Biomarkers for Narcolepsy: A Key to Unlocking Early Diagnosis and Advance Treatment

P. Selvarasu[1], S. Gokulakannan[2], S. Parthiban[3], P. Krishnakumar[4], P. Pradeep[5], N. Nandhakumar[6], P. Nithyadevi[7], A. Manoj[8], G. Rathinavel[9]

[1,4,6,7,8]*Assitant Professor, Department of Pharmacology, K.S.Rangasamy College of Pharmacy, Namakkal,637215, Tamilnadu, India*

[2]*Assistant Professor, Department of Pharmacology, Swamy Vivekanandha College of Pharmacy, Namakkal,637215, Tamilnadu, India*

[3]*Associate Professor, Department of Pharmacology, K.S.Rangasamy College of Pharmacy, Namakkal,637215, Tamilnadu, India*

[5]*Assistant Professor, Department of Pharmacy Practice, K.S.Rangasamy College of Pharmacy, Namakkal,637215, Tamilnadu, India*

[9]*Principal, Department of Pharmaceutical Chemistry, K.S.Rangasamy College of Pharmacy, Namakkal,637215, Tamilnadu, India*

The Tamilnadu Dr. MGR Medical University, Chennai-600032, Tamilnadu,India

***Abstract*—Narcolepsy is a rare, lifelong chronic neurological disorder that severely disrupts the brain's regulation of the sleep–wake cycle, leading to significant challenges in daily functioning. The condition is primarily characterized by excessive daytime sleepiness (EDS) and is categorized into Type 1 Narcolepsy (NT1), which typically presents with cataplexy, and Type 2 Narcolepsy (NT2), without cataplexy. NT1 pathophysiology is strongly associated with the loss of hypothalamic neurons that produce hypocretin (orexin), a deficiency diagnosed by low hypocretin-1 levels in the cerebrospinal fluid (CSF), and a strong link to the HLA-DQB1*06:02 genotype.**

Despite scientific advancements, narcolepsy diagnosis remains challenging due to symptom overlap with other sleep and psychiatric disorders, resulting in substantial diagnostic delays that often exceed a decade. Standard tools like the Multiple Sleep Latency Test (MSLT) and polysomnography (PSG) have limitations regarding specificity and reliability, especially for NT2, as they are affected by medication and comorbidities. Furthermore, CSF hypocretin-1 measurement, though highly specific for NT1, is invasive and not widely available.

This review highlights the causes of narcolepsy, the limitations of current diagnostic methods, and the critical need for objective and accessible biomarkers. Research is exploring novel, non-invasive approaches, including serum proteomics/glycoproteomics, electroretinography (to distinguish NT1 from idiopathic hypersomnia), digital biomarkers using wearable devices, and AI/Machine Learning techniques for automating PSG analysis. Management is symptomatic and lifelong, requiring a multidisciplinary approach that combines non-pharmacological strategies with pharmacological treatments tailored for EDS or cataplexy. Continued validation of these emerging biomarkers is essential to simplify diagnosis, reduce the profound psychosocial burden of delays, and improve clinical outcomes.

***Index Terms*—Narcolepsy, diagnosis, biomarker, recent treatment, emerging biomarkers.**

I. INTRODUCTION

A rare, long-lasting neurological condition called narcolepsy seriously impairs the brain's ability to regulate the sleep-wake cycle, making day-to-day functioning extremely difficult. The primary symptom, excessive daytime sleepiness (EDS), is typically accompanied by cataplexy (sudden muscle weakness), sleep paralysis, and intense hallucinations (1). Type 1 Narcolepsy (NT1), formerly known as narcolepsy with cataplexy, and Type 2 Narcolepsy (NT2), narcolepsy without cataplexy, are the two primary forms of the condition (2).

The pathophysiology of NT1 is strongly associated with the loss of hypothalamic neurons that produce the neuropeptide hypocretin (orexin), which regulates arousal and sleep states(3). This deficiency is typically diagnosed by low levels of hypocretin-1 in the cerebrospinal fluid (CSF), a test considered highly specific for NT1(4) .A strong association with the HLA-DQB1*06:02 genotype suggests a potential autoimmune cause for the destruction of these neurons. In contrast, NT2 is usually defined by the absence or rarity of cataplexy and normal hypocretin levels (5).

Despite scientific advancements, narcolepsy diagnosis remains challenging due to symptom overlap with other sleep and psychiatric disorders, often resulting in diagnostic delays that can exceed a decade. Current standard tools, such as the Multiple Sleep Latency Test (MSLT) and polysomnography (PSG), have limitations, especially for NT2, as their reliability is affected by factors like medication and comorbidities. Furthermore, while highly specific for NT1, CSF hypocretin-1 measurement is invasive and not widely available. (7)

These challenges highlight the continuous need for objective and accessible biomarkers. Beyond the established CSF hypocretin-1 and HLA genotype for NT1, research is exploring novel, less invasive biomarkers, including:

- Serum proteomics/glycoproteomics
- Electroretinography, which may help distinguish NT1 from idiopathic hypersomnia
- Digital biomarkers using wearable devices for long-term monitoring
- AI/Machine Learning approaches utilizing neural network analysis of PSG data, offering potential for automated and home-based assessments. *(8,20,11,7)*

This review aims to provide an overview of narcolepsy, discussing its causes, the limitations of current diagnostic methods, established and emerging biomarkers, and the resulting challenges in clinical practice.

Diagnostic Challenges

Heterogeneity and Symptom Overlap

Narcolepsy presents with a spectrum of symptoms—excessive daytime sleepiness, cataplexy, hallucinations, and sleep paralysis—that often overlap with other sleep and psychiatric disorders, leading to frequent misdiagnosis and substantial diagnostic delays, sometimes exceeding a decade *(11)(22)* .In pediatric populations, atypical presentations such as irritability or hyperactivity further complicate recognition. The absence of cataplexy in narcolepsy type 2 (NT2) makes diagnosis particularly difficult, as excessive sleepiness alone is nonspecific and can be caused by various conditions *(22)*.

Limitations of Current Diagnostic Tools

The Multiple Sleep Latency Test (MSLT) and polysomnography (PSG) are standard diagnostic tools but are influenced by factors such as prior sleep deprivation, comorbid sleep disorders, and medication use, reducing their specificity *(5,22,20).* MSLT is less reliable for NT2 and often requires repeat testing *(22).* Cerebrospinal fluid (CSF) hypocretin-1 measurement is highly specific for narcolepsy type 1 (NT1) but is invasive and not widely available *(20,22,14).* Additionally, a disconnect in language between clinicians and patients may contribute to under-recognition and delayed diagnosis *(16).*

Diagnostic Delay and Impact

Diagnostic delays are associated with increased psychosocial burden, misdiagnosis, and delayed treatment, negatively impacting quality of life and healthcare utilization *(11,17,22).*

Biomarkers of Narcolepsy
Established Biomarkers

BIOMARKER/METHOD	UTILITY IN NARCOLEPSY DIAGNOSIS	LIMITATIONS/NOTES	REFERENCE
CSF Hypocretin-1 (Orexin-A)	Highly specific and sensitive for NT1	Invasive, limited availability	*(6,7,14,22)*
HLA-DQB1*06:02 Genotype	Strong association with NT1	Not exclusive to narcolepsy	*(6,7,12, 22)*
MSLT/PSG (SOREMPs, sleep latency)	Objective sleep architecture assessment	Affected by comorbidities, medications	*(6,10,20,22)*
Sleep Stage Overlap (AI/ML)	Automated detection of T1N via PSG	Promising, but not yet standard	*(8,9)*
Electroretinography	Differentiates NT1 from idiopathic hypersomnia	Needs further validation	*(15)*
Serum Proteomics/Glycoproteomics	Candidate serum biomarkers for NT1	Early-stage, requires larger studies	*(12,19)*
Physiological Network Connectivity (TDS)	Potential NT2 biomarker via biosignal analysis	Needs replication	*(3)*
Digital Biomarkers (Wearables)	Sleep fragmentation, REM latency, heart rate	Feasibility shown, further validation needed	*(23)*

Figure-1: Table summarizing key biomarkers and diagnostic methods for narcolepsy.

Recent Advances and Emerging Biomarkers

- Serum Proteomics and Glycoproteomics: Recent studies have identified differentially expressed proteins and glycopeptides in NT1, implicating pathways such as complement activation and acute phase response signaling. These findings may lead to less invasive diagnostic tests in the future [(12, 19)]
- Electroretinography: Altered cone and rod responses in NT1 patients suggest retinal electrophysiology as a potential non-invasive biomarker, distinguishing NT1 from idiopathic hypersomnia [(15).]
- Physiological Network Connectivity: Analysis of biosignal connectivity during REM sleep shows promise for NT2 diagnosis, with high sensitivity and specificity [(13).]
- Digital Biomarkers: Long-term monitoring with wearable devices can detect sleep fragmentation and altered REM latency in NT1, offering a potential avenue for remote diagnosis [(23)]
- AI/ML Approaches: Neural network analysis of PSG data can automate sleep stage scoring and identify narcolepsy-specific patterns, potentially reducing diagnostic time and enabling home-based assessments [(8, 9).]

Biomarkers of Neurodegeneration

CSF biomarkers of neurodegeneration (tau, amyloid-beta, neurofilament light chain) are not informative in narcolepsy, indicating that neurodegenerative processes are not prominent in this disorder [(14, 23).]

II. CONCLUSION

Despite the definitive understanding of narcolepsy as a chronic neurological disorder characterized by hypocretin deficiency (particularly in NT1) and associated with the HLA-DQB1*06:02 genotype, significant gaps remain in transitioning scientific knowledge into efficient clinical practice. The established diagnostic criteria, utilizing the Multiple Sleep Latency Test (MSLT), Polysomnography (PSG), and invasive Cerebrospinal Fluid (CSF) hypocretin-1 measurement, face limitations regarding accessibility and specificity, particularly for Narcolepsy Type 2 (NT2).

A major implication for clinical practice is the necessity of a multidisciplinary approach to narcolepsy management, involving specialists in sleep medicine, neurology, psychiatry, and psychology. This holistic view is vital because patients frequently present with comorbidities, including psychiatric (depressive, bipolar, anxiety disorders), cardiovascular, and metabolic disorders, such as weight gain.

The current standard of care is symptomatic and required for the entirety of the patient's life. Management combines non-pharmacological strategies (such as strict sleep routines and scheduled brief naps) with pharmacological treatments. Pharmacological treatment is tailored to address either Excessive Daytime Sleepiness (EDS) using central nervous system stimulants like modafinil, armodafinil, or pitolisant, or cataplexy using medications such as sodium oxybate, venlafaxine, or tricyclic antidepressants.

Furthermore, research must pivot to address key mechanistic and diagnostic ambiguities:

1. NT2 Pathophysiology: While some studies suggest hypocretin cell loss may occur in NT2 despite normal CSF levels, the precise cause remains largely misunderstood, demanding further investigation.
2. Etiological Advances: A compelling recent finding suggests that a significant population of HCRT neurons remains present in patients but is rendered inactive through epigenetic silencing (DNA methylation) of genes like HCRT, CRH, and PDYN. This suggests that HCRT neurons may not be destroyed outright, opening potential avenues for reactivating these neurons and offering hope for future curative interventions rather than just lifelong symptomatic treatment.
3. Disease Nature: It is important to note that conventional CSF biomarkers for neurodegeneration, such as tau, amyloid-beta, and neurofilament light chain, are not informative in narcolepsy, indicating that classical neurodegenerative processes are not prominent in this disorder.

Despite the profound impact of symptoms (such as social vulnerability and altered self-esteem) on quality of life, the overall prognosis for individuals with narcolepsy is generally good with proper and lifelong treatment and management, affording them a normal life span. Continued validation of emerging biomarkers—including serum proteomics, electroretinography, and AI/ML analysis of PSG data—is essential to simplify diagnosis, reduce the profound psychosocial burden associated with diagnostic delay (which can exceed a decade), and ultimately translate these rapid scientific advances into improved clinical outcomes.

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