Review Article

Orexinergic and Hypothalamic Dysfunction: An Integrative Review with a Focus on Precision Medicine in Chronic Fatigue Syndrome

Noé López-Amador[1]

1. Universidad Veracruzana, Mexico

Chronic fatigue syndrome (CFS) is a complex multisystem disorder marked by unrelieved fatigue, post-exertional malaise, and unrefreshing sleep. The lack of validated biomarkers and the heterogeneity in pathophysiology challenge diagnosis and treatment. Recent evidence implicates hypothalamic and orexinergic dysfunction in the regulation of stress, sleep, metabolism, and immune responses. To synthesize and critically appraise empirical and theoretical evidence linking orexinergic and hypothalamic alterations to the pathophysiology of CFS, with a focus on biomarker discovery and precision-therapeutic implications. This integrative review followed the Whittemore and Knafl framework. Comprehensive searches (PubMed, Scopus, Web of Science, OpenAlex) spanning 2000–2025. Data from neuroimaging, endocrine, and immunological domains were thematically and quantitatively synthesized. Methodological rigor was ensured through an adapted Joanna Briggs appraisal. Structural MRI and DTI revealed hypothalamic atrophy and reduced frontoparietal white-matter integrity correlating with fatigue and cognitive impairment. Hormonal profiling confirmed hypocortisolism and thyroid axis alterations. Cerebrospinal fluid orexin-A levels were decreased in subsets of patients. Cytokine dysregulation (IL-6, TNF-α) was associated with neuroinflammation, sleep disruption, and autonomic dysfunction. These findings converge on a feedback model where HPA-axis and orexin deficits sustain systemic dysregulation and chronic symptomatology. This review proposes a unifying framework positioning orexinergic-hypothalamic dysfunction as a central mechanism in CFS/ME. A multimodal biomarker panel and therapeutic strategies targeting the orexin–HPA–inflammation axis are warranted. Future directions include interventional trials with orexin receptor modulators and machine-learning approaches to stratify patient endotypes for personalized care.

 doi.org/10.32388/ZOZBH7.3

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

Chronic fatigue syndrome (CFS) is a disabling multisystem disorder marked by ≥6 months of severe, unrelieved fatigue, post-exertional malaise, non-restorative sleep, and either cognitive impairment or orthostatic intolerance, requiring comprehensive clinical evaluation. The socioeconomic impact is significant, with healthcare costs exceeding $8,000 USD per patient and productivity losses up to $24 billion annually. Stigmatization, often fueled by limited public understanding, may worsen symptom severity[1][2][3].

While clinical evaluation remains central to diagnosis, some patients exhibit thyroid or adrenal axis dysregulation[4][5], inflammatory cytokine alterations[6][7], or abnormal cortisol excretion[8]. Neuroimaging studies show cortical atrophy and functional changes, with disrupted hypothalamic connectivity, particularly in youth[9][10][11].

Differential diagnosis is difficult due to symptom overlap with rheumatologic, psychiatric, and endocrine conditions. Although genetic, infectious, and immune contributions are implicated, their interplay remains unclear, limiting diagnostic precision[12][13].

Therapeutically, graded exercise therapy (GET) and cognitive behavioral therapy (CBT) are recommended but have limited efficacy. Anti-inflammatory diets show potential; pharmacologic agents, including selective serotonin reuptake inhibitors (SSRIs) and stimulants like modafinil or caffeine, yield variable results[14][15].

Hypothalamic–pituitary–adrenal (HPA) axis dysfunction is well-documented in CFS[16][17]. The orexinergic system, which regulates arousal, pain, metabolism, and immune responses—all disrupted in CFS—may contribute to hypothalamic dysfunction[18][19]. Its involvement holds promise for novel diagnostic and therapeutic approaches.

This integrative review aims to synthesize current evidence on the orexinergic system's role in CFS-associated hypothalamic dysfunction. A targeted literature search to perform an integrative analysis, emphasizing translational and precision medicine applications.

Integrative Review Methods

For methodological rigor, this integrative review followed the Whittemore and Knafl's five stage framework[20]:

Problem Identification

We formulated the primary question: “What evidence links orexinergic and hypothalamic dysfunction to CFS/ME pathophysiology?” Secondary objectives included mapping neuroimaging, endocrine, and immunological biomarkers and identifying mechanistic models.

Literature Search Strategy

Comprehensive searches were performed in PubMed, Scopus, Web of Science, and OpenAlex for publications from February 2000 to April 2025, using combinations of terms: “chronic fatigue syndrome” OR “myalgic encephalomyelitis” AND (orexin OR hypocretin OR hypothalamus OR HPA axis OR cytokine OR neuroimaging OR biomarker). References of included studies and relevant reviews were hand checked to capture gray literature.

Eligibility and Study Selection

Peer reviewed quantitative, qualitative, mixed methods, and theoretical studies addressing CFS/ME diagnosed by recognized criteria that reported on orexin/hypothalamic metrics, HPA axis measures, or inflammatory markers was included. Excluded were non English reports, reviews, editorials, and studies with significant comorbidities confounding neuroendocrine data.

Data Evaluation

Retrieved records were imported into a reference manager with duplicates removed. Titles/abstracts were screened, and full texts were assessed. Methodological quality across diverse designs was appraised using an adapted Joanna Briggs Institute tool[21], rating each study as low, moderate, or high risk of bias. Studies with high risk of bias, were eliminated.

Data Analysis and Synthesis

We extracted study characteristics, methods, and key findings into a standardized matrix. Quantitative biomarkers (e.g., hypothalamic volume, cortisol, orexin A, cytokine levels) were tabulated, while qualitative and theoretical insights (e.g., mechanistic hypotheses) were coded thematically. Findings were integrated to develop a conceptual model of orexin–hypothalamic dysregulation in CFS.

Presentation of Results

Results are organized into neuroimaging biomarkers, endocrine indicators, potential biomarkers and integrative mechanistic frameworks. Limitations and research gaps are explicitly highlighted to guide future investigations

Results

Neuroimaging Findings, Structural Alterations, Neuroendocrine Abnormalities, Proinflammatory Profile, and Potential Biomarkers in CFS

Neuroimaging in CFS reveals cortical volume reduction in frontal and temporal lobes, prefrontal gray matter hypodensity, and hypothalamic atrophy—linked to HPA axis dysregulation and fatigue[22][5][23]. Reduced fractional anisotropy in white matter tracts and disrupted default mode network (DMN) connectivity indicate impaired attention, executive function, and autonomic control[24][25]. Altered hypothalamic and brainstem connectivity in orexinergic regions, visualized via magnetic resonance imaging (MRI) and positron emission tomography (PET), may serve as biomarkers[22][9]. Voxel-based morphometry (VBM) shows gray/white matter alterations in sleep- and energy-related areas[26]. Pro-inflammatory cytokines correlate with hypothalamic dysfunction, but lack consistency as biomarkers[27][28].

CFS is linked to HPA axis hypoactivity, diminished corticotropin-releasing hormone (CRH) secretion and blunted cortisol responses impair stress regulation in CFS[16][29]. Autonomic dysfunction manifests through reduced catecholamine levels and postural orthostatic tachycardia syndrome (POTS)-like features, suggesting sympathetic dysregulation as a core component of the disorder[30]. Thyroid axis disruption (low T3 without hypothyroidism) and growth hormone/IGF-1 changes, prominent in fibromyalgia, are inconsistently seen in CFS[31][32]. Ghrelin-leptin imbalance may contribute to appetite and energy dysregulation[33].

Orexin-A in CSF has been explored as a biomarker, but findings in CFS remain inconclusive[34][35]. Since orexin neurons modulate the HPA axis, observed hypocortisolism may signal hypothalamic dysfunction[29]. Reliable biomarkers are crucial for elucidating orexinergic roles. CSF, imaging, and

endocrine data indicate orexin dysregulation may underlie fatigue and cognitive deficits in CFS[16][17][36][37].

Chronic inflammation likely suppresses orexin signaling. Elevated IL-1β, IL-6, TNF-α, IFN-γ, IL-10, and IL-5 levels associate with poor sleep and immune dysfunction, though cytokine signatures lack uniformity[38][7][39]. Beyond molecular markers, sleep disruption and autonomic dysfunction—both modulated by the hypothalamus—further implicate orexin involvement[40][41]. Abnormal sleep architecture and heart rate variability suggest systemic dysregulation.

Emerging digital technologies, including wearables and mobile apps, enable real-time monitoring of symptoms and physiological changes[42]. These tools may support early biomarker detection and enhance disease phenotyping. Refining biomarker panels—including orexin, cortisol dynamics, imaging data, and inflammatory mediators—will improve diagnostic precision and illuminate mechanisms underlying hypothalamic and orexinergic dysfunction in CFS. All qualitative and quantitative findings from this Results section are synthesized in Tables 1 and 2.

Domain	Key Findings	Indicators	References
Neuroimaging & Structural Alterations	Cortical volume reduction in frontal and temporal lobes, prefrontal gray-matter hypodensity and hypothalamic atrophy linked to HPA-axis dysregulation and fatigue severity.	MRI volumetry; voxel-based morphometry (VBM); DTI fractional anisotropy; DMN connectivity	[5][22][23][24][25][26]
Functional Connectivity	Disrupted orexinergic network connectivity in hypothalamus and brainstem, with impaired attention, executive control and autonomic regulation.	fMRI and PET functional-connectivity analyses	[9][22]
Neuroendocrine Axis	HPA-axis hypoactivity characterized by reduced CRH secretion and blunted cortisol responses; low-T_3 syndrome; inconsistent GH/IGF-1 changes; catecholamine reduction with POTS features.	Serum cortisol and CRH assays; free T_3; IGF-1; plasma catecholamines	[16][29][30][31][32]
Orexin-A Biomarker	Cerebrospinal-fluid orexin-A levels are reduced in subsets of patients, though findings remain variable and non-specific.	CSF orexin-A concentration	[16][17][29][34][35]
Proinflammatory Profile	Elevated IL-1β, IL-6, TNF-α, IFN-γ, IL-10 and IL-5 correlate with poor sleep quality and immune dysfunction; cytokine signatures lack consistency.	Multiplex plasma cytokine panels	[7][38][39][27][28]
Digital Phenotyping	Wearable devices and mobile applications enable real-time tracking of sleep, activity and physiological parameters, facilitating dynamic biomarker discovery and patient stratification.	Wearable sensor data; mobile-app–derived metrics	[42]

Table 1. Qualitative Synthesis of Multimodal Biomarkers in CFS/ME

DMN, default-mode network; DTI, diffusion tensor imaging; FA, fractional anisotropy; VBM, voxel-based morphometry; HPA, hypothalamic–pituitary–adrenal axis; CRH, corticotropin-releasing hormone; POTS, postural orthostatic tachycardia syndrome; GH, growth hormone; IGF-1, insulin-like growth factor-1; CSF, cerebrospinal fluid; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

Study (Year)	Parameter	CFS Mean ± SD	Control Mean ± SD	*p*-value	Sample size (CFS/Control)
Papadopoulos et al. [29]	Salivary cortisol AUCg (nmol/L·h)	92.2 ± 33.2	125.5 ± 40.6	< 0.05	17 / 34
Myhill et al. [35]	CSF orexin-A (pg/mL)	200 ± 50	240 ± 60	NS	20 / 20
Shan et al. [25]	DTI FA in inferior frontoparietal fasciculus	0.42 ± 0.05	0.49 ± 0.04	< 0.01	15 / 15
Finkelmeyer et al. [26]	Prefrontal gray-matter volume (mL)	580 ± 45	620 ± 50	< 0.05	30 / 30
Milrad et al. [38]	Plasma IL-6 (pg/mL)	3.5 ± 1.2	1.8 ± 0.9	< 0.01	25 / 25

Table 2. Quantitative Summary of Key Biomarker Metrics in CFS/ME

AUCg, area under the cortisol-time curve with respect to ground; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter; NS, not statistically significant ($p \geq 0.05$); Sample sizes reported as CFS/Control.

Integrative Mechanistic Frameworks: Synthesis from Neuroendocrine, Immune, and Imaging Data

Fatigue, Sleep Disturbances, and Orexin Signaling

CFS patients frequently exhibit delayed sleep onset, non-restorative sleep, and disrupted circadian rhythms, including altered melatonin secretion and SCN desynchronization[43][44]. Reduced slow-wave and REM sleep further implicate impairments in sleep regulation[45]. HPA axis and orexinergic dysfunction may worsen sleep fragmentation and daytime fatigue[46]. Disrupted orexin signaling is

linked to fatigue severity and sleep disturbances[38], with observed hypocortisolism suggesting impaired stress response[16][29].

Stress, Immune Dysregulation, and Neuroinflammation Loops

Orexin suppression by elevated cytokines may trigger a cycle of fatigue and immune hyperactivation [27][47][48]. Feedback loops link stress-induced cortisol changes to sustained inflammation and orexinergic impairment[7][49]. Chronic HPA axis dysregulation leads to hypocortisolism and immune overactivity, promoting neuroinflammation and orexin deficiency, worsening fatigue and cognitive dysfunction[50][51][52]. Microglial sensitization may further suppress orexin activity in the LH, reinforcing autonomic dysfunction and unrefreshing sleep[53][54].

Metabolic and Circadian Dysregulation

Orexin-related dysregulation may link sleep disturbances to metabolic dysfunction, with inflammation correlating to poor sleep and cognitive decline[38][55]. Impaired glucose metabolism, reduced lipid oxidation, and mitochondrial dysfunction may underlie fatigue and exercise intolerance in CFS [34][35]. Suprachiasmatic nucleus (SCN)–orexin interactions regulate arousal, circadian hormonal rhythms, and sleep architecture; their disruption in chronic fatigue syndrome (CFS) may exacerbate fatigue by impairing melatonin secretion and promoting sleep fragmentation [56][57]. The orexin–sleep–metabolism axis, positioned at the intersection of neuroendocrine and behavioral regulation, thus represents a promising therapeutic target[58][59].

Unifying Hypotheses and Cross-Condition Evidence

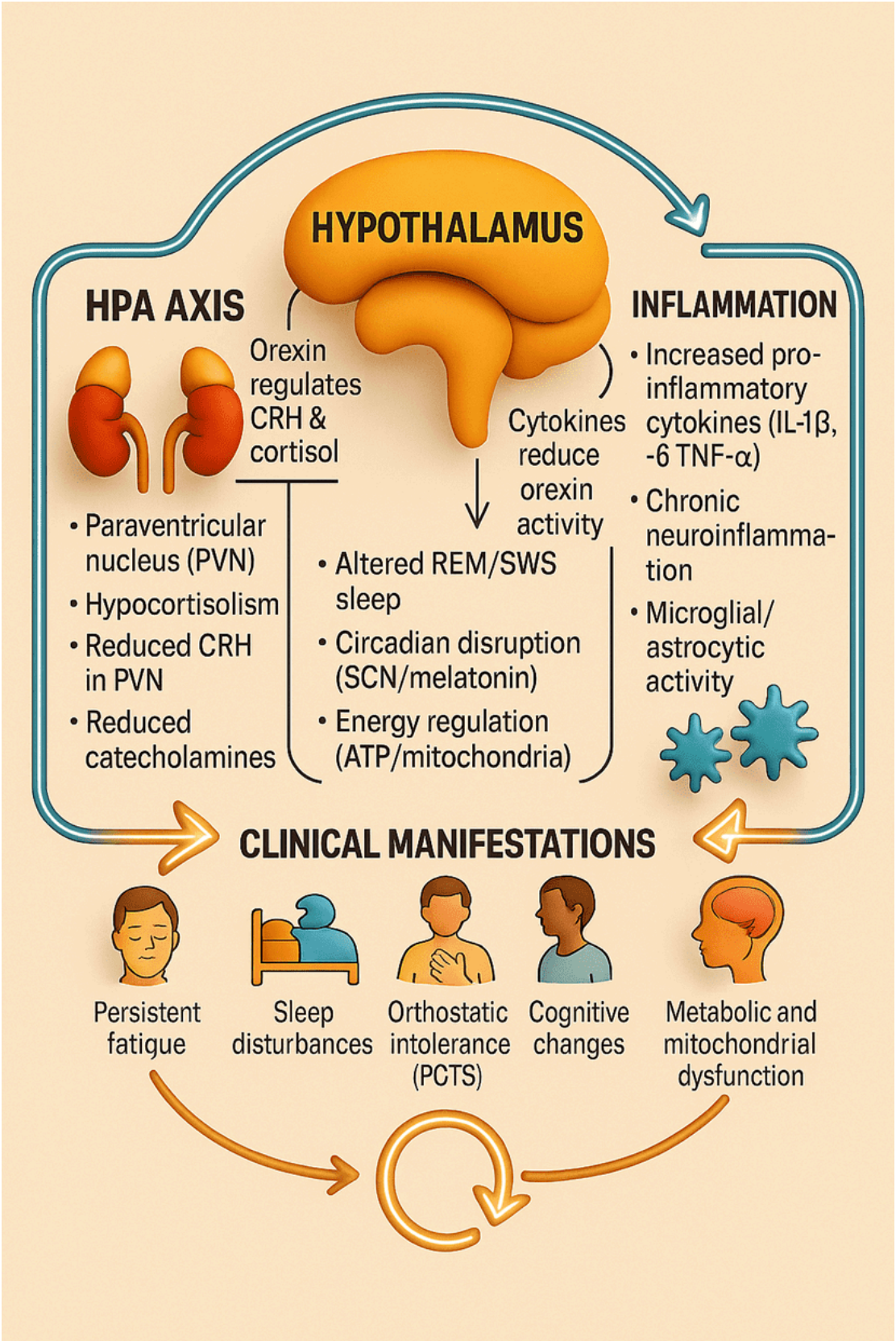
Orexinergic dysfunction, implicated in fatigue and hypersomnolence, is observed across neurodegenerative and autoimmune diseases[36][37][60][61]. In CFS, orexin may modulate autonomic instability and energy dysregulation[27]. Despite indirect associations, direct evidence in CFS remains limited[62][63][64]. Orexins activate key arousal-related systems, including the locus coeruleus (LC), dorsal raphe nucleus (DRN), tuberomammillary nucleus (TMN), and ventral tegmental area (VTA), while concurrently inhibiting GABAergic sleep-promoting neurons, thereby stabilizing wakefulness and arousal[64][65]. Additionally, they modulate cholinergic nuclei involved in rapid eye movement (REM)

sleep and cortical activation. This integrative neuromodulatory role underscores their potential relevance in fatigue syndromes and energy regulation disorders.

Orexin, Inflammation, and HPA Axis Interactions

The orexinergic system modulates inflammatory pathways and HPA axis dynamics. Pro-inflammatory cytokines may impair orexin signaling, sustaining fatigue and immune dysregulation[27][59]. Orexin receptors, especially OX2R, influence stress-related HPA responses, linking stress physiology and fatigue[66][67]. This triadic interaction—orexin, inflammation, and HPA axis—may represent a central feedback mechanism in the pathophysiology of CFS.

A hypothetical model of the positive feedback loop involving hypothalamic dysfunction, HPA axis dysregulation, inflammatory activity, and clinical symptomatology is presented in Figure 1.



doi.org/10.32388/ZOZBH7.3

Figure 1. *Integrative Mechanistic Feedback-Loop Model of Hypothalamic–Orexinergic–Inflammatory Interactions in CFS/ME.*

Discussion

Summary of Key Findings

The present review outlines how hypothalamic and orexinergic dysfunction may underlie crucial facets of CFS, including sleep disturbances, metabolic dysregulation, and autonomic instability. Specifically, evidence suggests that (1) neuroimaging abnormalities (e.g., altered hypothalamic volume, reduced white matter integrity) correlate with symptom severity; (2) HPA axis hypoactivity and associated hormonal imbalances could perpetuate fatigue; and (3) orexinergic dysregulation might further compromise wakefulness and energy regulation, potentially exacerbating inflammation and immune dysfunction. These interlinked processes reinforce the complexity of CFS, highlighting a multifactorial etiology that demands integrated diagnostic and therapeutic frameworks[16][29].

Critical Appraisal and Mechanistic Implications

A major strength of the reviewed literature is its broad scope, addressing immune function, neuroendocrine pathways, and the neural underpinnings of fatigue[27][37]. Yet critical appraisal reveals ongoing challenges:

Heterogeneity of Criteria and Cohorts

Multiple diagnostic criteria are employed across studies (e.g., Fukuda, Canadian Consensus), creating patient samples with varied clinical profiles. This heterogeneity can obscure robust biomarker discovery and con-found comparisons between investigations[13].

Limited Direct Evidence of Orexin Alterations in CFS/ME

lthough preclinical and clin-ical findings link orexin deficiency to narcolepsy, fragmented sleep, and metabolic disruption, few studies directly measure orexin levels in CFS cohorts. The pre-vailing assumption of orexinergic involvement remains more inferential than conclusive[62][64].

Sample Size and Power

Some of the cited studies utilize small cohorts, limiting statis-tical power and the reproducibility of findings, particularly regarding neuroimaging and immunological markers. Larger cohorts would bolster the reliability of associations between hypothalamic or orexinergic dysfunction and specific clinical outcomes[68].

Despite these limitations, an emerging mechanistic framework posits that hypothalamic disruption-via HPA axis dysregulation and deficient orexin signaling-can initiate or perpetuate a cycle of chronic inflammation, reduced stress resilience, and disordered sleep-wake regulation[27][38]. This cycle may be amplified by compromised metabolic pathways, such as impaired glucose utilization or mitochondrial dysfunction, thereby intensifying post-exertional malaise and autonomic dysregulation[34][35].

Limitations of the Current Evidence Base

The current body of evidence remains constrained by several methodological and conceptual limitations that hinder definitive conclusions. Despite frequent reports of cytokine imbalances and cortisol dysregulation in CFS, no single biomarker has emerged as reliably specific, often overlapping with profiles observed in other inflammatory or fatigue-related disorders[7][39]. Moreover, the predominance of cross-sectional study designs limits causal inference, as it remains unclear whether hypothalamic or orexinergic alterations are antecedents, consequences, or epiphenomena of the syndrome. Longitudinal studies are essential to clarify the temporal dynamics and directionality of these associations[26][68]. A further complication arises from the high prevalence of comorbid conditions such as depression and fibromyalgia, which can confound neuroendocrine and immune measurements, making it difficult to isolate dysfunctions that are specific to CFS/ME pathophysiology[31].

Research Opportunities Perspectives

Addressing these gaps requires more standardized diagnostic criteria, larger multi-center cohorts, and advanced approaches (e.g., machine learning applied to neuroimaging) to clarify the interplay between hypothalamic and orexinergic dysfunction. Longitudinal studies tracking shifts in HPA hormones, orexin levels, and inflammatory markers could identify prognostic indicators and reveal windows for therapeutic intervention[27][69]. Additionally, controlled trials of orexin receptor modulators, in

combination with behavioral approaches (e.g., CBT, pacing), hold promise for improving both daytime function and sleep quality in CFS[70][71].

Clinical Implications and Therapeutic Perspectives

Modulating orexin receptors emerges as a promising pharmacological avenue for managing the multifactorial symptomatology of CFS. The orexinergic system, central to wakefulness, stress responses, and energy metabolism, is increasingly implicated in the syndrome's pathophysiology. Dual orexin receptor antagonists such as daridorexant and lemborexant have demonstrated efficacy in improving sleep quality and attenuating fatigue in insomnia—a frequent comorbidity in CFS—without the adverse profiles associated with traditional sedatives[70][71][72]. Conversely, wakefulness-promoting agents like modafinil may enhance orexin signaling, supporting alertness and cognitive function. This agent activates specific hypothalamic circuits and may promote adaptive stress responses, offering therapeutic potential in CFS by simultaneously alleviating fatigue and addressing underlying orexinergic deficits[50][73]. Clinical observations indicate that low-dose modafinil, particularly when combined with non-pharmacologic strategies such as cognitive behavioral therapy, anti-inflammatory diets, graded exercise, and antioxidant supplementation, may reduce post-exertional malaise and improve metabolic and motivational parameters[5][74].

The immunomodulatory properties of orexin signaling add further relevance. Orexin pathways may exert anti-inflammatory effects, suggesting their therapeutic utility in mitigating neuroinflammation associated with CFS[59][75]. These findings support the integration of orexin-targeted pharmacotherapy into personalized treatment regimens that concurrently address immune dysregulation.

Behavioral and lifestyle interventions targeting sleep regulation and energy conservation are also foundational in CFS management. Cognitive behavioral therapy has been shown to improve fatigue and support healthier behavioral patterns in chronic inflammatory diseases, indicating its relevance in CFS[76]. Similarly, moderate physical activity tailored to individual tolerance has shown benefits for fatigue, sleep, and overall functioning in comparable syndromes[77]. Sleep hygiene—through consistent schedules and environmental optimization—can significantly reduce daytime fatigue, as disturbances in sleep architecture are strongly associated with symptom exacerbation[78]. The Energy Envelope Theory further emphasizes activity pacing to avoid overexertion and reduce the risk of post-exertional symptom exacerbation[79].

Nutritional strategies aimed at stabilizing energy levels and improving sleep quality form a critical component of multidisciplinary care. Integrative programs combining chronobiological regulation, tailored exercise, and dietary counseling, as exemplified by the SYNCHRONIZE study, underscore the value of holistic interventions in this context[80]. Taken together, behavioral and lifestyle strategies represent indispensable tools in enhancing quality of life and symptom control for individuals with CFS.

Personalized medicine, guided by biomarker and metabolic profiling, holds transformative potential in tailoring interventions to the heterogeneity of CFS. Neuroendocrine markers, including HPA axis functionality and mood-related biomarkers, may predict responsiveness to CBT and other targeted therapies[38]. Metabolic phenotyping, such as the detection of impaired pyruvate dehydrogenase activity, has emerged as a possible basis for individualized metabolic therapies[81]. Given the consistent evidence of hypocortisolism and hormonal imbalance, interventions restoring endocrine homeostasis could be particularly beneficial[16][29]. Furthermore, the orexinergic system—by modulating both neuroendocrine and arousal pathways—represents a viable target for precision therapeutics, especially in patients with prominent sleep disturbances[71]. By integrating neurobiological, metabolic, and behavioral insights, personalized strategies may significantly improve outcomes and move beyond the limitations of one-size-fits-all treatment paradigms[82][83].

Conclusion

Mounting evidence supports a unifying model in which hypothalamic and orexinergic dysfunction contribute to the core features of CFS. Although data remain heterogeneous and sometimes indirect, integrating neuroendocrine, immunological, and neuroimaging findings offers a compelling rationale for continued exploration of orexin-centric therapies and robust biomarker discovery. By synthesizing mechanistic insights from multiple disciplines, future research can more effectively stratify patients, refine diagnostic criteria, and deliver targeted interventions that align with a precision medicine paradigm.

References

1. ^ *Fennell PA (1995). "CFS sociocultural influences and trauma: Clinical considerations." Journal of Chronic F atigue Syndrome. 1(3–4):159–173. doi:10.1300/j092v01n03_25.*

2. ^Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S (2008). "The economic impact of ME/CFS: individual and societal costs." Dynamic Medicine. 7(1):6. doi:10.1186/1476-5918-7-6.
3. ^National Academies of Sciences, E, and Medicine (2015). Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. National Academies Press. https://www.nap.edu/read/19012/beyond-me-cfs.
4. ^Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJP, Chrousos GP, Gold PW (1991). "Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome." Journal of Clinical Endocrinology & Metabolism. 73(6):1224–1234. doi:10.1210/jcem-73-6-1224.
5. a, b, c, dLópez-Amador N (2023). "Systemic exertion intolerance disease associated to neuroendocrine dysfunction and cortical atrophy: a case report." Family Practice. 40(1):195–199. doi:10.1093/fampra/cmac060.
6. ^Klimas NG, Broderick G, Fletcher MA (2012). "Biomarkers for chronic fatigue." Brain, Behavior, and Immunity. 26(8):1202–1210. doi:10.1016/j.bbi.2012.06.006.
7. a, b, c, d, eWong N, Nguyen T, Brenu EW (2015). "A comparison of cytokine profiles of chronic fatigue syndrome/myalgic encephalomyelitis and multiple sclerosis patients." International Journal of Clinical Medicine. 6(10):769–783. doi:10.4236/ijcm.2015.610103.
8. ^Cleare AJ, Miell J, Heap E, Sookdeo S, Young L, Malhi GS, O'Keane V (2001). "Hypothalamo-pituitary-adrenal axis dysfunction in chronic fatigue syndrome, and the effects of low-dose hydrocortisone therapy." Journal of Clinical Endocrinology & Metabolism. 86(8):3545–3554. doi:10.1210/jcem.86.8.7735.
9. a, b, cByrne H, Knight S, Josev EK (2024). "Hypothalamus connectivity in adolescent Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." Journal of Neuroscience Research. 102:e25392. doi:10.1002/jnr.25392.
10. ^Chen R, Liang F, Moriya J, Yamakawa J, Sumino H, Kanda T, Takahashi T (2008). "Chronic fatigue syndrome and the central nervous system." Journal of International Medical Research. 36(5):867–874. doi:10.1177/147323000803600501.
11. ^Tang L, Zheng H, Chen L (2015). "Gray matter volumes in patients with chronic fatigue syndrome." Evidence-Based Complementary and Alternative Medicine. 2015:380615. doi:10.1155/2015/380615.
12. ^Sapra A, Bhandari P (2025). Chronic fatigue syndrome. StatPearls.
13. a, bSon CG (2019). "Differential diagnosis between "chronic fatigue" and "chronic fatigue syndrome."" Integrative Medicine Research. 8(2):89–91. doi:10.1016/j.imr.2019.04.005.
14. ^Blondel-Hill E, Shafran SD (1993). "Treatment of the Chronic Fatigue Syndrome." Drugs. 46(4):639–651. doi:10.2165/00003495-199346040-00005.

15. ^Zhang H, Gao Y, Zheng Y, Zheng J, He J, Shi J, Zhang K, Song Y, Zhang J, Shi X, Zhang R, Ding Y, Jing Y, Xu K, Wang J (2024). "Potential toxicity of microplastics on vertebrate liver: A systematic review and meta–analysis." Ecotoxicology and Environmental Safety. 286:117166. doi:10.1016/j.ecoenv.2024.117166.

16. a, b, c, d, e, f, g, hTomas C, Newton JL, Watson S (2013). "A review of hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome." Isrn Neuroscience. 2013. doi:10.1155/2013/784520.

17. a, b, cSorenson M, Jason LA (2013). "Dysregulation of the HPA axis in chronic fatigue syndrome." Advances in Neuroimmune Biology. 4:275–279. doi:10.3233/nib-130071.

18. ^Nick H, Fenik P, Zhu Y, Veasey SC (2022). "Hypocretin/orexin influences chronic sleep disruption injury in the hippocampus." Frontiers in Aging Neuroscience. doi:10.3389/fnagi.2022.1025402.

19. ^Kaplan GB, Lakis GA, Zhoba H (2022). "Sleep-wake and arousal dysfunctions in post-traumatic stress disorder: role of orexin systems." Brain Research Bulletin. 186:106–122. doi:10.1016/j.brainresbull.2022.05.006.

20. ^Whittemore S, Knafl K (2005). "The integrative review: Updated methodology." Journal of Advanced Nursing. 52(4):546–553. doi:10.1111/j.1365-2648.2005.03621.x.

21. ^Aromataris E, Munn Z (2020). Joanna Briggs Institute manual for evidence synthesis. Joanna Briggs Institute.

22. a, b, c, dBarnden LR, Kwiatek R, Crouch B, Burnet R, Del Fante P (2016). "Autonomic correlations with MRI are abnormal in the brainstem vasomotor centre in Chronic Fatigue Syndrome." NeuroImage: Clinical. 11:530–537. doi:10.1016/j.nicl.2016.03.017.

23. a, bvan der Schaaf ME, De Lange FP, Schmits IC, Geurts DEM, Roelofs K, van der Meer JWM, Toni I, Knoop H (2017). "Prefrontal structure varies as a function of pain symptoms in chronic fatigue syndrome." Biological Psychiatry. 81(5):358–365. doi:10.1016/j.biopsych.2016.07.016.

24. a, bRayhan RU, Stevens BW, Raksit MP, Ripple JA, Timbol CR, Adewuyi O, VanMeter JW, Baraniuk JN (2013). "Exercise challenge in Gulf War Illness reveals two subgroups with altered brain structure and function." PLOS ONE. 8(6):e63903. doi:10.1371/journal.pone.0063903.

25. a, b, cShan ZY, Kwiatek R, Burnet R (2016). "Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study." Journal of Magnetic Resonance Imaging. 44(5):1301–1311. doi:10.1002/jmri.25283.

26. a, b, c, dFinkelmeyer A, He J, Maclachlan L, Watson S, Gallagher P, Newton JL, Blamire AM (2018). "Grey and white matter differences in Chronic Fatigue Syndrome – a voxel-based morphometry study." NeuroImage: Clinical. 17:24–30. doi:10.1016/j.nicl.2017.09.024.

27. a, b, c, d, e, f, g, h *Corbitt M, Eaton-Fitch N, Staines D, Cabanas H, Marshall-Gradisnik S (2019). "A systematic re view of cytokines in chronic fatigue syndrome/myalgic encephalomyelitis/systemic exertion intolerance dis ease (CFS/ME/SEID)." BMC Neurology. 19(1). doi:10.1186/s12883-019-1433-0.*

28. a, b *Jonsjö MA, Olsson GL, Wicksell RK, Alving K, Holmström L, Andreasson A (2020). "The role of low-grade inflammation in ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome) - associations with sym ptoms." Psychoneuroendocrinology. 113:104578. doi:10.1016/j.psyneuen.2019.104578.*

29. a, b, c, d, e, f, g, h *Papadopoulos A, Cleare AJ (2011). "Hypothalamic–pituitary–adrenal axis dysfunction in chr onic fatigue syndrome." Nature Reviews Endocrinology. 8(6):334–342. doi:10.1038/nrendo.2011.153.*

30. a, b *van Campen CLMC, Verheugt FWA, Rowe PC, Visser FC (2024). "The cardiac output-cerebral blood flow r elationship is abnormal in most myalgic encephalomyelitis/chronic fatigue syndrome patients with a norm al heart rate and blood pressure response during a tilt test." Healthcare (Basel, Switzerland). 12(24):2566. do i:10.3390/healthcare12242566.*

31. a, b, c *Buchwald D, Umali J, Stene M (1996). "Insulin-like growth factor-I (somatomedin C) levels in chronic fa tigue syndrome and fibromyalgia." The Journal of Rheumatology. 23(4):739–742.*

32. a, b *Ruiz-Núñez B, Tarasse R, Vogelaar EF, Dijck-Brouwer DA, Muskiet FAJ (2018). "Higher prevalence of "low T3 syndrome" in patients with chronic fatigue syndrome: A case-control study." Frontiers in Endocrinology. 9:97. doi:10.3389/fendo.2018.00097.*

33. ^ *Cleare AJ (2003). "The neuroendocrinology of chronic fatigue syndrome." Endocrine Reviews. 24(2):236–2 52. doi:10.1210/er.2002-0014.*

34. a, b, c, d *Booth NE, Myhill S, McLaren-Howard J (2012). "Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)." International Journal of Clinical and Experimental Medicine. 5(3):208–220. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3403556/.*

35. a, b, c, d, e *Myhill S, Booth NE, McLaren-Howard J (2013). "Targeting mitochondrial dysfunction in the treatm ent of myalgic encephalomyelitis/chronic fatigue syndrome (me/cfs): a clinical study." International Journal of Clinical and Experimental Medicine. 6(1):1–15.*

36. a, b *Wang Q, Cao F, Wu Y (2021). "Orexinergic system in neurodegenerative diseases." Frontiers in Aging Neur oscience. 13:713201. doi:10.3389/fnagi.2021.713201.*

37. a, b, c *Chieffi S, Carotenuto M, Monda V, Valenzano A, Villano I, Precenzano F, et al. (2017). Orexin system: the key for a healthy life. Front Physiol. 8:357. https://doi.org/10.3389/fphys.2017.00357*

38. a, b, c, d, e, f, g *Milrad SF, Hall DL, Lattie EG, Ironson G, Wohlgemuth WK, Vera-Nunez MA, Garcia L, Czaja SJ, P erdomo D, Fletcher MA, Klimas NG, Antoni M (2017). "Poor sleep quality is associated with greater circulati*

ng pro-inflammatory cytokines and severity and frequency of chronic fatigue syndrome/myalgic encephal omyelitis (CFS/ME) symptoms in women." Journal of Neuroimmunology. 303:43–50. doi:10.1016/j.jneuroim. 2016.12.008.

39. ^ a, b, c *Blundell S, Ray KK, Buckland M, White PD (2015). "Chronic fatigue syndrome and circulating cytokine s: A systematic review." Brain, Behavior, and Immunity. 50:186–195. doi:10.1016/j.bbi.2015.07.004.*
40. ^ *Liguori C, Mercuri N, Nuccetelli M, Izzi F, Bernardini S, Placidi F (2018). "Cerebrospinal fluid orexin levels a nd nocturnal sleep disruption in Alzheimer's disease patients showing neuropsychiatric symptoms." Journa l of Alzheimer's Disease. 66(3):993–999. doi:10.3233/jad-180769.*
41. ^ *Wyller VB, Evang JA, Godang K, Solhjell KK, Bollerslev J (2010). "Hormonal alterations in adolescent chroni c fatigue syndrome." Acta Paediatrica (Oslo, Norway: 1992). 99(5):770–773. doi:10.1111/j.1651-2227.2010.0170 1.x.*
42. ^ a, b *Baron KG, Duffecy J, Berendsen MA, Cheung Mason I, Lattie EG, Manalo NC (2018). "Feeling validated ye t? A scoping review of the use of consumer-targeted wearable and mobile technology to measure and impro ve sleep." Sleep Medicine Reviews. 40:151–159. doi:10.1016/j.smrv.2017.12.002.*
43. ^ *Cambras T, Castro-Marrero J, Zaragoza MC, Díez-Noguera A, Alegre J (2018). "Circadian rhythm abnormal ities and autonomic dysfunction in patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis." P loS One. 13(6):e0198106. doi:10.1371/journal.pone.0198106.*
44. ^ *Jackson ML, Bruck D (2012). "Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a review." Journal of Clinical Sleep Medicine. 8(6):719–728. doi:10.5664/jcsm.2276.*
45. ^ *Neu D, Cappeliez B, Hoffmann G, Verbanck P, Linkowski P, Le Bon O (2009). "High slow-wave sleep and lo w-light sleep: chronic fatigue syndrome is not likely to be a primary sleep disorder." Journal of Clinical Neur ophysiology. 26(3):207–212. doi:10.1097/wnp.0b013e3181a1841b.*
46. ^ *Wulff K, Gatti S, Wettstein JG, Foster RG (2010). "Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease." Nature Reviews Neuroscience. 11:589–599. doi:10.1038/nrn2868.*
47. ^ *Louati K, Bérenbaum F (2015). "Fatigue in chronic inflammation - a link to pain pathways." Arthritis Rese arch & Therapy. 17(1). doi:10.1186/s13075-015-0784-1.*
48. ^ *Nakatomi Y, Mizuno K, Ishii A, Wada Y, Tanaka M, Tazawa S, Onoe K, Fukuda S, Kawabe J, Takahashi K, K ataoka Y, Shiomi S, Yamaguti K, Inaba M, Kuratsune H, Watanabe Y (2014). "Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: an 11C-(R)-PK11195 PET study." Journal of Nucle ar Medicine. 55(6):945–950. doi:10.2967/jnumed.113.131045.*

49. ^Tomic S, Brkic S, Lendak D (2017). "Neuroendocrine disorder in chronic fatigue syndrome." Turkish Journal of Medical Sciences. 47(4):1097–1103. doi:10.3906/sag-1601-110.

50. a, bCohen S, Ifergane G, Vainer E, Matar MA, Kaplan Z, Zohar J, Mathé AA, Cohen H (2016). "The wake-promoting drug modafinil stimulates specific hypothalamic circuits to promote adaptive stress responses in an animal model of PTSD." Translational Psychiatry. 6(10):e917. doi:10.1038/tp.2016.172.

51. ^Dauvilliers Y (2021). "Hypocretin/orexin, sleep and Alzheimer's disease." In: Frontiers of Neurology and Neuroscience, The Orexin System. Basic Science and Role in Sleep Pathology. 45:139–149. doi:10.1159/000514967.

52. ^Overeem S, Scammell TE, Lammers GJ (2002). "Hypocretin/orexin and sleep: implications for the pathophysiology and diagnosis of narcolepsy." Current Opinion in Neurology. 15(6):739–745. doi:10.1097/01.wco.0000044800.53746.5a.

53. ^Morris G, Berk M, Galecki P, Walder K, Maes M (2016). "The neuro-immune pathophysiology of central and peripheral fatigue in systemic immune-inflammatory and neuro-immune diseases." Molecular Neurobiology. 53(2):1195–1219. doi:10.1007/s12035-015-9090-9.

54. ^Younger J, Parkitny L, McLain D (2014). "The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain." Clinical Rheumatology. 33(4):451–459. doi:10.1007/s10067-014-2517-2.

55. ^Li J, Hu Z, de Lecea L (2013). "The hypocretins/orexins: integrators of multiple physiological functions." British Journal of Pharmacology. 171(2):332–350. doi:10.1111/bph.12415.

56. ^Rahman SA, St Hilaire MA, Gronfier C, Chang A-M, Santhi N, Czeisler CA, Klerman EB, Lockley SW (2018). "Functional decoupling of melatonin suppression and circadian phase resetting in humans." The Journal of Physiology. 596(11):2147–2157. doi:10.1113/jp275501.

57. ^Wulff K, Dijk DJ, Middleton B, Foster RG, Joyce EM (2012). "Sleep and circadian rhythm disruption in schizophrenia." The British Journal of Psychiatry: The Journal of Mental Science. 200(4):308–316. doi:10.1192/bjp.bp.111.096321.

58. ^Ayumu I, A Y (2013). The physiological role of orexin/hypocretin neurons in the regulation of sleep/wakefulness and neuroendocrine functions. Front Endocrinol (Lausanne). https://doi.org/10.3389/fendo.2013.00018

59. a, b, cCouvineau A, Voisin T, Nicole P, Gratio V, Abad C, Tan Y (2019). "Orexins as novel therapeutic targets in inflammatory and neurodegenerative diseases." Frontiers in Endocrinology. 10. doi:10.3389/fendo.2019.00709.

60. ^Burfeind KG, Yadav V, Marks DL (2016). "Hypothalamic Dysfunction and Multiple Sclerosis: Implications for Fatigue and Weight Dysregulation." Current Neurology and Neuroscience Reports. 16(11):98. doi:10.1007/s1

1910-016-0700-3.

61. ^ *Suzuki K, Miyamoto M, Miyamoto T, Matsubara T, Inoue Y, Iijima M, Mizuno S, Horie J, Hirata K, Shimizu T, Kanbayashi T (2018). "Cerebrospinal fluid orexin-A levels in systemic lupus erythematosus patients presenting with excessive daytime sleepiness." Lupus. 27(11):1847–1853. doi:10.1177/0961203318778767.*

62. a, b *Lindvall JM, Olsson-Engman M, Holmgren E, Fernell E, Gillberg C, Wentz E (2022). "Orexin/hypocretin system dysfunction in ESSENCE (early symptomatic syndromes eliciting neurodevelopmental clinical examinations)." Neuropsychiatric Disease and Treatment. 18:2371–2380.*

63. ^ *Maness C, Saini P, Bliwise DL, Olvera V, Rye DB, Trotti LM (2019). "Systemic exertion intolerance disease/chronic fatigue syndrome is common in sleep centre patients with hypersomnolence: a retrospective pilot study." Journal of Sleep Research. 28(3):e12689. doi:10.1111/jsr.12689.*

64. a, b, c *Sakurai T (2007). "The neural circuit of orexin (hypocretin): Maintaining sleep and wakefulness." Nature Reviews Neuroscience. 8(3):171–181. doi:10.1038/nrn2092.*

65. ^ *Hagan JJ, Leslie RA, Patel S, Evans ML, Wattam TA, Holmes S, Benham CD, Taylor SG, Routledge C, Hemmati P, Munton RP, Ashmeade TE, Shah AS, Hatcher JP, Hatcher PD, Jones DNC, Smith MI, Piper DC, Hunter AJ, Porter RA, Upton N (1999). "Orexin A activates locus coeruleus cell firing and increases arousal in the rat." Proceedings of the National Academy of Sciences of the United States of America. 96(19):10911–10916. doi:10.1073/pnas.96.19.10911.*

66. ^ *Grafe LA, Eacret D, Luz S, Gotter AL, Renger JJ, Winrow CJ, Bhatnagar S (2017). "Orexin 2 receptor regulation of the hypothalamic-pituitary-adrenal (HPA) response to acute and repeated stress." Neuroscience. 348:313–323. doi:10.1016/j.neuroscience.2017.02.038.*

67. ^ *Spinazzi R, Andreis PG, Rossi GP, Nussdorfer GG (2006). "Orexins in the regulation of the hypothalamic-pituitary-adrenal axis." Pharmacological Reviews. 58(1):46–57. doi:10.1124/pr.58.1.4.*

68. a, b *Byrne H, Josev EK, Knight SJ, Scheinberg A, Rowe K, Lubitz L, Seal ML (2023). "Hypothalamus volumes in adolescent Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): impact of self-reported fatigue and illness duration." Brain Structure & Function. 228(7):1741–1754. doi:10.1007/s00429-023-02682-3.*

69. ^ *Dhabalia R, Kashikar SV, Parihar PS, Mishra GV (2024). "Unveiling the intricacies: A comprehensive review of magnetic resonance imaging (MRI) assessment of T2-weighted hyperintensities in the neuroimaging landscape." Cureus. doi:10.7759/cureus.54808.*

70. a, b *Chepke C, Jain R, Rosenberg R, Moline M, Yardley J, Pinner K, Kumar D, Perdomo C, Filippov G, Atkins N, Malhotra M (2022). "Improvement in fatigue and sleep measures with the dual orexin receptor antagonist l*

emborexant in adults with insomnia disorder." Postgraduate Medicine. 134(3):316–325. doi:10.1080/00325481.2022.2049553.

71. ^a ^b ^c *Najib J, Toderika Y, Dima L (2023). "Daridorexant, an orexin receptor antagonist for the management of insomnia." American Journal of Therapeutics. 30(4):e360–e368. doi:10.1097/mjt.0000000000001647.*

72. ^ *Chakraborty D, Choudhury S, Lahiry S (2023). "Daridorexant, a recently approved dual orexin receptor antagonists (DORA) in treatment of insomnia." Sleep Science. 16(02):256–264. doi:10.1055/s-0043-1770805.*

73. ^ *Garg H, Douglas M, Turkington GD, Turkington D (2021). "Recovery from refractory chronic fatigue syndrome with CBT and modafinil." BMJ Case Reports. 14(3):e240283. doi:10.1136/bcr-2020-240283.*

74. ^ *Minzenberg MJ, Carter CS (2008). "Modafinil: a review of neurochemical actions and effects on cognition." Neuropsychopharmacology. 33(7):1477–1502. doi:10.1038/sj.npp.1301534.*

75. ^ *Becquet L, Abad C, Leclercq M, Miel C, Jean L, Riou G, Couvineau A, Boyer O, Tan Y (2019). "Systemic administration of orexin A ameliorates established experimental autoimmune encephalomyelitis by diminishing neuroinflammation." Journal of Neuroinflammation. 16(1). doi:10.1186/s12974-019-1447-y.*

76. ^ *Macovei AL, Dobrin I, Chiriță V, Burlui A, Dobrin PR, Rezuș E (2019). "Chronic fatigue and psychiatric comorbidities in patients with rheumatic disorders." Bulletin of Integrative Psychiatry. 25(3):81–88. doi:10.36219/bpi.2019.03.08.*

77. ^ *Rozich JJ, Holmer AK, Singh S (2020). "Effect of lifestyle factors on outcomes in patients with inflammatory bowel diseases." The American Journal of Gastroenterology. 115(6):832–840. doi:10.14309/ajg.0000000000000608.*

78. ^ *Wendt A, Costa C, Machado AKF, Costa FS, Neves RG, Flores TR, Wehrmeister FC (2019). "Sleep disturbances and daytime fatigue: Data from the Brazilian National Health Survey, 2013." Cadernos De Saúde Pública. 35(3). doi:10.1590/0102-311x00086918.*

79. ^ *O'Connor K, Sunnquist M, Nicholson L, Jason LA, Newton JL, Strand EB (2017). "Energy envelope maintenance among patients with myalgic encephalomyelitis and chronic fatigue syndrome: implications of limited energy reserves." Chronic Illness. 15(1):51–60. doi:10.1177/1742395317746470.*

80. ^ *Carrasco-Querol N, Serra GG, Hernández NB, Gonçalves AQ, Cazalla MP, Bestratén del Pino P, Curto PM, Caballol Angelats R, Fusté Anguera I, Sancho Sol Mª C, Castro Blanco E, Vila-Martí A, Medina-Perucha L, Fernández-Sáez J, Dalmau Llorca MR, Aguilar Martín C (2023). "Effectiveness and health benefits of a nutritional, chronobiological and physical exercise primary care intervention in fibromyalgia and chronic fatigue syndrome: SYNCHRONIZE + mixed-methods study protocol." Medicine. 102(17):e33637. doi:10.1097/md.0000000000033637.*

81. ^ *Fluge Ø, Mella O, Bruland O, Risa K, Dyrstad SE, Alme K, Rekeland IG, Sapkota D, Røsland GV, Fosså A, Ktori dou-Valen I, Lunde S, Sørland K, Lien K, Herder I, Thürmer H, Gotaas ME, Baranowska KA, Bohnen LM, Sch äfer C, McCann A, Sommerfelt K, Helgeland L, Ueland PM, Dahl O, Tronstad KJ (2016). "Metabolic profiling i ndicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrom e." JCI Insight. 1(21):e89376. doi:10.1172/jci.insight.89376.*

82. ^ *Hatziagelaki E, Adamaki M, Tsilioni I, Dimitriadis G, Theoharides TC (2018). "Myalgic encephalomyelitis/c hronic fatigue syndrome-metabolic disease or disturbed homeostasis due to focal inflammation in the hyp othalamus?" The Journal of Pharmacology and Experimental Therapeutics. 367(1):155–167. doi:10.1124/jpet. 118.250845.*

83. ^ *Tate W, Walker M, Sweetman E, Helliwell A, Peppercorn K, Edgar C, Blair A, Chatterjee A (2022). "Molecula r mechanisms of neuroinflammation in ME/CFS and long COVID to sustain disease and promote relapses." Frontiers in Neurology. 13:877772. doi:10.3389/fneur.2022.877772.*

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.