procedure simple, fast, and mildly uncomfortable due to the punctures. P1 reported temporary lip asymmetry after one procedure and P2 experienced no adverse effects. After 7 and 3 trimestral procedures, respectively, both patients maintained pain relief and expressed satisfaction and desire to continue the treatment.
Conclusion: Previous studies suggested BoNT-A to be effective in managing pain of craniofacial pain disorders. Our results indicate that this treatment may be an option for managing pain in BMS patients who do not respond to or experience side effects from first-line therapies.
The patient gave their explicit informed consent to publish their information in an open access journal.

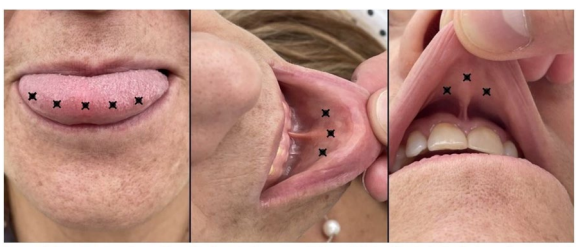

Image 1. Puncture locations – 5 applications in tongue and 3 in each lip (as illustrated in the image), separated by approximately 5mm; each application contains 2.5 Units of BoNT-A in each puncture site.

Fig. 1 (Abstract P039). See text for description

P040

Targeting noradrenergic tone to compensate for glymphatic dysfunction in post-traumatic headaches after mild traumatic brain injury

A. Della Pietra[1], A. Kuburas[1], E. Partridge[1], M. Sevao[2], J. Cho[2], A. Schindler[2], M. Raskind[3,4], J. Iliff[2,3,4], A. Russo[1,5]
[1]University of Iowa, Molecular Physiology & Biophysics, Iowa City, IA, United States; [2]University of Washington, Psychiatry and Behavioral Sciences, Seattle, WA, United States; [3]University of Washington, Neurology, Seattle, WA, United States; [4]Veterans Affairs (V.A.), Seattle, WA, United States; [5]Veterans Affairs (V.A.), Iowa City, IA, United States
Correspondence: A. Della Pietra
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Objective: Mild traumatic brain injury (mTBI) is a common and complex head injury, affecting 69 million people worldwide. This condition results in many symptoms, including migraine-like post-traumatic headaches (PTH). The mechanisms underlying these headaches are unknown. A clue to PTH may be the shared clinical associations between mTBI, migraine, and sleep-wake disruption. Indeed, sleep disruption, which is common after mTBI, is also a migraine trigger. Instead, sleep is known as migraine abortive. In this setting, sleep disruption may impair the glymphatic system, a recently characterized brain-wide network of perivascular spaces that supports the rapid exchange of cerebrospinal and interstitial fluid. Glymphatic function is most rapid during sleep, while it is inhibited during wakefulness by central noradrenergic tone and is reduced by mTBI. Therefore, our hypothesis is that the disruption of glymphatic function after mTBI may contribute to the trigger and endurance of PTH symptoms.
Methods: Repetitive impact mTBI mouse models have been used to develop PTH phenotypes. The mice were treated with the α1-adrenergic antagonist prazosin (PZN). Their PTH symptoms, induced by the injection of a sub-threshold calcitonin gene-related peptide (CGRP) dose, the main migraine mediator, were assessed through light aversion and mechanical facial allodynia tests. Moreover, glymphatic system impairment was measured via glymphatic CSF tracer influx compared to sham control mice.
Results: Our data demonstrate that treatment with PZN prevents and treats sub-threshold CGRP cephalic allodynia sensitivity in mice, with faster rescue in males than females. Finally, prazosin administration in mice increases glymphatic CSF tracer influx compared to vehicle-treated mice.
Conclusion: These results suggest noradrenergic tone as novel target to improve PTH symptoms and glymphatic function, potentially improving sleep disruption as therapeutic strategies for mTBI patients.

P041

Barriers to accessing anti-CGRP monoclonal antibodies (mAbs) in Spain: a survey of neurologists, Hospital Pharmacists (HP), and patients

P. Irimia[1], P. Díaz-Ruiz[2], I. Colomina[3], R. Belvís[4], J. M. Lainez[5]
[1]Clínica Universidad de Navarra, Neurology, Pamplona, Spain; [2]Hospital Universitario Nuestra Señora de Candelaria., Servicio de Farmacia Hospitalaria., Santa Cruz de Tenerife, Spain; [3]Asociación de Pacientes de Migraña y Cefalea (AEMICE), Madrid, Spain; [4]Hospital de la Santa Creu i Sant Pau, Neurology, Barcelona, Spain; [5]Hospital Clínico Universitario, Universidad Católica de Valencia, Neurology, Valencia, Spain
Correspondence: P. Irimia
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Objective: To identify the barriers to accessing anti-CGRP mAbs in Spain
Methods: Cross-sectional study was conducted using online surveys targeting neurologists, HP, and patients. Descriptive statistics were employed to evaluate the data. Categorical variables were expressed in terms of frequency and percentage. The Therapeutic Positioning Report (TPR) elaborated by the Spanish Ministry of Health has limited the funding of mAbs targeting CGRP in Spain to patients with ≥8 migraine days/month and at least 3 prior