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Contents

Dear colleagues,

I read with great interest and pleasure the new issue of the "Archives of Clinical Neurology", the first issue of the year 2026, containing three articles, two research and one review article.

In the first article, Alexoudi et al measured several biomarkers, such as plasma calcitonin gene-related peptide (CGRP), NLRP3 inflammasome components, IL-1β, and IL-18, and hair cortisol, in 7 individuals with Synuclein-Associated Neurodegenerative Disorders (SAND) and 8 controls with features of prodromal SAND, aiming to investigate possible associations of CGRP related inflammatory biomarkers across different circadian stages, therefore blood samples were collected before and after overnight sleep. This preliminary study found that levels of inflammatory molecules do not follow the same patterns of temporal fluctuation in patients and controls. Importantly, CGRP levels in controls show stronger correlations with the measured inflammatory biomarkers than those observed in SAND patients, suggesting a possible role of dysregulated inflammatory responses in disease initiation and progression. Nevertheless, additional data from larger patient cohorts and control groups are required to further elucidate the contribution of these molecular pathways to the development of synucleinopathies.

Next, Alivizatou et al translated in Greek language, culturally adapted and validated in patients with Parkinson's disease the initial psychometric properties of the Swallowing Disturbance Questionnaire (SDQ). The SDQ is a brief, self-report questionnaire, consisting of 15 items, which, by addressing impairments of the oral and pharyngeal phases of the swallowing process, is designed to capture early the development of dysphagia in patients with PD. The Greek SDQ (g-SDQ) displayed an excellent internal consistency (Cronbach's $\alpha = 0.841$) and a high diagnostic accuracy (AUC = 0.820). Moreover, the authors found positive correlations of the g-SDQ with the Dysphagia in Multiple Sclerosis questionnaire (DYMUS; $r = 0.86$, $p < .001$) and the Speech Pathology-Specific Questionnaire for Persons with Multiple Sclerosis questionnaire (SMS; $r = 0.73$, $p < .001$). Moreover, negative correlations were found between the g-SDQ and the Montreal Cognitive Assessment (MoCA) and the Verbal Fluency Test (VFT). The results of the study are clinically relevant, as they provide solid evidence of the utility and accuracy of the translated SDQ tool for early screening of dysphasia in patients with PD.

Finally, Kyriakopoulou and Kargiotis present a narrative review on the potential role of vitamin C– and E–containing supplements as adjunct prophylactic treatments for migraine. Vitamins C and E exert antioxidant and anti-inflammatory effects, both of which are implicated in migraine pathophysiology. By presenting data from randomized clinical trials, non-randomized clinical studies, and cross-sectional studies, they conclude that there is some low-quality evidence suggesting a potential benefit of vitamin C and D supplementation in migraine prophylaxis. Because in most studies vitamins C and E were not administered as single interventions but rather in combination with other antioxidant compounds, further research and randomized trials are needed to evaluate their potential efficacy in migraine when administered alone or in combination with other supplements.

We thank all authors for contributing their valuable research to this issue. We invite Greek neurologists, both in Greece and abroad, to support our efforts to broaden the journal's visibility and continue to submit high-quality work that strengthens the scientific voice of our Society.

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Άρθρα...

TEMPORAL ASSOCIATIONS OF CGRP-RELATED INFLAMMATORY PATHWAY BIOMARKERS IN SYNUCLEIN-ASSOCIATED NEURODEGENERATIVE DISORDERS (SAND)

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ABSTRACT

Aim: This study investigates the role of calcitonin gene-related peptide (CGRP) and its related inflammatory biomarkers in individuals with Synuclein-Associated Neurodegenerative Disorders (SAND), encompassing conditions like Parkinson's disease (PD) and Multiple System Atrophy (MSA). Given CGRP's known anti-inflammatory and neuroprotective properties demonstrated in vitro and in animal models, we aimed to explore its association with inflammatory pathways in humans across different circadian stages. **Material and Methods:** We analysed plasma levels of biomarkers such as CGRP, NLRP3 inflammasome components, IL-1β, and IL-18, along with hair cortisol, in 15 participants (7 with SAND, 8 controls). Blood samples were collected before and after overnight sleep studies, and correlations between these markers were assessed using non-parametric tests. **Results:** Across groups, all plasma biomarkers showed significant correlations before and after sleep. In controls, strong temporal associations within the CGRP pathway were observed, particularly between pre-sleep IL18, post-sleep CGRP, and hair cortisol, driven primarily by control group variance. These biomarkers also related to clinical features such as cognition and motor function, with notable associations between inflammatory markers and cognitive scores. In the SAND group, fewer biomarker correlations were found, with pre-sleep NLRP3 correlating with hair cortisol. Only pre-sleep CGRP and IL18 levels significantly differed between groups, suggesting disease-specific alterations in circadian biomarker patterns. **Conclusions:** The above highlights that temporal fluctuations of inflammatory biomarkers differ in patients with SAND compared to controls. By extension, the lack of association of CGRP to these inflammatory markers in patients, but its association in controls suggests that under healthy conditions CGRP exerts some control over the inflammatory cascade, but its absence allows for stronger inflammatory biomarker co-expressions at 4-5 years of disease onset.

Keywords: CGRP, biomarkers, neuroinflammation, Parkinson disease, sleep

ΧΡΟΝΙΚΕΣ ΣΥΣΧΕΤΙΣΕΙΣ ΤΩΝ ΒΙΟΔΕΙΚΤΩΝ ΦΛΕΓΜΟΝΗΣ ΣΧΕΤΙΖΟΜΕΝΩΝ ΜΕ ΤΟ ΜΟΝΟΠΑΤΙ CGRP ΣΤΙΣ ΣΥΝΟΥΚΛΕΪΝΟΠΑΘΕΙΕΣ

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ΠΕΡΙΛΗΨΗ

Στόχος: Αυτή η μελέτη διερευνά τον ρόλο του πεπτιδίου CGRP και των σχετιζόμενων με αυτό βιοδεικτών φλεγμονής σε άτομα με Συνουκλεϊνοπάθειες (SAND), όπως η νόσος Πάρκινσον και η ατροφία πολλαπλών συστημάτων. Δεδομένου ότι το CGRP έχει γνωστές αντιφλεγμονώδεις και νευροπροστατευτικές ιδιότητες που έχουν αποδειχθεί in vitro και σε ζωικά μοντέλα, στόχος μας ήταν να διερευνήσουμε τη σύνδεσή της με φλεγμονώδη μονοπάτια σε ανθρώπους κατά την διάρκεια κιρκάδιων ρυθμών. **Υλικά και Μέθοδοι:** Αναλύσαμε τα επίπεδα βιοδεικτών στο πλάσμα, όπως το CGRP, τα συστατικά του ινφλαμμασώματος NLRP3, IL-1β και IL-18, καθώς και κορτιζόλης μαλλιών, σε 15 συμμετέχοντες (7 με SAND, 8 υγιείς μάρτυρες). Τα δείγματα αίματος συλλέχθηκαν πριν και μετά από ολονύκτια μελέτη ύπνου, και οι συσχετίσεις μεταξύ αυτών των βιοδεικτών αξιολογήθηκαν με μη παραμετρικές μεθόδους. Αποτελέσματα: Σε όλες τις ομάδες, όλοι οι βιοδείκτες στο πλάσμα έδειξαν σημαντικές συσχετίσεις πριν και μετά τον ύπνο. Στους υγιείς μάρτυρες, παρατηρήθηκαν ισχυρές χρονικές συσχετίσεις στο μονοπάτι του CGRP, ιδίως μεταξύ προ-ύπνου IL-18, μετά τον ύπνο CGRP και κορτιζόλης μαλλιών, κυρίως λόγω της διαφοράς στη variance της ομάδας ελέγχου. Αυτοί οι βιοδείκτες συνδέονταν επίσης με κλινικά χαρακτηριστικά όπως η γνωστική λειτουργία και η κινητική ικανότητα, με σημανικές συσχετίσεις μεταξύ φλεγμονωδών δεικτών και γνωστικών λειτουργιών. Στην ομάδα SAND, βρέθηκαν λιγότερες συσχετίσεις βιοδεικτών, με το προ-ύπνου NLRP3 να συσχετίζεται με την κορτιζόλη των μαλλιών. Μόνο τα επίπεδα προ-ύπνου της CGRP και IL-18 διαφέρουν σημαντικά μεταξύ των δύο ομάδων, υποδεικνύοντας διαταραχές στα κιρκάδια μοτίβα των βιοδεικτών. **Συμπεράσματα:** Τα ανωτέρω υπογραμμίζουν ότι οι χρονικές διακυμάνσεις των φλεγμονωδών βιοδεικτών διαφέρουν σε ασθενείς με SAND σε σύγκριση με τους υγιείς. Η απουσία συσχέτισης του CGRP με αυτούς τους βιοδείκτες στους ασθενείς, σε αντίθεση με τους υγιείς, υποδηλώνει ότι υπό φυσιολογικές συνθήκες το CGRP ασκεί κάποιον έλεγχο στην φλεγμονώδη αλυσίδα, ενώ η απουσία του επιτρέπει ισχυρότερες συν-εκφράσεις φλεγμονωδών βιοδεικτών 4-5 χρόνια μετά από την έναρξη της νόσου.

Λέξεις-κλειδιά: CGRP, βιοδείκτες, νευροφλεγμονή, νόσος Πάρκινσον, ύπνος

INTRODUCTION

Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD), and it is associated with significant morbidity and mortality—carrying a 1.75 to 3.86 times higher risk compared to the general population.[1] In 2017, approximately one million individuals were diagnosed with PD in the United States, with direct healthcare costs reaching $51.9 billion.[2] A key pathological feature of PD is the aggregation and propagation of α-synuclein (α-syn), which correlates with disease severity and prognosis. Recent research also links α-syn with inflammasome-induced inflammation.[3] Inflammasomes are multiprotein complexes within the cytosol of immune cells that play a crucial role in disease development.[4-6] Chronic activation of inflammasomes — triggered by pathogenic microorganisms, mitochondrial oxidative stress, endogenous cytokines, and protein aggregates — is proposed as a mechanism underlying neurodegeneration.[3] In PD, fibrillar α-syn released into the extracellular space due to neuronal degeneration activates microglia and amplifies inflammatory responses.[7,8] Studies have shown that NLRP3 inflammasome activation and elevated inflammatory cytokines are involved in PD onset.[9,10]

A key protein involved in the regulation of inflammatory and other pathways is the Calcitonin gene-related peptide (CGRP), which is part of the calcitonin family of peptides and is extensively expressed in neuronal tissues.[11-13] Binding CGRP to its receptor activates multiple signalling pathways that can influence neurodegeneration, with disruptions potentially contributing to disease progression.[14,15] Emerging evidence indicates that CGRP exerts neuroprotective effects across various neuronal populations by engaging multi-kinase signalling pathways.[16] Specifically, CGRP appears to diminish anti-apoptotic signalling while enhancing proliferative pathways in an Akt-dependent manner.[17] Additionally, in vitro and animal studies suggest CGRP possesses anti-inflammatory properties, possibly through modulation of macrophages and inhibition of the NLRP3 inflammasome.[18,19] Long-acting CGRP analogues have shown promise as therapeutic agents for type 2 diabetes due to their favourable metabolic effects and promotion of GLP-1 secretion.[20] Activation of the GLP-1 receptor can increase gene expression of peptides involved in energy regulation, such as CGRP and IL-6, within the parabrachial nucleus.[21] Conversely, the use of DPP4 inhibitors and GLP-1 mimetics has been associated with a reduced risk of developing PD compared to other oral antidiabetic agents. These findings suggest that anti-inflammatory strategies could delay PD progression.[22,23] Furthermore, exogenous CGRP administration has been shown to inhibit macrophage infiltration and reduce inflammatory mediator expression, thereby

mitigating inflammation-related damage in AD. Consequently, targeting CGRP receptor pathways may offer a novel therapeutic approach for both AD and PD.[24]

In the present study, we explored the associations of CGRP related plasma biomarkers in individuals who underwent detailed deep phenotyping of SAND and matched controls before and after sleep. Specifically, we examined the relationship between CGRP and inflammatory biomarkers in relation to detailed phenotypic features of people with SAND, and more specifically, whether NLRP3, IL-1β, IL-18, and hair and blood cortisol were associated with CGRP levels, and whether this association differed between groups and before and after sleep. We hypothesised that CGRP has a neuroprotective role; therefore, we expected CGRP related patterns to reveal increased expression early in the disease process, and conversely, we anticipated that their expression would decline as the disease progresses. We further hypothesised that pre- to post- sleep fluctuations of CGRP-related biomarkers would be more closely associated with disease severity than their absolute levels, and further mediated by sleep disturbances and executive dysfunction rather than to motor symptoms.

MATERIAL AND METHODS

Participants

We recruited 18 participants with SAND (age 48-80; F:M 9:9; 16 PD and 2 MSA; years of disease 4.73; UPDRSIII 29.89; H&Y 2.29; S&E 87.65) and 13 non-impaired controls (age 42-78; F:M 8:5) from the Movement Disorders and Sleep & Memory Centres at the Neurological Institute of Athens (NIA) and after obtaining informed consent post Institutional Review Board approval (**Tables 1 and 2**). Participants with SAND were older than 18 years old, had a clinical diagnosis of SAND, Hoehn and Yahr ≤ 3, and MMSE ≥ 24. Participants were excluded if they presented with major vascular brain disease, and/or history of major psychiatric disease or medication use affecting movement, cognition, or sleep regulation, features suggesting atypical parkinsonism, and features of prodromal PD. The control group included people with features of prodromal PD (i.e., idiopathic REM behaviour disorder, constipation).

In the present study, we present the preliminary results from the plasma analysis on 15 participants (7 with SAND and 8 controls).

Clinical Protocol

All participants underwent multisource-multidisciplinary clinical assessments of structured interviews and questionnaires on history & physical information, including motor assessments (e.g., UPDRS-III, Schwab and England), and neuropsychological testing. Structured questionnaires included the Neurological Institute of Athens Cognitive Behavioural Symptoms Questionnaire (Q-CBS) for patients and caregivers, a 51-item questionnaire, of which the first three items capture gross impressions of cognition (Q-CBS-1), movement (Q-CBS-2), and sleep (Q-CBS-3), respectively. Plasma biomarker levels (CGRP, NLRP3, IL1β, IL18, cortisol, NFL, GFAP, insulin) were collected before and after an overnight in-lab sleep study. Hair cortisol, representing average cortisol levels over the previous three months, was collected from hair post-sleep (**Figure 1**).

Biosample processing: Blood biomarker quantification, including CGRP, NLRP3, IL-1β and IL-18 Western Blot and ELISA were pursued at the National Centre for Scientific Research (NCSR) "Demokritos" and blood cortisol, NFL, GFAP, and insulin levels were pursued in at Uppsala and Gothenburg Universities in Sweden.

Statistical Analysis

We performed non-parametric tests (Spearman and Mann Whitney test) between markers across and between the two groups to assess associations within and between biomarkers and groups across circadian stages.

Table 1. Demographics of control and SAND participants.

	SAND	CONTROLS	P-value
F:M	9:9	8:5	0.394
AGE Mean (SD); Range	66.06 (9.53); 47-80	61.23 (9.51); 42-78	0.063

Table 2. Baseline demographics and rating scales' scores of SAND group.

Metric	SAND	
	Mean (SD)	**range**
AGE OF ONSET	59.00 (9.87)	44-77
YEARS OF DISEASE	4.73 (3.41)	1-11
UPDRS III	29.89 (14.74)	12-63
Hoehn **&Y**ahr	2.29 (0.71)	2-4
Schwab **& E**ngland	87.65 (16.02)	50-100

RESULTS

Across groups, all plasma biomarkers correlated to themselves before and after sleep Within the CGRP-related pathway across circadian rhythms, in control's group temporal associations were strongest between pre-sleep IL18 and to post-sleep CGRP, IL-18 and hair cortisol. IL-18 and CGRP were correlated both within times and across circadian rhythms (r = 0.97 – 0.99; p

< 0.05). CGRP before sleep was only associated with pre- and post-sleep IL18, an observation driven by variance in the control group. Post-sleep IL-18 and CGRP were correlated with hair cortisol (**Figure 1**). These plasma associations were primarily driven by biomarker variance in the control group rather than the SAND group (**Figure 2**). Actually, only pre-sleep NLRP3 was correlated with hair cortisol in people with SAND.

Figure 1. Cross-sectional and longitudinal biomarker associations in Controls.

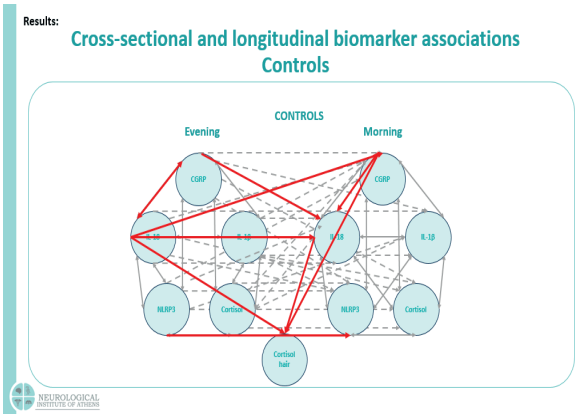
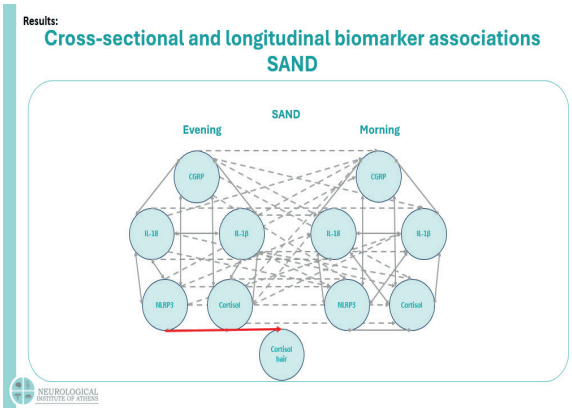


Figure 2. Cross-sectional and longitudinal biomarker associations in SAND.



The CGRP-related pathway biomarkers across circadian rhythms were also associated with clinical features. In the control group, pre-sleep CGRP correlated with phonemic fluency, while post-sleep CGRP was linked to MMSE scores. A significant relationship was observed between evening NLRP3 and phonemic fluency and Q-CBS-1 (cognitive), and morning NLRP3 with Q-CBS-3 (sleep). Pre-sleep IL18 was associated with MMSE, and post-sleep IL18 with Q-CBS-1 (cognitive) and MMSE. Cortisol levels in hair showed a significant correlation with recall. Additionally, morning NFL levels were related to phonemic fluency (**Table 3a**). In the SAND group, post-sleep CGRP was associated with phonemic fluency. Evening IL18 and IL1β levels were linked to recall. Pre-sleep NFL correlated with UPDRS III scores. Both pre- and post-sleep GFAP levels were associated with CBS 1, with post-sleep GFAP also showing a significant relationship with phonemic fluency. Lastly, morning cortisol and insulin levels were associated with Schwab and England and digit span backward tasks, respectively (**Table 3b**).

When comparison of biomarkers was carried out, only pre-sleep CGRP and IL18 levels were significantly different between the two groups (z = -2.78; p = 0.004) (**Table 4**).

Table 3. Longitudinal biomarker and clinical manifestation associations in a. Controls, b. SAND.

PS, pre-sleep; AS, post-sleep. Q-CBS, Structured questionnaires included the Neurological Institute of Athens Cognitive Behavioural Symptoms Questionnaire; Q-CBS-1, Cognition, Q-CBS-2, Movement; Q-CBS-3, Sleep.

a.

P	Q-CBS- 1	N	Q-CBS- 2	N	Q-CBS- 3	N	MMSE	N	Digit backwards	N	recall_PS	N	phonemic_fluency PS	N
CGRP_PS	0.8	4	0.058	5	0.604	5	0.854	6	0.305	6	0.084	6	*0.037	5
CGRP_AS	0.499	6	0.854	6	0.381	6	*0.039	8	0.974	8	0.326	8	0.432	7
NLRP3_PS	*0	4	0.638	5	0.306	5	0.573	6	0.512	6	0.913	6	*0.037	5
NLRP3_AS	0.288	6	0.573	6	*0.02	6	0.689	8	0.446	8	0.583	8	0.294	7
IL18_PS	0.6	4	0.638	5	0.361	5	*0.021	6	0.749	6	0.173	6	0.505	5
IL18_AS	*0.036	6	0.854	6	0.956	6	*0.008	8	0.821	8	0.563	8	0.432	7

Cortisol_ hair	0.211	9	0.774	10	0.653	10	0.385	11	0.221	10	*0.043	11	0.608	8
NFL_nl_AS	0.08	6	0.067	7	0.658	7	1	8	0.717	8	0.204	8	*0.049	7

b.

p	**UPDR-SIII**	**N**	**Schwab & England**	**N**	**CBS 1**	**N**	**CBS2**	**N**	**CBS 3**	**N**	**MMSE**	**N**	**Digit backwards**	**N**	**recall_ PS**	**N**	**phonemic_fluency PS**	**N**
CGRP_AS	0.913	6	0.32	6	0.14	6	0.518	6	*0.041	5	0.816	6	0.117	6	0.468	6	0.104	5
IL18_PS	0.935	5	0.638	5	1	5	0.269	5	0.684	4	0.638	5	0.434	5	*0.037	5	0.8	4
IL1β_PS	0.741	5	0.638	5	1	5	0.614	5	0.684	4	0.308	5	0.434	5	*0.037	5	0.6	4
cortisol_ng/ml_AS	0.452	11	*0.038	11	0.759	11	0.462	11	0.833	11	1	11	0.639	11	0.6	11	0.623	9
NFL_nl_PS	*0.032	9	0.384	9	0.168	9	0.067	9	0.325	8	0.717	9	0.041	9	0.827	9	0.957	6
GFAP_nl_PS	0.795	9	0.197	9	*0.045	9	0.948	9	0.833	8	0.331	9	0.576	9	0.695	9	0.072	6
GFAP_nl_AS	0.965	9	0.284	9	*0.005	9	0.965	9	0.563	8	0.097	9	0.414	9	0.347	9	*0.019	6
Insulin_pg/ml_AS	0.531	9	0.98	9	0.78	9	0.449	9	0.281	8	0.768	9	*0.031	9	0.703	9	0.439	6

p<0,5

Table 4. Biomarker associations between two groups (Controls and SAND).

Marker		**SAND**			**CONTROLS**		
	N	**Mean (SD)**	**range**	**N**	**Mean (SD)**	**range**	**P-value**
MMSE	17	28.33 (1.85)	24-30	13	29.23 (0.83)	27-30	0.157
p-tau 217 AS	9	0.34 (0.24)	0.00-0.72	8	0.14 (0.14)	0.00-0.30	0.057
p-tau 217 PS	9	0.33 (0.36)	0.00-0.85	8	0.18 (0.12)	0.00-0.29	0.176
Cortisol hair	11	13.87 (14.32)	4.64-52.20	11	10.11 (8.83)	2.77-26.43	0.311
Cortisol blood AS	9	174.11 (53.29)	90.18-254.72	8	212.50 (63.54)	128.86-311.19	0.377
Cortisol blood PS	10	107.15 (49.61)	46.39-200.92	8	64.73 (34.70	28.13-130.08	0.126
CGRP AS	6	67.57 (68.47)	4-186	6	41.07 (18.30)	18-67	*0.030
CGRP PS	6	95.35 (73.65)	6-191	8	61.70 (39.85)	23-140	0.801
NLRP3 AS	5	20.13 (14.89)	10-50	6	17.03 (4.13)	12-22	0.362
NLRP3 PS	6	21.51 (19.48)	13-66	8	17.86 (4.12)	13-25	0.119
IL18 AS	5	98.76 (36.08)	68-157	6	74.73 (20.72)	53-106	0.133
IL18 PS	6	105.33 (28.56)	74-154	8	74.83 (14.25)	53-90	*0.009
IL 1β AS	5	7.03 (4.06)	2-12	6	12.36 (12.8)	2-29	0.563
IL 1β PS	6	17.64 (19.05)	2-45	8	12.29 (8.5)	3-30	0.837

p<0,5

DISCUSSION

The relationship between CGRP and inflammatory biomarkers in relation to detailed phenotypic features of individuals with synuclein-associated neurodegenerative disorders has not been investigated yet. We examined whether inflammatory markers — such as NLRP3 inflammasome components, IL-1β, IL-18, and also hair and blood cortisol were associated with CGRP levels before and after sleep.

In the present study, the primary objective was to explore the relationship between CGRP and inflammatory biomarkers in relation to the detailed phenotypic features of individuals with SAND. Specifically, we aimed to assess whether inflammatory markers—such as NLRP3 inflammasome components, IL-1β, IL-18, as well as hair and blood cortisol—are associated with CGRP levels. Our hypothesis was that CGRP plays a neuroprotective role; thus, we expected to see increased expression of CGRP and

related inflammatory biomarkers in the preclinical stages of the disease. Conversely, we anticipated that their levels would decrease as the disease advances.

The second objective was to investigate the associations and the dynamic fluctuations of CGRP-related pathways, particularly the nighttime-to-morning variations, in relation to clinical and neurophysiological features across motor, cognitive-behavioural, sleep, and circadian domains. We hypothesised that reduced fluctuations in CGRP-related biomarkers would be more strongly linked to disease severity than their absolute levels, with particular connections to sleep disturbances and executive dysfunction, rather than to motor symptoms such as rigidity and bradykinesia.

This comprehensive analysis highlights the dynamic relationships within the CGRP-related pathway across circadian rhythms and their associations with clinical features in both control and SAND groups. In the control group, strong temporal associations were observed between pre-sleep IL18 and post-sleep CGRP, as well as between IL-18 and hair cortisol. The high correlation coefficients ($r = 0.97–0.99$; $p < 0.05$) indicate a tightly coordinated fluctuation of these biomarkers within and across circadian phases. Specifically, pre-sleep CGRP was primarily linked with IL18 at the same time points, whereas post-sleep IL-18 and CGRP correlated with hair cortisol, emphasising the interconnectedness of inflammatory and neuroendocrine pathways in controls. These plasma associations were predominantly driven by variability in the control group, with minimal associations observed in the SAND population, except for pre-sleep NLRP3's correlation with hair cortisol.

The fact that only pre-sleep CGRP and IL18 levels significantly differed between controls and people with SAND, suggests disease-specific alterations in these biomarkers related to sleep or circadian regulation. These findings underline notable differences between healthy controls and people with SAND.

From a clinical perspective, results suggest that biomarkers related to the CGRP pathway exhibit circadian variations that are linked to specific clinical manifestations. In the control group, pre-sleep CGRP influencing phonemic fluency, and post-sleep CGRP being associated with general cognitive function (MMSE. The relationship between evening NLRP3 and both phonemic fluency and cognition, as well as morning NLRP3 and sleep, indicates that inflammasome activity fluctuates across the day and impacts cognitive and sleep-related aspects. IL18 levels before and after sleep are linked to cognitive performance, further emphasising the role of inflammation in cognition. In the SAND group, post-sleep CGRP correlates with phonemic fluency, and evening inflammatory markers (IL18 and IL1β) are associated with recall, suggesting inflammation may influence memory in these patients. The correlation between pre-sleep NFL and motor function (UPDRS III) points to neurodegeneration impacting sleep-related processes. GFAP, a marker of astroglial activity, is associated with cognition, especially after sleep, hinting at glial involvement in neurodegenerative processes. Morning cortisol and insulin levels' links to functional and cognitive assessments imply that stress and metabolic regulation also play roles in symptom expression. Overall, these findings highlight the complex interplay between circadian biomarker fluctuations, inflammatory responses, neurodegeneration, and clinical features, suggesting that timing of biological processes significantly influences disease manifestation and progression.

Pursuing this study, we hypothesised that at late disease stages CGRP expression would be significantly reduced, and, indeed, results from people with SAND indicate that CGRP has limited correlation with other markers of the inflammatory cascade. As already has been discussed, there are five primary pathophysiological mechanisms through which CGRP may influence SAND: (a) neuroinflammatory, (b) anti-apoptotic and proliferative, (c) metabolic, (d) neuromodulatory, and (e) antimicrobial.[25] Among these, most existing data pertain to CGRP-related neuroinflammatory processes in SAND, which also intersect with the other mechanisms. Despite these considerations, although the dynamic regulation of CGRP pathways appears relevant to SAND, there is still a lack of definitive causal evidence and circadian data to confirm whether these pathways are necessary or sufficient drivers of the disease.

PD is generally regarded as a condition that develops with increasing age.[26] Inflammation is a prevalent factor in many age-related diseases, including Parkinson's disease. Prior studies have examined the inflammatory response associated with aging, a process referred to as inflammaging.[27,28] The inflammasome plays a role in inflammaging, a process associated with the early phases of neurodegeneration.[28-31] Neuroinflammation has been linked to the initiation and progression of pathological changes in numerous neurodegenerative diseases, including Parkinson's disease.[32] Central to these inflammatory processes is the overactivation of microglia, particularly via the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome pathway, which has been detected in tissues from patients with SAND.[33]

The inflammatory response contributes to the progress of age-related macular degeneration (AMD) which is a progressive degenerative disease. In a recent study researchers found that the levels of the NLRP3 component, Apoptosis-Associated Speck-like Protein (ASC) and IL-18 are elevated in patients with AMD, and the protein levels of IL-18 are partially the result of ASC protein expression.[34] CGRP levels can be altered in neurodegeneration. Elevated CGRP

levels were found in cerebrospinal fluid in PD patients compared to people with major depressive disorder according to Svenningsson et al.[35] These findings align with our results, where aside from post-sleep IL-1β, all pre- and post-sleep biomarkers tended to be higher in the SAND participants compared to controls.

The present study also has certain limitations. Besides the small number of participants, the control group had people with REM Sleep Behaviour Disorder (RBD) which is strongly associated with SAND, and people with comorbidities (such as autoimmune or systematic diseases), which can influence inflammatory biomarkers levels. Another point is that no reliable biomarkers exist to define the preclinical and prodromal stages of SAND towards correlating these stages with CGRP levels.

In conclusion, the present study identified that: (a) temporal fluctuations of inflammatory biomarkers differ in patients with SAND compared to controls, and (b) the lack of association of CGRP to these inflammatory markers in patients, but its association in controls suggests that under healthy conditions CGRP exerts some control over the inflammatory cascade, but its absence allows for stronger inflammatory biomarker co-expressions at 4-5 years of disease onset.

Larger multidisciplinary projects with longitudinal design, including biomarker panels, skin biopsy or/and seeding amplification assays are needed to examine the unexplored cross-sectional and dynamic associations of blood and skin biopsy CGRP-related pathway biomarkers to multidimensional real-world data.

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VALIDATION AND CULTURAL ADAPTATION OF THE SWALLOWING DISTURBANCE QUESTIONNAIRE (SDQ) INTO GREEK FOR PEOPLE LIVING WITH PARKINSON'S DISEASE

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ABSTRACT

Background: Dysphagia is a frequent and impactful symptom of Parkinson's Disease (PD), associated with malnutrition, dehydration, and increased mortality. Early detection is essential, yet reliable screening tools remain limited. The Swallowing Disturbance Questionnaire (SDQ) is a validated tool for dysphagia screening in PD. However, no culturally adapted and validated Greek version currently exists. **Methods:** Forty individuals diagnosed with PD participated in this study. The original SDQ was translated into Greek and a pilot administration was conducted with healthy controls. To evaluate validity, participants completed two additional self-questionnaires (Speech Pathology-Specific Questionnaire for Persons with Multiple Sclerosis; SMS and Dysphagia in Multiple Sclerosis questionnaire; DYMUS) and performed the 3-ounce Water Swallow Test (3oz WST). Cognitive and language functions were evaluated with the Montreal Cognitive Assessment (MoCA) and the Verbal Fluency Test (VFT). **Results:** The Greek SDQ (g-SDQ) showed excellent internal consistency (Cronbach's $\alpha = 0.841$) and good diagnostic accuracy (AUC = 0.820). Strong positive correlations were found between the g-SDQ and both the DYMUS ($r = 0.86$, $p < .001$) and SMS questionnaires ($r = 0.73$, $p < .001$). A positive but not statistically significant correlation was observed with the 3oz WST ($r = 0.48$, $p = .002$). Cognitive assessments revealed significant negative correlations between the g-SDQ and MoCA, as well as the VFT. **Conclusion:** The g-SDQ is a reliable and valid tool for early screening and monitoring of dysphagia in Greek people with PD, aiding clinicians in identifying swallowing difficulties and supporting personalised care.

Keywords: Parkinson's disease, Dysphagia, Early detection, Self-report Questionnaire, Validation

ΣΤΑΘΜΙΣΗ ΚΑΙ ΠΟΛΙΤΙΣΜΙΚΗ ΠΡΟΣΑΡΜΟΓΗ ΤΟΥ ΕΡΩΤΗΜΑΤΟΛΟΓΙΟΥ SWALLOWING DISTURBANCE QUESTIONNAIRE (SDQ) ΣΤΗΝ ΕΛΛΗΝΙΚΗ ΓΛΩΣΣΑ ΓΙΑ ΑΤΟΜΑ ΠΟΥ ΖΟΥΝ ΜΕ ΝΟΣΟ ΤΟΥ ΠΑΡΚΙΝΣΟΝ

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η δυσφαγία αποτελεί ένα συχνό σύμπτωμα της νόσου του Πάρκινσον (ΝΠ), το οποίο συνδέεται με υποσιτισμό, αφυδάτωση και αυξημένη θνησιμότητα. Η έγκαιρη ανίχνευσή της είναι κρίσιμη, ωστόσο τα αξιόπιστα μέσα διάγνωσης παραμένουν περιορισμένα. Το SwallowingDisturbanceQuestionnaire (SDQ) αποτελεί ένα αξιόπιστο εργαλείο για την ανίχνευση της δυσφαγίας στη ΝΠ, όμως έως σήμερα δεν έχει σταθμιστεί στα Ελληνικά. **Μεθοδολογία:** Στη μελέτη συμμετείχαν 40 άτομα με ΝΠ. Το πρωτότυπο SDQ μεταφράστηκε στα ελληνικά και δοκιμάστηκε πιλοτικά σε υγιή άτομα. Για την αξιολόγηση της εγκυρότητάς του,

οι συμμετέχοντες συμπλήρωσαν δύο επιπλέον ερωτηματολόγια αυτό-αναφοράς (Speech Pathology-Specific Questionnaire for Persons with Multiple Sclerosis; SMS και Dysphagia in Multiple Sclerosis questionnaire; DYMUS) και υποβλήθηκαν σε δοκιμασία κατάποσης νερού (3-ounce Water Swallow Test; 3oz WST). Οι γνωστικές και γλωσσικές λειτουργίες αξιολογήθηκαν με το Montreal Cognitive Assessment (MoCA) και το Verbal Fluency Test (VFT). **Αποτελέσματα:** Η ελληνική εκδοχή του SDQ (g-SDQ) παρουσίασε άριστη εσωτερική συνοχή (Cronbach's α = 0,841) και καλή διαγνωστική ακρίβεια (AUC = 0,820). Βρέθηκαν ισχυρές θετικές συσχετίσεις μεταξύ του g-SDQ και των ερωτηματολογίων DYMUS (r = 0,86, p< .001) και SMS (r = 0,73, p< .001). Παρατηρήθηκε, επίσης, θετική, αλλά όχι στατιστικά σημαντική, συσχέτιση με τη δοκιμασία 3ozWST (r = 0,48, p = .002). Οι γνωστικές αξιολογήσεις έδειξαν σημαντικές αρνητικές συσχετίσεις μεταξύ του g-SDQ και των δοκιμασιών MoCA και VFT. **Συμπεράσματα:** Το g-SDQ αποτελεί ένα αξιόπιστο εργαλείο για την έγκαιρη ανίχνευση και παρακολούθηση της δυσφαγίας σε άτομα με ΝΠ, συνεισφέροντας στην κλινική πρακτικήμέσωτης αναγνώρισης προβλημάτων κατάποσης και της παροχής εξατομικευμένης φροντίδας.

Λέξεις-κλειδιά: Νόσος Πάρκινσον, Δυσφαγία, Έγκαιρη ανίχνευση, Ερωτηματολόγιο Αυτοαναφοράς, Στάθμιση

INTRODUCTION

Parkinson's Disease (PD) has been defined as "***a core clinical motor syndrome (parkinsonism) accompanied by substantia nigra pars compacta neurodegeneration and synuclein deposition***" by the International Parkinson and Movement Disorders Society (IPMDS) Task Force.[1] Epidemiological data show an increasing global prevalence that goes beyond the effects of aging alone; higher rates are observed among older individuals, while healthcare accessibility may have an impact on geographic and ethnic disparities. However, there are unclear trends in incidence, particularly among women and low-/middle-income countries, because there is a lack of high-quality data. As the second most common neurodegenerative disease, PD seems to be a global priority and a significant social concern.[2]

PD is diagnosed using clinical criteria, as there is no definitive test available. The primary symptoms include rest tremor, bradykinesia, rigidity, and loss of postural reflexes, accompanied by secondary motor symptoms such as dysphagia and non-motor symptoms that encompass autonomic and cognitive challenges.[3] Dysphagia may occur at any stage of the disease, including early onset, significantly diminishing the quality of life for affected individuals.[4] Specifically, weight loss, dehydration, and malnutrition might arise from difficulties in swallowing food, liquids, or medications, while individuals with dysphagia frequently withdraw from social interactions. Aspiration pneumonia is among the most serious complications and a common cause of hospitalisation and mortality.[5],[6],[7]

According to a recent meta-analysis research, more than one-third of persons with PD experience subjective oropharyngeal dysphagia (OD), with prevalence increasing in advanced stages, and up to 80% when subclinical cases are included.[8] However, estimates of OD prevalence range greatly, from 11% to 81%, depending on the assessment method employed. This current knowledge is constrained by the variety of detection methods, emphasising the urgent need for a reliable, standardised, and validated approach to accurately identify dysphagia in PD.[9] To this purpose, a multinational expert group reviewed literature on neurogenic dysphagia and PD (Jan 1990–Feb 2021) following PRISMA guidelines. The expert group addressed the screening, diagnosis, impact on quality of life, and prognostic significance of dysphagia in PD, providing guidelines for an efficient detection and treatment. Among the guidelines, several questionnaire-based tools are recommended for screening dysphagia in PD, including the Swallowing Disturbance Questionnaire (SDQ).[10]

The SDQ is a self-report instrument validated for the early detection of dysphagia occurring during all the stages of swallowing. The original version, specifically developed for individuals with PD, demonstrated a sensitivity of 80.5% and a specificity of 81.3%.[11] The instrument, originally available in English, has also been translated and validated in Persian, Japanese, Portuguese, and Brazilian Portuguese.[12],[13],[14],[15]

In this context, the current study aims to translate, culturally adapt, and validate the initial psychometric properties of the SDQ questionnaire in the Greek language, with the purpose of facilitating the early detection of dysphagia in people living with PD.

MATERIALS AND METHODS

Participants

The sample consisted of 40 individuals diagnosed with PD. Demographic (age, sex, and years of education) and clinical (year of diagnosis) data were collected for each one of them. Participants were eligible for inclusion in this study if they met the following criteria: (1) have a diagnosis of PD; (2) be ≥ 18 years of age; (3) be native speakers of the Greek

language; (4) be able to fill out the questionnaire by him/herself; and (5) have a Montreal Cognitive Assessment (MoCA) score above 15. Exclusion criteria included any conditions that could interfere with participants' performance: (1) the presence of psychiatric disorders (e.g., untreated depression, psychotic symptoms, alcohol or drug abuse); (2) concomitant neurological disorders (e.g., epilepsy, stroke, or traumatic brain injury); (3) malignancies of the larynx or other relevant regions; and (4) severe visual and/or hearing impairments.

Greek version of the Swallowing Disturbance Questionnaire (g-SDQ)

The original SDQ[11] is a self-report questionnaire consisting of 15 items that assess symptoms of dysphagia arising at any stage of swallowing. Questions 1 to 5 pertain to the oral-stage symptoms, while questions 6 to 15 concern pharyngeal-stage dysphagia. Items 1 through 14 are graded on a 4-point Likert scale to determine the symptom frequency: 0 – 'never'; 1 – 'rarely' (≥ once per month); 2– 'often' (1–7 times per week); and 3 – 'very often' (> 7 times per week). Item 15 requires a "yes" or "no" response, which is scored as 2.5 or 0.5, respectively. A total SDQ score of ≥11 indicates a potential diagnosis of dysphagia, based on findings from individuals with diverse underlying conditions. The original English version was translated and converted into Greek by three Greek native speakers, including two speech language pathologists and a neurologist. No items from the original edition were omitted, modified or replaced. The final Greek version of the SDQ questionnaire (g-SDQ) was tested on ten healthy control subjects to determine its perceptiveness and was authorised by the research team.

Swallowing Assessment

For assessing convergent validity, the participants completed two other patient-reported outcome measures (PROMs), which have already been validated in Greek:

The Speech Pathology-Specific Questionnaire for Persons with Multiple Sclerosis (SMS[16]) is a 16-item questionnaire that examines speech/language, voice, and swallowing abilities, with each item rated on a 5-point scale for a maximum total score of 64 points.

The Dysphagia in Multiple Sclerosis (DYMUS[17]) questionnaire consists of ten yes/no questions with a 10-point score. The questionnaire was created especially for people with multiple sclerosis. It evaluates both liquid and solid dysphagia; a single affirmative response denotes dysphagia, whereas three or more indicate severe difficulties.

For assessing criterion validity, the participants performed the non-invasive physical assessment 3-ounce Water Swallow Test (3oz WST[18]). Specifically, a speech-language pathologist (SLP) specialising in dysphagia observed the individuals as they consumed 90 mL of water either through a straw or by sipping from a cup in their usual manner. The SLP monitored symptoms of aspiration, including coughing, choking, changes in the voice quality, nasal regurgitation of fluids or food, and post-swallowing respiratory distress. The examination was scored as either impaired (1) or normal (0).

Cognitive and Language Assessment

Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA),[19] and linguistic performance was assessed with the Verbal Fluency Test (VFT).[20]

MoCA is a brief test that evaluates the following cognitive and language domains: visuospatial and executive functioning, naming, attention, language, abstraction, delayed recall (short-term memory), and orientation. Scores range from 0 to 30, with a score of 26 and higher generally considered normal. Notably, participants with 12 years or less of formal education receive an additional point on their score.[19]

VFTs assess the ability to produce words within a limited timeframe. There are two main types: **phonemic (PhVFT),** where words begin with a specific letter, and **categorial (CVFT),** where words belong to a target category. VFTs measure cognitive functions like semantic memory, language ability, attention, processing speed, and executive functions such as inhibition, self-monitoring, and information differentiation.[20]

Procedure

The study was conducted in accordance with the Declaration of Helsinki ethical principles.[21] Data processing and analysis were approved by the ethics committee of the University of Ioannina (reference number 48936/17-12-2024). All participants were informed about the study's objectives and procedures and provided written informed consent prior to participation. They were notified they could opt out of the study at any time as they wished, without any impact on their medical treatment.

All tasks were carried out in a quiet room to minimise external distractions, and no other individuals were present during the procedure. Furthermore, the administration of all questionnaires followed a consistent, pre-determined order.

Statistical Analysis

Descriptive statistics were applied to the collected data. The internal consistency of the g-SDQ scale was evaluated using the Cronbach's alpha coefficient. The global g-SDQ scor***e*** was assessed for its diagnostic accuracy via Receiver Operating Characteristic (ROC) curve analysis, while its external reliability was examined using results from the

DYMUS questionnaire. All correlations to the g-SDQ were determined through the Pearson correlation coefficient (PCC). The significance level was set at $p < 0.05$, and the statistical analysis was conducted using the SPSS v26.0.

RESULTS

Study population

The study sample consisted of 40 patients (10 women corresponding to 25%) with a mean age of 74.1 years (SD = ±8.1). Educational level was recorded in years (mean = 11.1, SD = ±3.8) and ranged from 6, indicating only mandatory education, to 16 years, indicating university graduates.

Internal Consistency and Diagnostic Accuracy of the g-SDQ

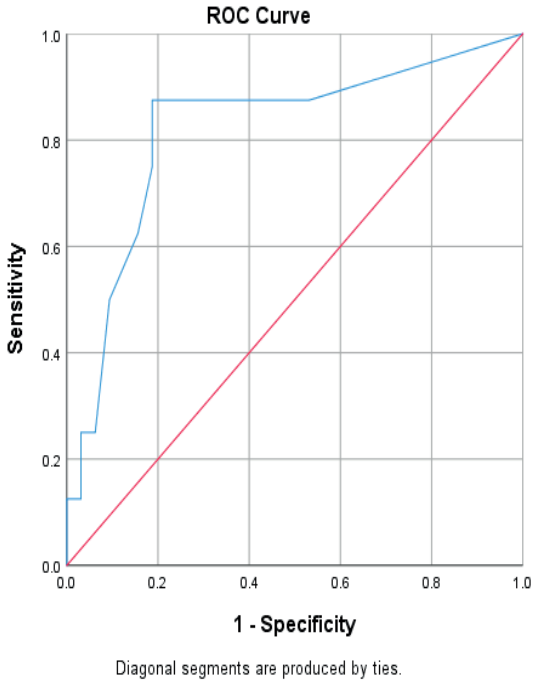
The internal consistency of the g-SDQ was assessed using Cronbach's alpha coefficient, and it was found to be 0.841, demonstrating excellent internal consistency of the questionnaire. "Corrected item–total correlations" and "Cronbach's alpha if item deleted" are presented in Table 1. The initial Cronbach's alpha for the 15 items could be improved, changing up to 0.846 after deleting specific items, but their importance regarding content validity, as well as the practically negligible increase, led to the decision to maintain the scale in its original form, following similar studies.[12],[13],[14] Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of the 15-items g-SDQ. The ROC analysis demonstrated a good accuracy of the instrument, with an area under the curve (AUC) of 0.820, as shown in Figure 1.

Table 1. Internal Consistency Indices for the 15 items of the g-SDQ.

	Corrected Item - Total Correlation	Cronbach's Alpha if Item Deleted
SDQ1	.742	.813
SDQ2	.695	.815
SDQ3	.000	.845
SDQ4	.269	.841
SDQ5	.523	.829
SDQ6	.544	.827
SDQ7	.735	.812
SDQ8	.000	.845
SDQ9	.146	.844
SDQ10	.733	.811
SDQ11	.765	.811
SDQ12	.475	.831
SDQ13	.306	.839
SDQ14	.239	.842
SDQ15	.188	.846

"Corrected Item–Total Correlation" and "Cronbach's Alpha if Item Deleted" estimations, demonstrating excellent reliability of the scale.

Figure 1. Diagnostic Accuracy of the g-SDQ. ROC curve with an AUC of 0.820, indicating good discriminative ability of the questionnaire.



ROC curve = Receiver Operating Characteristic curve

Swallowing Assessment: Correlation of the g-SDQ with the SMS, DYMUS, and 3oz WST

The correlation between the total g-SDQ score and the DYMUS score was statistically significant and positive ($r=0.860$; $p<.001$), indicating a very strong positive linear correlation between the two assessment tools. With respect to the SMS, the correlation was positive to g-SDQ ($r=0.734$; $p<.001$). In addition, a statistically significant positive correlation was found between the g-SDQ and the 3oz WST score ($r=0.482$; $p=.002$). All correlations are presented in **Table 2**.

Table 2. *Correlation Between g-SDQ Scores and Related Clinical Measures.*

		3oz WST	SDQ	DYMUS	SMS	PhVFT	CVFT
MoCA	*Pearson r*	-.201	-.376	-.268	-.368	.808	.818
	P	.213	.017	.095	.019	.000	.000
	N	40	40	40	40	40	40
3oz WST	*Pearson r*		.482	.445	.254	-.094	-.080
	P		.002	.004	.114	.565	.624
	N		40	40	40	40	40
SDQ	*Pearson r*			.860	.734	-.390	-.292
	P			.000	.000	.013	.068
	N			40	40	40	40
DYMUS	*Pearson r*				.527	-.301	-.157
	P				.000	.059	.333
	N				40	40	40
SMS	*Pearson r*					-.386	-.340
	P					.014	.032
	N					40	40
PhVFT	*Pearson r*						.825
	P						.000
	N						40

DYMUS, SMS, and 3oz WST for swallowing assessment; MoCA and VFTs (PhVFT and CVFT) for cognitive evaluation.
Pearson r: Correlation strength; p: Statistical significance; N: Sample size; 3oz WST: 3-ounce Water Swallow Test; CVFT: Categorial Verbal Fluency Test; DYMUS: Dysphagia in Multiple Sclerosis questionnaire; MoCA: Montreal Cognitive Assessment; PhVFT: Phonemic Verbal Fluency Test; SDQ: Swallowing Disturbance Questionnaire; SMS Speech Pathology-Specific Questionnaire for Persons with Multiple Sclerosis

Cognitive and Language Assessment: Correlation of the g-SDQ with the MoCA and the VFT

Statistically significant correlations between the g-SDQ and MoCA as well as VFT were observed. Specifically, a negative correlation was found for MoCA (r=-0.376; p=.017). Regarding the VFT, both its dimensions were negatively correlated to g-SDQ, with r=-0.390 (p=.013) for PhVFT and r=-0.292 (p=.068) r=0.818 for CVFT, respectively. All correlations are presented in **Table 2**.

DISCUSSION

The current study presents the adaptation and validation of the SDQ into Greek language (g-SDQ). The SDQ is a brief assessment tool designed to facilitate the early detection of dysphagia in individuals with PD, by addressing impairments associated with the oral and pharyngeal phases of the swallowing process. The g-SDQ demonstrated excellent internal consistency (α=0.846), comparable to the original version of the questionnaire (α=0.890).[11] Our results demonstrated a strong positive correlation between the g-SDQ and the other PROMs (SMS and DYMUS), indicating its convergent validity and its reliability in reflecting swallowing difficulties in a manner consistent with established, validated PROMs. Specifically, the DYMUS questionnaire had also shown a strong positive correlation with the SDQ in the study conducted by Sparaco et al.[22] A statistically significant correlation was observed between the g-SDQ and the 3oz WST, supporting the criterion validity of the tool. This finding is consistent with the literature, which suggests that the test's high sensitivity makes it a quick, non-invasive, and useful screening tool for the detection of dysphagia in individuals with PD.[18],[23]

To ensure the reliability of self-reported data,

participants with significant cognitive impairment, defined as a MoCA score below 15,[19] were excluded from the study. Severe cognitive decline can compromise a person's ability to understand and accurately respond to self-assessment tools, making their responses less valid.[24] This highlights the critical importance of pairing self-report instruments with objective cognitive measures such as the MoCA. By doing so, clinicians and researchers can determine whether individuals have the cognitive capacity to provide meaningful responses. Moreover, the use of standardised severity levels further enhances the interpretability of PROMs. When combined with robust tools like the MoCA, this approach not only improves the accuracy of symptom assessment but also supports more informed clinical decision-making by identifying when interventions are needed and when symptoms have normalised.[25]

The statistical analysis revealed a strong negative correlation between the g-SDQ and the MoCA, indicating that higher cognitive function is associated with fewer symptoms of dysphagia. This finding aligns with the literature, as cognitive decline significantly affects the swallowing mechanism across all phases of swallowing.[26],[27],[28] Similarly, the VFTs were negatively correlated with the g-SDQ, demonstrating that reduced verbal fluency may be associated with increased self-reported swallowing disturbances. In addition, both dimensions of the VFT (phonemic and categorical) were positively correlated with MoCA scores. Although a direct association between verbal fluency deficits and dysphagia has not been firmly established, the present findings suggest that the observed relationship between verbal fluency and swallowing difficulties may represent an indirect link between cognitive decline and dysphagia. Supporting this interpretation, verbal fluency has consistently been shown to be closely associated with overall cognitive performance.[29],[30]

A potential limitation of our study is the absence of an objective clinical assessment of the swallowing mechanism, such as the Video-Fluoroscopic Swallowing Study (VFSS) or the Fiberoptic Endoscopic Evaluation of Swallowing (FEES). However, the SDQ has been previously compared with both VFSS and FEES. Notably, its performance has been consistent across both the original and translated version of the SDQ,[11],[13] demonstrating good sensitivity and specificity in identifying dysphagia. Similarly, given its excellent internal consistency, reliability, and diagnostic accuracy, the g-SDQ may serve as a valuable tool for screening dysphagia in Greek-speaking PD population. Further research could strengthen these findings by combining the use of the g-SDQ with objective clinical methods, such as VFSS or FEES, to further investigate its diagnostic accuracy.

Epidemiological data from PD in Greece highlight a crude incidence of 48 cases and a mortality rate of 71 deaths per 100,000 person-years, along with a prevalence of 400 per 100,000 persons. Regional disparities were evident, with the lowest incidence in Crete (35/100,000) and the highest in Thessaly (69/100,000). The fact that mortality exceeds incidence during the study period may suggest underdiagnosis, late-stage detection, or external factors such as the COVID-19 pandemic.[31] These findings underscore the urgent need not only for improved disease surveillance and early diagnosis, but also for the development and wider implementation of effective, patient-centred therapeutic strategies to reduce disease burden and enhance quality of life for individuals living with PD. Considering the high prevalence of dysphagia in PD,[9] and its serious, potentially fatal complications,[6],[7] along with the importance of culturally and linguistically appropriate PROMs to support effective healthcare communication,[32] the translation and validation of the SDQ self-report questionnaire into Greek represents a valuable contribution to clinical practice.

CONCLUSION

Overall, this study indicates that the 15-item g-SDQ processes good psychometric properties, as well as adequate validity and reliability measurement capacities. Our results support its suitability for the preliminary screening of dysphagia in adults with PD, as well as for assessing the frequency of dysphagia-related symptoms. Analysis of g-SDQ responses may help clinicians detect subtle or intermittent swallowing disturbances that are often overlooked during routine clinical evaluations, thereby supporting more personalised and safer dietary management. Consequently, the g-SDQ stands out as a brief yet sensitive instrument for the detection and monitoring of swallowing difficulties in clinical settings within the Greek-speaking PD population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ANTIOXIDANT VITAMINS C AND E IN MIGRAINE: A NARRATIVE REVIEW

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Abstract
Background: Although the pathophysiology of migraine is still unclear, oxidative stress is implicated as part of the mechanism, while several studies have reported a redox imbalance in migraine patients.
Objective: This narrative review examines the role of the antioxidant vitamins C and E in the treatment of migraine.
Results: Observational studies suggest that increased—but balanced—consumption of dietary antioxidants, including vitamins C and E, resulted in a lower risk of migraine and a lower frequency and severity of migraine attacks, especially in women of reproductive age. In addition, other observational studies and one randomised trial provide evidence that vitamin C supplementation (when taken alone or concomitantly with other antioxidants) may be beneficial for migraine outcomes in terms of frequency, duration, and intensity. However, a cross-sectional study from Taiwan reported an increase in migraine attacks in women taking vitamin C supplements. As for vitamin E, its antioxidant and anti-inflammatory properties may help control some migraine symptoms, particularly those associated with menstrual migraine.
Conclusions: Overall, the current evidence offers some hope for the use of vitamins C and E in the treatment of migraine. Future research and randomised controlled trials may help identifying dosing and specific patient groups who might benefit from vitamin C and E supplementation.

Keywords: migraine, antioxidants, supplements, vitamin C, vitamin E

ΑΝΤΙΟΞΕΙΔΩΤΙΚΕΣ ΒΙΤΑΜΙΝΕΣ C ΚΑΙ Ε ΣΤΗΝ ΗΜΙΚΡΑΝΙΑ: ΜΙΑ ΑΦΗΓΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ

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Περίληψη
Ιστορικό: Παρόλο που η παθοφυσιολογία της ημικρανίας είναι ακόμη ασαφής, το οξειδωτικό στρες εμπλέκεται ως μέρος του μηχανισμού, ενώ αρκετές μελέτες έχουν αναφέρει μια οξειδοαναγωγική ανισορροπία σε ασθενείς με ημικρανία.
Σκοπός: Αυτή η αφηγηματική ανασκόπηση εξετάζει τον ρόλο των αντιοξειδωτικών βιταμινών C και Ε στη θεραπεία της ημικρανίας.
Αποτελέσματα: Παρατηρητικές μελέτες υποδηλώνουν ότι η αυξημένη - αλλά ισορροπημένη - κατανάλωση διαιτητικών αντιοξειδωτικών, συμπεριλαμβανομένων των βιταμινών C και Ε, είχε ως αποτέλεσμα χαμηλότερο κίνδυνο ημικρανίας και χαμηλότερη συχνότητα και σοβαρότητα των κρίσεων ημικρανίας, ειδικά σε γυναίκες αναπαραγωγικής ηλικίας. Επιπλέον, άλλες παρατηρητικές μελέτες και μία τυχαιοποιημένη δοκιμή παρέχουν στοιχεία ότι η βιταμίνης C (όταν λαμβάνεται μόνη της ή ταυτόχρονα με άλλα αντιοξειδωτικά) μπορεί να είναι ευεργετική για τα αποτελέσματα της ημικρανίας όσον αφορά τη συχνότητα, τη διάρκεια και την ένταση. Ωστόσο, μια συγχρονική μελέτη από την Ταϊβάν ανέφερε αύξηση των κρίσεων ημικρανίας σε γυναίκες που λαμβάνουν συμπληρώματα βιταμίνης C. Όσον αφορά τη βιταμίνη Ε, οι αντιοξειδωτικές και αντιφλεγμονώδεις ιδιότητές της μπορεί να βοηθήσουν στον έλεγχο ορισμένων συμπτωμάτων ημικρανίας, ιδιαίτερα εκείνων που σχετίζονται με την ημικρανία της περιόδου.
Συμπεράσματα: Συνολικά, τα τρέχοντα στοιχεία προσφέρουν κάποια ελπίδα για τη χρήση των βιταμινών C και Ε στη θεραπεία της ημικρανίας. Μελλοντική έρευνα και τυχαιοποιημένες ελεγχόμενες δοκιμές μπορεί να βοηθήσουν στον προσδιορισμό της δοσολογίας και συγκεκριμένων ομάδων ασθενών που θα μπορούσαν να ωφεληθούν από τη συμπλήρωση βιταμινών C και Ε.

Λέξεις-κλειδιά: ημικρανία, αντιοξειδωτικά συμπληρώματα, βιταμίνη C, βιταμίνη Ε

INTRODUCTION

Migraine is a common neurological condition affecting 14% of the population.[1] Despite its prevalence, only recently have the pathophysiological mechanisms begun to be elucidated. Investigating neuroinflammation and oxidative stress in relationship to migraine provides further insights into specific pathophysiological mechanisms.[2] Within this new framework antioxidant-based mechanisms are becoming promising adjunctive therapeutic targets in migraine.[3] This narrative review will explore the role of the well-studied antioxidant vitamins C and E that may reduce oxidative damage and regulate inflammation.[4,5]

The role of oxidative stress in migraine pathophysiology

While migraine's pathophysiology is not fully understood, there are two main accepted theories: the trigeminovascular system (TGVS) and cortical spreading depression (CSD). In the TGVS model, the trigeminal nerves become activated, resulting in the release of neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P, which are known mediators of neurogenic inflammation and migraine pain sensitisation. CSD is a wave of neuronal depolarisation spreading across the cortex, marked by ionic shifts and decreased brain activity. These ionic shifts increase reactive oxygen species (ROS), leading to oxidative stress and triggering pro-inflammatory pathways. Such changes may underlie the aura phase in migraine aura.[6]

Oxidative stress arises when there is an imbalance between the generation of oxidants (such as ROS) and the ability of the body to neutralise them by both enzymatic (superoxide dismutase[SOD], catalase[CAT], and glutathione peroxidase[Gpx]) and non-enzymatic (vitamin C, vitamin E, and glutathione[GSH]) antioxidants resulting in damage to important molecules such as lipid, protein, and DNA. The primary source of ROS in the brain is from mitochondria. Dysfunctional mitochondria can lead to increased levels of ROS, causing oxidative stress.[7] Additionally, migraine is associated with a specific mitochondrial disorder termed mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome which involves impaired mitochondrial function resulting in the prolonged presence of "toxic" substances, including ROS.[8] Interestingly, many recognisable migraine triggers also induce oxidative stress and are agonists of transient receptor potential cation channels, subfamily A, member 1 (TRPA1), which are located on perivascular meningeal nociceptors and second-order trigeminal neurons, detecting oxidative stress.[9,10] In animal studies, TRPA1 agonists stimulate the release of CGRP and substance P, inducing migraine attacks.[10] Oxidative stress may also be involved in cortical spreading depression (CSD) which is associated with migraine aura. Research has shown that TRPA1 activation by ROS enhances CSD, while administering antioxidants decreases the likelihood of developing CSD in vivo.[11,12] In addition, studies utilising animal models have demonstrated that CSD itself produces oxidative stress, triggering a migraine attack.[13] The role of oxidative stress in migraine pathogenesis is demonstrated in **Figure 1.**

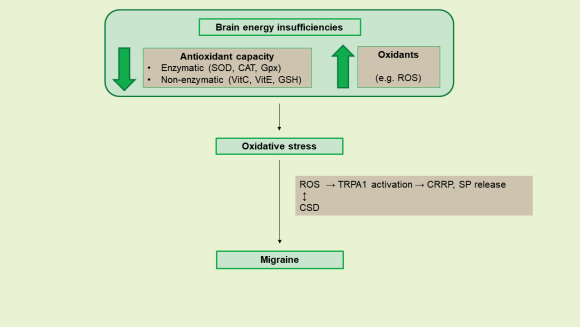

Figure 1. Schematic representation of oxidative stress role in migraine pathophysiology. SOD: superoxide dismutase; CAT: catalase; Gpx: glutathione peroxidase; VitC: vitamin C; VitE: vitamin E; GSH: glutathione; ROS: reactive oxygen species; TRPA1: transient receptor potential cation channels, subfamily A, member 1; CRRP: calcitonin gene-related peptide; SP: substance P; CSD: cortical spreading depression

Migraine is linked to brain energy insufficiencies between attacks, and these may arise from either increased energy utilisation or decreased energy production as a result of mitochondrial dysfunction.[14] Prooxidant molecules, among which are thiobarbituric acid reactive substances (TBARS), namely malonyl dialdehyde acid (MDA) and 4-hydroxynonenal, and nitric oxide have also been proposed as potential markers of oxidative stress.[15] Several research articles on oxidative stress markers in migraine individuals indicate substantial differences in redox balance compared to healthy controls (HC). Total oxidant status (TOS) and oxidative stress index (OSI) levels were elevated in migraine patients during the attack phase compared to HC.[16] Similarly, higher TOS levels were observed in patients with migraine without aura,[17] although these data were not replicated by others.[18,19] Elevated plasma MDA levels were also reported in adult migraine patients compared to controls, either during interictal periods, or independently of attack status.[20–22] On the other hand, one study of children with migraine showed significantly lower concentrations of MDA compared to HC.[23] Furthermore, some findings showed increased plasma 8-OHdG levels—more

prominently in patients with migraine without aura than in those with aura.[18] Finally, while the role of oxidative stress in migraine pathophysiology remains questionable, some interesting new evidence emerged regarding TBARS, with meta-analytic data suggesting that during attack-free periods, plasma TBARS levels were over twofold elevated in migraineurs compared to controls. The meta-analysis also suggested that individuals with migraine had increased oxidative stress due to impaired antioxidant reserves and decreased SOD activity in most studies conducted during interictal periods.[24] In addition, studies have shown that migraine patients had significantly lower GSH, glutathione-S-transferase (GST), and total antioxidant capacity (TAC) levels compared to matched controls, particularly at the ictal phases.[25] One study stated that roughly 40% of people with recurrent migraines demonstrated lower levels of TAC. Interestingly, the levels of total antioxidant status (TAS) were found lower in people with migraine without aura, although these data were not supported by a different study.[17,18] Finally, controversial data have been reported regarding levels of CAT activity in children and adolescents with migraine.[16,21,23]

Overall, these results imply that oxidative stress may be an important modulator in migraine pathophysiology and highlight antioxidant-based therapeutic strategies as potential options for migraine management.[4]

Antioxidant vitamins C and E

Dietary supplements have emerged as promising options for the management of migraine due to their antioxidant and anti-inflammatory properties.[4] Among these, vitamins C and E stand out because they have synergistic antioxidant properties; vitamin C can recycle and regenerate vitamin E from its oxidised form, thereby sustaining its protective function. Furthermore, vitamin C, being water-soluble, and vitamin E, being fat-soluble, together provide comprehensive antioxidant protection across both hydrophilic and lipophilic body compartments.[26]

Vitamin C

Vitamin C, whose active form is ascorbic acid, has a variety of biological functions. As an antioxidant, vitamin C is a high-energy electron donor to free radicals, effectively preventing free radicals from damaging cells. Moreover, it supports collagen production and helps regulate **immune responses** by reducing pro-inflammatory cytokines. In the nervous system, vitamin C contributes to the **synthesis** of **neurotransmitters** (e.g., conversion of dopamine to norepinephrine) and provides **neuroprotection** against oxidative stress.[27] The needs of Vitamin C daily intake vary by age, sex, and physiological state, and are generally in the range of 40-120 mg/day. Most can meet their daily vitamin C requirements through food, since fruits and vegetables are often a good source of vitamin C (10–100 mg/100 g).[28] Oral absorption of vitamin C is usually efficient at moderate intakes (30–180 mg per day), while levels above 1 g/day result in increasing amounts of unabsorbed vitamin C, which are eliminated in the urine. Supplementation (100–500 mg/day) may be useful in cases of deficiency, oxidative stress, or illness, though high doses (>1 g/day) offer no further benefit and may cause side effects like gastrointestinal discomfort or kidney stones.[29] Studies have demonstrated the potential benefit of using vitamin C in the treatment of a range of pathological conditions, from cancer, sepsis, and inflammation to neurological disorders such as post-shingles neuralgia, epilepsy, multiple sclerosis, and Parkinson's disease.[3,4,30,31]

Vitamin E

Vitamin E is known for its variety of biological functions. Alpha-tocopherol, the most active form, is an important antioxidant with an important function of terminating chain reactions produced by free radicals, thereby preventing lipid peroxidation and protecting cell membranes from oxidative damage. It can also inhibit the release of arachidonic acid and its enzymatic conversion to pro-inflammatory prostaglandins as part of the complex modulation of inflammatory processes.[32] In the nervous system, vitamin E helps protect from the damaging effects of excess calcium entry and lipid peroxidation.[33] The average adult's daily requirement for vitamin E is about 15 mg. Typically, a balanced diet with foods such as nuts, seeds, and vegetable oils generally supplies enough vitamin E.[34] National Institutes of Health (NIH) reports that multivitamins provide approximately 13-15 mg of vitamin E per day, while vitamin E-specific supplements often contain over 67 mg of vitamin E, which is considerably higher than the dietary requirement. The adult upper tolerable limit for vitamin E supplementation (both natural and synthetic forms) is 1,000 mg/day due to possible increased bleeding risk with higher doses. Of note, vitamin E amounts are sometimes given in International Units (IU), where 1 IU of natural vitamin E equals 0.67 mg, and 1 IU of synthetic equals 0.45 mg.[35] The protective role of vitamin E has been widely studied in conditions such as diabetes cardiovascular diseases, epilepsy and Parkinsonism.[30,33,36] **Figure 2** provides a visual summary of the mechanisms through which vitamins C and E may exert their protective effects in the context of migraine.

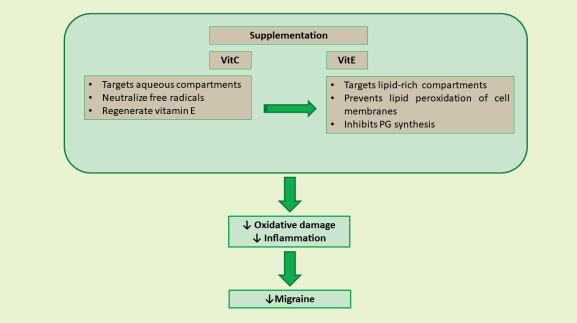

Figure 2. Representation of vitamin C and E roles in migraine treatment. VitC: vitamin C; VitE: vitamin E; PG: prostaglandin

VITAMINS C AND E IN MIGRAINE THERAPY

As more studies show that vitamin C and E supplementation can reduce markers of oxidative stress in numerous pathological conditions where inflammation and/ or oxidative stress have been implicated, the investigation of their potential role in managing migraines is promising.[37–40] The clinical studies reviewing the supplementation of vitamin C and E in migraine patients are summarised in **Table 1**.

Vitamin C

The association of vitamin C with migraine has been increasingly studied in the literature. Cross-sectional studies of American patients found that vitamin C intake was inversely associated with migraine prevalence,[41] especially in women.[42] Furthermore, other studies examined antioxidant factors, including vitamin C, reporting that higher consumption of dietary antioxidants was associated with lower migraine risk.[43–46] This finding was strongest in women of reproductive age.[43] Of note, participants benefited from moderately increased antioxidant intake, while excessive intake did not provide any additional benefit.[45,46] In addition, studies examining Iranian female patients with migraine found that increased intake of antioxidant nutrients, including vitamin C, was negatively associated with headache intensity and frequency.[47,48] Collectively, these results indicate that vitamin C may help improve migraine outcomes possibly by counteracting oxidative stress, a key factor in migraine pathophysiology, through its antioxidant properties.[3]

The positive effects of dietary vitamin C intake on migraine outcomes have prompted more research into the possible therapeutic role of vitamin C supplementation in migraine patients. Initially, Visser et al noted that the administration of vitamin C (200–1,500 mg per day) up to 50 days after wrist and ankle injury was associated with reduced incidence of complex regional pain syndrome (CRPS); given that both CRPS and migraine exhibit increased substance P and CGRP levels, as well as ROS—both disorders have been associated with neurogenic inflammation—vitamin C could be a candidate for migraine treatment as an antioxidant, as well.[49] Following this, Visser et al. conducted a (RCT) with 35 participants from Australia and evaluated the effects of NEC supplementation (600 mg N-acetylcysteine, 250 IU vitamin E, and 500 mg vitamin C) — all free radical scavengers— taken twice per day for 3 months. The NEC group (19 subjects) experienced a significant reduction in monthly headache, migraine frequency and total monthly duration, as well as pain intensity and acute abortive medication use compared to controls (16 subjects), suggesting that this antioxidant supplementation 'cocktail' may improve migraine outcomes in adults with 3 to 8 monthly migraine attacks.[50] In addition, Chayasirisobhon et al., in an uncontrolled preliminary clinical trial on 12 patients with refractory migraine in the U.S., participants received a daily antioxidant combination—120 mg pine bark extract, 60 mg vitamin C, and 30 IU vitamin E—for 3 months. Compared to their baseline, patients experienced significant decreases in headache frequency and severity.[51] Furthermore, Chayasirisobhon et al., in another uncontrolled trial involving 50 patients with chronic, treatment-resistant migraine, daily supplementation with 1,200 mg Pinus radiata bark extract plus 150 mg vitamin C over 3 months resulted in a notable decrease in headache frequency, severity, and Migraine Disability Assessment (MIDAS) scores, with sustained relief observed over a year in responders—suggesting that the antioxidant combination, including vitamin C, may help reduce migraine burden.[52] Interestingly, in a single-patient case report, an 11-year-old boy with MELAS—which is a degenerative disease attributed to oxidative phosphorylation deficiency—had decreased frequency and severity of migraine attacks following a short trial of Coenzyme Q10 (50 mg/day), vitamin B2 (100 mg twice daily), vitamin C (500 mg/day), Super B-complex with B10, alfalfa (1,000 mg/day), and a high-fat diet with 50% energy from fat.[53] Nonetheless, contrasting these positive results, a large cross-sectional study of over 15,000 adults (18-65 years) from Taiwan, Chiu et al. concluded that the use of vitamin C supplements was associated with a higher incidence of self-reported headaches or migraines among females who used these vitamin supplements compared to females who did not.[54]

In conclusion, these data indicate that vitamin C may help reduce migraine frequency and severity through its antioxidant effects. While the evidence looks promising, RCTs are needed to confirm these data.[4]

Vitamin E

Research in both humans and animals has underscored the positive effects of vitamin E on the brain and suggests that supplemental vitamin E may enhance the antioxidant capacity and help decrease oxidative stress.[33,55–57] Expanding upon this, there is a growing number of studies indicating a potential role for vitamin E in the context of migraine. In a case-control study, it was found that women with migraine had significantly lower plasma vitamin E levels compared to HC, as well as had markers indicative of increased oxidative stress. Importantly, there were no differences in vitamin E concentrations between the migraine attack and non-attack periods.[58] Similarly to vitamin C outlined above, studies showed that greater antioxidant intake, including vitamin E, was associated with a lower risk of migraine.[45,59] Of note, one study found that the strongest protective effect of dietary vitamin E against migraine frequency was observed at an intake of approximately 7.3 mg/day—beyond which no additional benefit was noted.[60] In addition to this, a reverse correlation was identified between headache frequency and consumption of increasing doses of antioxidant nutrients, among which was vitamin E.[48] Overall, these findings lend some support to the concept of a protective role of vitamin E against migraine.

Pursuant to these observational outcomes, some interventional studies specifically examined vitamin E supplementation for migraine treatments. Ziae et al. conducted a double-blind, placebo-controlled clinical trial on 72 women with menstrual migraine, using a vitamin E supplementation trial (400 units/day for 5 days beginning 2 days before menses and 3 days after, in 2 cycles), and reported a statistically significant decrease in the following migraine-related outcomes: pain severity, functional disability, photophobia, phonophobia, and nausea. This study supports a potential mechanism of vitamin E in lessening symptoms of menstrual migraines due possibly to its antioxidant properties and inhibitory effect on prostaglandin synthesis, which are thought to be involved in the pathogenesis of migraine.[61] Additionally, the previously mentioned studies by Chayasirisobhon et al. and Visser et al. found that combinations of supplements containing vitamin E reduced headache frequency, headache severity, and acute abortive medication use in migraineurs compared to controls.[50,51]

In summary, vitamin E may act as an adjunct form of antioxidant and anti-inflammatory therapy for migraines, particularly menstrual migraines.

Table 1. Summary of Clinical Studies Investigating Vitamin C and/or Vitamin E Supplementation in Patients with Migraine.

Author (Publication Year)	**Design**	**Settings**	**Intervention/Exposure**	**Participants' characteristics, N (Female%), Age**	**Results**
Visser (2020)[50]	Randomised, double-blind, sham-controlled pilot study.	Patients from Australian community.	NEC supplementation (600 mg N-acetylcysteine, 250 IU **vitamin E**, 500 mg **vitamin C**) was given twice daily for 3 months to patients with 2–8 migraines per month for at least 1 year.	NEC group=19 (89%), mean age 44.6 years Sham group=16 (81%), mean age 44.8 years	NEC treatment led to monthly reductions in migraine episodes, days, duration, intensity, and medication use.
Chiu (2014)[54]	Cross-sectional study	Representative sample from a 2005 national health survey, Taiwan.	Self-reported use of **vitamin C** and other supplements	Headache patients=3,795 (64.1%), mean age 39.2 years Headache-Free patients=11,619 (43.6%), mean age 40.7 years	Vitamin C use was associated with increased incidence of headache or migraine complaints in female participants.

Chayasirisobhon (2013) [52]	Open-label study	Outpatients, Anaheim, California, U.S.A.	1200 mg Pinus radiata bark extract and 150 mg **vitamin C** were given daily for 3 months to chronic migraineurs.	50 patients (88%), mean age 41.6 years	Twenty-nine patients (58%) showed significant improvement in MIDAS score, headache days, and severity after 3 months of treatment, with continued benefits in responders up to 12 months.
Ziae (2009)[61]	Randomised, double-blind, placebo-controlled trial	Students of Tarbiat Modarres University, Tehran, Iran	**Vitamin E** supplementation (400 IU daily for 5 days around menstruation over 2 cycles) in women with menstrual migraine	72 women, between 20-30 years old	Reduced migraine pain severity, functional disability, photophobia, phonophobia, and nausea.
Chayasirisobhon (2006) [51]	Uncontrolled, open-label study	Anaheim, California, U.S.A.	One capsule daily containing 120 mg pine bark extract, 60 mg **vitamin C**, and 30 IU **vitamin E** for 3 months in patients with chronic migraine with or without aura.	12 patients (83%), mean age 41.1 years	A significant improvement in the MIDAS score was observed after 3 months of treatment, alongside notable reductions in headache frequency and severity.
Panetta (2004) [53]	Case-report	Royal Children's Hospital and Monash Medical Centre, Melbourne, Australia	Short-term regimen including CoQ10 (50 mg/day), vitamin B2 (100 mg twice daily), **vitamin C** (500 mg/day), a Super B-complex (including B10), alfalfa (1000 mg/day), and a high-fat diet (50% calories from fat).	11-year-old male with MELAS syndrome	Reduction in the number and severity of migraine attacks.

IU: International Units; MIDAS: Migraine Disability Assessment score; CoQ10: Coenzyme Q10; MELAS: Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes. Note: Highlight in bold whether the supplement contains vitamin C and/ or vitamin E.

LIMITATIONS AND FUTURE DIRECTIONS

Although there is reasonable current evidence supporting a possible role for vitamins C and E in migraine treatment, there are important limitations to consider. First, most of the studies are observational, with many cross-sectional designs, and some evidence derives from case reports or uncontrolled, open-label studies. Importantly, in most studies, vitamins C and E were not administrated as a single intervention, but in combination with other antioxidant compounds. Therefore, it is difficult to determine the independent effect of each vitamin on migraine outcomes. To date, there is no RCT examining vitamin C- only supplementation in migraine. Only one pilot RCT has investigated a combined antioxidant regimen including vitamins C and E in migraine patients, and one double-blind RCT has assessed vitamin E supplementation specifically for menstrual migraine.[50,61]

Second, although this review has primarily focused on vitamins C and E, there are other micronutrients with antioxidant capabilities, such as riboflavin (vitamin B2), magnesium, alpha-lipoic acid, and coenzyme Q10 that have shown efficacy in the migraine setting, as indicated by several meta-analyses.[24,62,63]

Future work can help to address these limitations by implementing RCT designs that are well-designed and adequately powered, assessing both vitamins C and E as separate entities (including differences in doses and duration of treatment), and also assessing them as part of larger nutrient-based food approaches based on antioxidant consumption.

Until further evidence arises, vitamin C and E supplementation for migraine should be considered as an off-label and adjunctive treatment, at the clinician's discretion and by way of individualised patient care.

CONCLUSION

Current evidence suggests that vitamins C and E are promising adjunctive treatment options for migraine, based on their antioxidant and anti-inflammatory properties. Oxidative stress has been implicated in migraine pathophysiology, and since these two vitamins have synergistic antioxidant activities, their combined treatment effect may be more pronounced. Observational and interventional studies have shown that vitamin C and E supplementation is related to a reduction in the frequency, severity, and duration of migraine; specifically, vitamin E showed promise for menstrual migraine. Areas of uncertainty, including the dose-dependent effects and the conflicting results in certain populations, highlight the importance of future well-designed RCTs. Taking together, vitamins C and E may offer accessible and low-risk adjunctive treatments for migraine, warranting further clinical exploration.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ

Το φάρμακο αυτό τελεί υπό συμπληρωματική παρακολούθηση. Αυτό θα επιτρέψει το γρήγορο προσδιορισμό νέων πληροφοριών ασφάλειας. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες. Βλ. παράγραφο 4.8 για τον τρόπο αναφοράς ανεπιθύμητων ενεργειών.

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: AQUIPTA 10 mg δισκία. AQUIPTA 60 mg δισκία. **2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ:** AQUIPTA 10 mg δισκία: Κάθε δισκίο περιέχει 10 mg ατογκεπάντης. AQUIPTA 60 mg δισκία: Κάθε δισκίο περιέχει 60 mg ατογκεπάντης. *Έκδοχο με γνωστή δράση:* Κάθε δισκίο των 60 mg περιέχει 31,5 mg νατρίου. Για τον πλήρη κατάλογο των εκδόχων, βλ. παράγραφο 6.1. **3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ:** Δισκίο. AQUIPTA 10 mg δισκία: Λευκό έως υπόλευκο, στρογγυλό αμφίκυρτο δισκίο, διαμέτρου 6 mm και χαραγμένο με το «A» και το «10» στη μία πλευρά. AQUIPTA 60 mg δισκία: Λευκό έως υπόλευκο, ωοειδές αμφίκυρτο δισκίο, 16 mm x 9 mm και χαραγμένο με το «A60» στη μία πλευρά. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1 Θεραπευτικές ενδείξεις:** Το AQUIPTA ενδείκνυται για την προφύλαξη από την ημικρανία σε ενήλικες που έχουν τουλάχιστον 4 ημέρες ημικρανίας ανά μήνα. **4.2 Δοσολογία και τρόπος χορήγησης:** Δοσολογία: Η συνιστώμενη δόση είναι 60 mg ατογκεπάντης μία φορά την ημέρα. Τα δισκία μπορούν να λαμβάνονται με ή χωρίς τροφή. *Παράλειψη δόσης:* Μια δόση που ξεχάστηκε θα πρέπει να ληφθεί αμέσως μόλις η παράλειψη γίνει αντιληπτή. Εάν έχει ξεχαστεί για μια ολόκληρη ημέρα, η δόση που ξεχάστηκε θα πρέπει να παραλειφθεί και θα πρέπει να ληφθεί η επόμενη δόση όπως έχει προγραμματιστεί. *Τροποποιήσεις δόσης:* Οι τροποποιήσεις της δόσης για την ταυτόχρονη χρήση συγκεκριμένων φαρμακευτικών προϊόντων παρατίθενται στον Πίνακα 1 (βλ. παράγραφο 4.5).

Πίνακας 1: Τροποποιήσεις δόσης για αλληλεπιδράσεις

Τροποποιήσεις δόσης	Συνιστώμενη δόση μία φορά την ημέρα
Ισχυροί αναστολείς του CYP3A4	10 mg
Ισχυροί αναστολείς του OATP	10 mg

Ειδικοί πληθυσμοί: Ηλικιωμένοι: Η πληθυσμιακή φαρμακοκινητική μοντελοποίηση δεν δείχνει κλινικά σημαντικές διαφορές της φαρμακοκινητικής μεταξύ των ηλικιωμένων και των νεότερων ατόμων. Δεν απαιτείται προσαρμογή της δόσης σε ηλικιωμένους ασθενείς. *Νεφρική δυσλειτουργία:* Δεν συνιστάται προσαρμογή της δόσης για ασθενείς με ήπια ή μέτρια νεφρική δυσλειτουργία (βλ. παράγραφο 5.2). Σε ασθενείς με βαριά νεφρική δυσλειτουργία (κάθαρση κρεατινίνης [CLcr] 15-29 ml/λεπτό) και σε ασθενείς με νεφρική νόσο τελικού σταδίου (ΝΝΤΣ) (CLcr < 15 ml/λεπτό), η συνιστώμενη δόση είναι 10 mg μία φορά την ημέρα. Για ασθενείς με ΝΝΤΣ που υποβάλλονται σε διαλείπουσα αιμοκάθαρση, το AQUIPTA θα πρέπει να λαμβάνεται κατά προτίμηση μετά την αιμοκάθαρση. *Ηπατική δυσλειτουργία:* Δεν συνιστάται προσαρμογή της δόσης για ασθενείς με ήπια ή μέτρια ηπατική δυσλειτουργία (βλ. παράγραφο 5.2). Η ατογκεπάντη θα πρέπει να αποφεύγεται σε ασθενείς με βαριά ηπατική δυσλειτουργία. *Παιδιατρικός πληθυσμός:* Η ασφάλεια και η αποτελεσματικότητα της ατογκεπάντης σε παιδιά (ηλικίας < 18 ετών) δεν έχουν ακόμα τεκμηριωθεί. Δεν υπάρχουν διαθέσιμα δεδομένα. Τρόπος χορήγησης: Το AQUIPTA προορίζεται για από στόματος χρήση. Τα δισκία θα πρέπει να καταπίνονται ολόκληρα και δεν πρέπει να κόβονται, να θρυμματίζονται ή να μασώνται. **4.3 Αντενδείξεις:** Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα που αναφέρονται στην παράγραφο 6.1 (βλ. παράγραφο 4.4). **4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:** Σοβαρές αντιδράσεις υπερευαισθησίας: Σοβαρές αντιδράσεις υπερευαισθησίας, συμπεριλαμβανομένων της αναφυλαξίας, της δύσπνοιας, του εξανθήματος, του κνησμού, της κνίδωσης και του οιδήματος προσώπου, έχουν αναφερθεί με τη χρήση του AQUIPTA (βλ. παράγραφο 4.8). Οι περισσότερες σοβαρές αντιδράσεις έχουν εμφανιστεί εντός 24 ωρών από την πρώτη χρήση, ωστόσο, ορισμένες αντιδράσεις υπερευαισθησίας μπορεί να εμφανιστούν ημέρες μετά τη χορήγηση. Οι ασθενείς θα πρέπει να προειδοποιούνται για τα συμπτώματα που σχετίζονται με την υπερευαισθησία. Εάν εμφανιστεί αντίδραση υπερευαισθησίας, διακόψτε το AQUIPTA και ξεκινήστε την κατάλληλη θεραπεία. Ηπατική δυσλειτουργία: Η ατογκεπάντη δεν συνιστάται σε ασθενείς με βαριά ηπατική δυσλειτουργία (βλ. παράγραφο 4.2). Έκδοχα με γνωστή δράση: Τα AQUIPTA 10 mg δισκία περιέχουν λιγότερο από 1 mmol νατρίου (23 mg) ανά δισκίο, είναι αυτό που ονομάζουμε «ελεύθερο νατρίου». Τα AQUIPTA 60 mg δισκία περιέχουν 31,5 mg νατρίου ανά δισκίο, που ισοδυναμεί με 1,6% της συνιστώμενης από τον ΠΟΥ μέγιστης ημερήσιας πρόσληψης 2 g νατρίου μέσω διατροφής, για έναν ενήλικα. **4.5 Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης:** Αναστολείς του CYP3A4: Οι ισχυροί αναστολείς του CYP3A4 (π.χ. κετοκοναζόλη, ιτρακοναζόλη, κλαριθρομυκίνη, ριτοναβίρη) μπορούν να αυξήσουν σημαντικά τη συστηματική έκθεση στην ατογκεπάντη. Η συγχορήγηση της ατογκεπάντης με ιτρακοναζόλη οδήγησε σε αυξημένη έκθεση (C_{max} κατά 2,15 φορές και AUC κατά 5,5 φορές) στην ατογκεπάντη σε υγιή άτομα (βλ. παράγραφο 4.2). Οι μεταβολές στην έκθεση στην ατογκεπάντη όταν αυτή συγχορηγείται με ασθενείς ή μέτριους αναστολείς του CYP3A4 δεν αναμένεται να είναι κλινικά σημαντικές. Αναστολείς μεταφορέων: Οι αναστολείς των πολυπεπτιδίων μεταφοράς οργανικών ανιόντων (OATP) (π.χ. ριφαμπικίνη, κυκλοσπορίνη, ριτοναβίρη) μπορούν να αυξήσουν σημαντικά τη συστηματική έκθεση στην ατογκεπάντη. Η συγχορήγηση της ατογκεπάντης με εφάπαξ δόση ριφαμπικίνης οδήγησε σε αυξημένη έκθεση (C_{max} κατά 2,23 φορές και AUC κατά 2,85 φορές) στην ατογκεπάντη σε υγιή άτομα (βλ. παράγραφο 4.2). Συχνά συγχορηγούμενα φαρμακευτικά προϊόντα: Η συγχορήγηση της ατογκεπάντης με τα συστατικά αιθινυλοιστραδιόλη και λεβονοργεστρέλη των από στόματος αντισυλληπτικών, με την παρακεταμόλη, τη ναπροξένη, τη σουματριπτάνη, ή την ουμπροκεπάντη δεν οδήγησε σε σημαντικές φαρμακοκινητικές αλληλεπιδράσεις, είτε για την ατογκεπάντη είτε για τα συγχορηγούμενα φαρμακευτικά προϊόντα. Η συγχορήγηση με τη φαμοτιδίνη ή την εσομεπραζόλη δεν οδήγησε σε κλινικά σημαντικές μεταβολές στην έκθεση στην ατογκεπάντη. **4.6 Γονιμότητα, κύηση και γαλουχία:** Κύηση: Είναι περιορισμένα τα κλινικά δεδομένα σχετικά με τη χρήση της ατογκεπάντης σε εγκύους. Μελέτες σε ζώα κατέδειξαν αναπαραγωγική τοξικότητα (βλ. παράγραφο 5.3). Η ατογκεπάντη δεν συνιστάται κατά τη διάρκεια της κύησης καθώς και σε γυναίκες αναπαραγωγικής ηλικίας που δεν χρησιμοποιούν αντισύλληψη. Θηλασμός: Τα φαρμακοκινητικά δεδομένα μετά από την χορήγηση μίας εφάπαξ δόσης έδειξαν ελάχιστη μεταφορά της ατογκεπάντης στο μητρικό γάλα (βλ. παράγραφο 5.2). Δεν υπάρχουν διαθέσιμα δεδομένα σχετικά με τις επιδράσεις της ατογκεπάντης στο θηλάζον βρέφος ή τις επιδράσεις της ατογκεπάντης στην παραγωγή του γάλακτος. Τα οφέλη του θηλασμού στην ανάπτυξη και την υγεία θα πρέπει να λαμβάνονται υπόψη μαζί με την κλινική ανάγκη της μητέρας για ατογκεπάντη και τις πιθανές ανεπιθύμητες ενέργειες στο θηλάζον βρέφος από την ατογκεπάντη ή από την υποκείμενη κατάσταση της μητέρας. Γονιμότητα: Δεν υπάρχουν διαθέσιμα δεδομένα στον άνθρωπο σχετικά με την επίδραση της ατογκεπάντης στη γονιμότητα. Μελέτες σε ζώα με τη θεραπεία με ατογκεπάντη δεν κατέδειξαν αντίκτυπο στη γονιμότητα θηλυκών και αρσενικών (βλ. παράγραφο 5.3). **4.7 Επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανημάτων:** Η ατογκεπάντη δεν έχει καμία ή έχει ασήμαντη επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανημάτων. Ωστόσο, μπορεί να προκαλέσει υπνηλία σε κάποιους ασθενείς. Οι ασθενείς θα πρέπει να προσέχουν πριν οδηγήσουν ή χειριστούν μηχανήματα μέχρι να νιώσουν αρκετά βέβαιοι ότι η ατογκεπάντη δεν έχει επηρεάσει αρνητικά την απόδοσή τους. **4.8 Ανεπιθύμητες ενέργειες:** Περίληψη του προφίλ ασφάλειας: Η ασφάλεια αξιολογήθηκε σε 2.657 ασθενείς με ημικρανία που είχαν λάβει τουλάχιστον μία δόση ατογκεπάντης σε κλινικές μελέτες. Από αυτούς, 1.225 ασθενείς εκτέθηκαν στην ατογκεπάντη για τουλάχιστον 6 μήνες και 826 ασθενείς εκτέθηκαν για 12 μήνες. Σε ελεγχόμενες με εικονικό φάρμακο κλινικές μελέτες 12 εβδομάδων, 678 ασθενείς λάμβαναν τουλάχιστον μία δόση ατογκεπάντης των 60 mg μία φορά την ημέρα και 663 ασθενείς λάμβαναν εικονικό φάρμακο. Οι πιο συχνά αναφερόμενες ανεπιθύμητες ενέργειες φαρμάκου ήταν ναυτία (9%), δυσκοιλιότητα (8%) και κόπωση/υπνηλία (5%). Οι περισσότερες από τις ανεπιθύμητες ενέργειες ήταν ήπιες ή μέτριες ως προς τη βαρύτητα. Η ανεπιθύμητη ενέργεια που οδήγησε πιο συχνά σε διακοπή της θεραπείας ήταν η ναυτία (0,4%). Κατάλογος ανεπιθύμητων ενεργειών σε μορφή πίνακα: Οι ανεπιθύμητες ενέργειες που αναφέρθηκαν σε κλινικές δοκιμές και από την εμπειρία μετά την κυκλοφορία στην αγορά παρατίθενται παρακάτω ανά κατηγορία/οργανικό σύστημα και συχνότητα, με τις πιο συχνές ανεπιθύμητες ενέργειες να παρατίθενται πρώτες. Οι συχνότητες ορίζονται ως εξής: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως < 1/1.000), πολύ σπάνιες (< 1/10.000) ή μη γνωστής συχνότητας (δεν μπορούν να εκτιμηθούν με βάση τα διαθέσιμα δεδομένα). Εντός κάθε ομάδας συχνότητας, οι ανεπιθύμητες ενέργειες παρατίθενται κατά φθίνουσα σειρά σοβαρότητας.

Πίνακας 2. Ανεπιθύμητες ενέργειες που έχουν διαπιστωθεί με την ατογκεπάντη

Κατηγορία/οργανικό σύστημα	Συχνότητα	Ανεπιθύμητη ενέργεια
Διαταραχές ανοσοποιητικού συστήματος	Μη γνωστής συχνότητας	Υπερευαισθησία (π.χ., αναφυλαξία, δύσπνοια, εξάνθημα, κνησμός, κνίδωση, οίδημα προσώπου)
Μεταβολικές και διατροφικές διαταραχές	Συχνές	Μειωμένη όρεξη
Γαστρεντερικές διαταραχές	Συχνές	Ναυτία, δυσκοιλιότητα
Γενικές διαταραχές και καταστάσεις στη θέση χορήγησης	Συχνές	Κόπωση/υπνηλία
Διερευνήσεις	Συχνές	Σωματικό βάρος μειωμένο*
	Όχι συχνές	Αυξημένη ALT/AST**

* Σε κλινικές δοκιμές έχει οριστεί ως μείωση σωματικού βάρους κατά τουλάχιστον 7% σε οποιοδήποτε χρονικό σημείο.

** Σε κλινικές δοκιμές παρατηρήθηκαν περιπτώσεις αυξήσεων της ALT/AST (οριζόμενων ως ≥ 3× το ανώτατο όριο του φυσιολογικού) που συσχετίζονταν χρονικά με την ατογκεπάντη, συμπεριλαμβανομένων περιπτώσεων με δυνητικό ιστορικό θετικού αποτελέσματος σε διακοπή της χορήγησης όπου οι τιμές υποχώρησαν εντός 8 εβδομάδων από τη διακοπή της χορήγησης. Ωστόσο, η συνολική συχνότητα των αυξήσεων των ηπατικών ενζύμων μεταξύ της ομάδας ατογκεπάντης και της ομάδας εικονικού φαρμάκου ήταν παρόμοια.

Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών: Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους-κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω του εθνικού συστήματος αναφοράς που αναγράφεται παρακάτω. **Ελλάδα:** Εθνικός Οργανισμός Φαρμάκων, Μεσογείων 284, GR-15562 Χολαργός, Αθήνα, Τηλ: + 30 21 32040337, Ιστότοπος: http://www.eof.gr, http://www.kitrinikarta.gr. **Κύπρος:** Φαρμακευτικές Υπηρεσίες, Υπουργείο Υγείας, CY-1475 Λευκωσία, Τηλ: +357 22608607, Φαξ: + 357 22608669, Ιστότοπος: www.moh.gov.cy/phs. **4.9 Υπερδοσολογία:** Σε κλινικές μελέτες, η ατογκεπάντη χορηγήθηκε ως εφάπαξ δόσεις έως τα 300 mg και ως πολλαπλές δόσεις έως τα 170 mg μία φορά την ημέρα. Οι ανεπιθύμητες ενέργειες ήταν συγκρίσιμες με εκείνες που παρατηρήθηκαν σε χαμηλότερες δόσεις και δεν εντοπίστηκαν ειδικές τοξικότητες. Δεν υπάρχει γνωστό αντίδοτο για την ατογκεπάντη. Η αντιμετώπιση της υπερδοσολογίας θα πρέπει να αποτελείται από γενικά υποστηρικτικά μέτρα που περιλαμβάνουν την παρακολούθηση των ζωτικών σημείων και την παρατήρηση της κλινικής κατάστασης του ασθενούς. **6. ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 6.1 Κατάλογος εκδόχων:** Συμπολυμερές πολυβινυλοπυρρολιδόνης/βινυλεστέρα οξικού. Πολυαιθυλενογλυκόλης ηλεκτρικός εστέρας βιταμίνης Ε. Μαννιτόλη. Μικροκρυσταλλική κυτταρίνη. Νάτριο χλωριούχο. Καρμελλόζη νατριούχος διασταυρούμενη. Πυριτίου διοξείδιο κολλοειδές. Νάτριο στεατυλοφουμαρικό. **6.2 Ασυμβατότητες:** Δεν εφαρμόζεται. **6.3 Διάρκεια ζωής:** 3 χρόνια. **6.4 Ιδιαίτερες προφυλάξεις κατά τη φύλαξη του προϊόντος:** Το φαρμακευτικό αυτό προϊόν δεν απαιτεί ιδιαίτερες συνθήκες φύλαξης. **6.5 Φύση και συστατικά του περιέκτη:** AQUIPTA 10 mg δισκία: Κυψέλες από φύλλο αλουμινίου και PVC/PE/PCTFE, καθεμία από τις οποίες περιέχει 7 δισκία. Συσκευασίες που περιέχουν 28 ή 98 δισκία. AQUIPTA 60 mg δισκία: Κυψέλες από φύλλο αλουμινίου και PVC/PE/PCTFE, καθεμία από τις οποίες περιέχει 7 δισκία. Συσκευασίες που περιέχουν 28 ή 98 δισκία. Μπορεί να μην κυκλοφορούν όλες οι συσκευασίες. **6.6 Ιδιαίτερες προφυλάξεις απόρριψης:** Κάθε αχρησιμοποίητο φαρμακευτικό προϊόν ή υπόλειμμα πρέπει να απορρίπτεται σύμφωνα με τις κατά τόπους ισχύουσες σχετικές διατάξεις. **7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Γερμανία. **8. ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** EU/1/23/1750/001. EU/1/23/1750/002. EU/1/23/1750/003. EU/1/23/1750/004. **9. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ/ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ:** Ημερομηνία πρώτης έγκρισης: 11 Αυγούστου 2023. **10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ:** 05/2025. Λεπτομερείς πληροφορίες για το παρόν φαρμακευτικό προϊόν είναι διαθέσιμες στον δικτυακό τόπο του Ευρωπαϊκού Οργανισμού Φαρμάκων https://www.ema.europa.eu.

Ενημερωτικές Σελίδες...

Συνέδρια - Ημερίδες - Συμπόσια - Επιστημονικές εκδηλώσεις

2026

- **18-22 Απριλίου 2026: American Academy of Neurology Annual Meeting,** ***Chicago, USA***
- **6-8 Μαΐου 2026: European Stroke Organization Conference,** *Maastricht, the Netherlands*
- **7-9 Μαΐου 2026: 20ο Συμπόσιο Νευρολογίας,** *Κέρκυρα*
- **15-17 Μαΐου 2026: 14ο Διεθνές Συμπόσιο της εταιρείας για την έρευνα της παρεγκεφαλίδας και των αταξιών,** *Λευκωσία*
- **4-7 Ιουνίου 2026: 37ο Πανελλήνιο Συνέδριο Νευρολογίας,** *Καλαμάτα*
- **27-30 Ιουνίου 2026: EAN Congress 2026,** *Geneva, Switzerland*

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Σημειώσεις

Σημειώσεις

Σημειώσεις

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Ύλη του Περιοδικού

1. Ανασκοπικά Άρθρα: Η έκτασή τους δεν πρέπει να υπερβαίνει τις 6.000 λέξεις.
2. Εργασίες: Κλινικές ή εργαστηριακές μελέτες. Δεν πρέπει να υπερβαίνουν τις 4.000 λέξεις (συμπεριλαμβανομένων έως 6 πινάκων και εικόνων). Δεν πρέπει να έχει προηγηθεί δημοσίευσή τους σε άλλο έντυπο. Περιλαμβάνουν σελίδα τίτλου, δομημένη περίληψη, εισαγωγή, μέθοδο, αποτελέσματα, συζήτηση και βιβλιογραφία.
3. Σύντομες ανακοινώσεις και Γράμματα προς τη σύνταξη: Σχόλια για εργασίες που έχουν δημοσιευθεί ή σύντομες αναφορές σε ένα θέμα. Δεν πρέπει να υπερβαίνουν τις 1.500 λέξεις και περιλαμβάνουν έως 2 πίνακες ή εικόνες.
4. Ενδιαφέροντα περιστατικά: Όριο λέξεων 1.500, με τη σελίδα τίτλου, περίληψη και τις βιβλιογραφικές αναφορές. Επιτρέπονται μέχρι 2 εικόνες ή πίνακες.
5. Νευρολογικές Εικόνες με εκπαιδευτικό ενδιαφέρον: Όριο 4 εικόνες για το ίδιο θέμα και 200 λέξεις.
6. Επιλογές και σχολιασμός της βιβλιογραφίας.
7. Νευρολογικά Νέα - Ειδήσεις - Ενημερωτικές Σελίδες, όπως νέα της Ελληνικής Νευρολογικής Εταιρείας και συγγενών εταιρειών, ανακοινώσει συνεδρίων και άλλων εκπαιδευτικών δραστηριοτήτων.

Δομή της ύλης

Γίνονται δεκτές εργασίες στα ελληνικά ή αγγλικά.
Υποβάλλεται πάντοτε ο τίτλος, τα ονόματα των συγγραφέων και η περίληψη και στα αγγλικά.
Τα κείμενα θα πρέπει να αποστέλλονται σε μορφή Microsoft Word document.
Σελίδα τίτλου: Περιέχει τον τίτλο, τα πλήρη ονόματα των συγγραφέων, το ίδρυμα προέλευσης, τη διεύθυνση και το τηλέφωνο του υπευθύνου για την αλληλογραφία και τον καταμετρημένο αριθμό λέξεων.
Περίληψη: Παρουσιάζει τα κυριότερα σημεία της εργασίας. Δεν πρέπει να υπερβαίνει τις 250 λέξεις. Στο τέλος της παρατίθενται 3-10 λέξεις ευρετηρίου.
Αγγλική περίληψη: Παρουσιάζει σε συντομία την εργασία. Η έκτασή της είναι ως 400 λέξεις. Στην αρχή της γράφονται τα ονόματα των συγγραφέων και ο τίτλος της εργασίας στα αγγλικά.
Λέξεις-κλειδιά: έως 6 λέξεις κλειδιά.
Βιβλιογραφία: Οι βιβλιογραφικές παραπομπές αριθμούνται με αύξοντα αριθμό ανάλογα με τη σειρά εμφάνισής τους στο κείμενο (Vancouver). Όλες οι βιβλιογραφικές παραπομπές να αναφέρονται μέσα σε αγκύλες. Π.χ. Ο Smith [1] ανέφερε ότι ... και τα ευρήματα αυτά επιβεβαιώθηκαν από τον Adams και συν [2]. Αναγράφονται έως και οι 3 πρώτοι συγγραφείς. Στον πίνακα της βιβλιογραφίας περιλαμβάνονται μόνο εκείνες οι βιβλιογραφικές παραπομπές που αναφέρονται στο κείμενο και ο πίνακας συντάσσεται με αύξοντα αριθμό που αντιστοιχεί στη σειρά εμφάνισης των βιβλιογραφικών παραπομπών στο κείμενο π.χ.
Πίνακες: Γράφονται σε ξεχωριστή σελίδα, μετά το τέλος των βιβλιογραφικών αναφορών. Αριθμούνται με τη σειρά εμφάνισής τους στο κείμενο και συνοδεύονται από σύντομη επεξήγηση.
Εικόνες: Αποστέλλονται τα πρωτότυπα σχέδια ή φωτογραφίες καλής ποιότητας. Να υποβάλλονται σαν αρχεία εικόνας ξεχωριστά από το κείμενο του MS Word. Αριθμούνται με τη σειρά εμφάνισης στο κείμενο. Στο κείμενο θα πρέπει να υπάρχει σαφής παραπομπή στον τίτλο των ηλεκτρονικών αρχείων. Σε ξεχωριστή σελίδα αναγράφονται οι τίτλοι των εικόνων και οι τυχόν επεξηγήσεις.
Ιατρική Δεοντολογία: Σε περιπτώσεις ερευνών που αφορούν ανθρώπους, η έρευνα πρέπει να έχει γίνει με βάση τη διακήρυξη του Ελσίνκι (1975). Σε περιπτώσεις φωτογραφιών ασθενών, θα πρέπει να υπάρχει έγγραφη συγκατάθεση.

Συνοδευτικό έντυπο υποβαλλόμενης εργασίας

Θα πρέπει να συμπληρωθούν ΟΛΑ τα σημεία του εντύπου. Άλλη συνοδευτική επιστολή δεν είναι απαραίτητη.

Είδος άρθρου (σημειώστε μόνο ένα)

❑ Ερευνητική εργασία ❑ Βραχεία εργασία - ενδιαφέρον περιστατικό ❑ Ανασκόπηση

❑ Βραχεία ανασκόπηση ❑ Ειδικό άρθρο ❑ Γράμμα στη σύνταξη ❑ Νευρο-εικόνες

Τίτλος:

Υπεύθυνος για την αλληλογραφία συγγραφέας:

Διεύθυνση:

Τηλέφωνο: FAX: e-mail:

Επιβεβαιώστε την πληρότητα της υποβολής του χειρογράφου σας, σημειώνοντας ΟΛΑ τα παρακάτω σημεία

- ❑ Τίτλος του άρθρου στα Ελληνικά και στα Αγγλικά με μικρά γράμματα
- ❑ Ονόματα συγγραφέων στα Ελληνικά και στα Αγγλικά *(πλήρη ονόματα π.χ. Νικόλαος Παπαδόπουλος)*
- ❑ Κέντρο προέλευσης της εργασίας στα Ελληνικά και στα Αγγλικά
- ❑ Δομημένη περίληψη στα Ελληνικά και στα Αγγλικά
- ❑ Έως πέντε λέξεις ευρετηριασμού *(κατά προτίμηση από το MeSH Hellas-Βιοϊατρική Ορολογία)* στα Ελληνικά και στα Αγγλικά
- ❑ Όλα τα ονόματα των συγγραφέων στις βιβλιογραφικές παραπομπές (*μέχρι 3 και στη συνέχεια* «*και συν.*» *ή* «*et al*»)
- ❑ Η βιβλιογραφία στις τελευταίες σελίδες των άρθρων

Δήλωση

Δηλώνω υπεύθυνα ότι:

1. Όλοι οι συγγραφείς της εργασίας συμφωνούν με το περιεχόμενό της και με την υποβολή της στο περιοδικό: *Αρχεία Κλινικής Νευρολογίας.*
2. Το ίδιο κείμενο ή τα αποτελέσματα της εργασίας δεν έχουν υποβληθεί για δημοσίευση σε άλλο Ελληνικό ή ξένο περιοδικό.
3. Δηλώνω υπεύθυνα ότι δεν υπάρχει θέμα υποκλοπής πνευματικής ιδιοκτησίας (σε περίπτωση εικόνων, πινάκων ή υλικού από άλλες δημοσιεύσει έχει ζητηθεί και ληφθεί η νόμιμη άδεια η οποία και συνυποβάλλεται).
4. Δεν υπάρχουν θέματα σύγκρουσης συμφερόντων – σε περίπτωση εξωτερικής χρηματοδότησης αυτό θα πρέπει να αναφέρεται στο τέλος της εργασίας.

Ο υπεύθυνος για την αλληλογραφία συγγραφέας

(υπογραφή)