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NARCOLEPSY: LIKE A ROLLING STONE, A DISORDER WITHOUT A NEUROBIOLOGICAL HOME…IN NEED OF ANSWERS

Edward J. Modestino[1*], Alireza Sharafshah[2], Kai -Uwe Lewandrowski[3], David Baron[4,5], Panayotis K. Thanos[6], Alexander P.L., Lewandrowski[7], Rajendra D. Badgaiyan[8], Catherine A. Dennen[9], Kenneth Blum[1,3,4*]

[1]Brain & Behavior Laboratory, Department of Psychology, Curry College, Milton, MA, USA.
[2]Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
[3]Division of Personalized Pain Therapy, Center for Advanced Spine Care of Southern Arizona, Tucson, AZ, USA.
[4]Division of Addiction Research & Education, Center for Sports and Mental Health, Western University of Health Sciences, Pomona, CA, USA.
[5]Department of Psychiatry, Stanford University School; of Medicine, Palo Alto, CA., USA.
[6]Behavioral Neuropharmacology and Neuroimaging Laboratory, Clinical Research Institute on Addictions, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA.
[7]Department of Biological Sciences, Dornsife College of Letters, Arts & Sciences, University of Southern California, Los Angeles, CA., USA.
[8]Department of Psychiatry, Texas Tech University Health Sciences, School of Medicine, Midland, TX., USA.
[9]Department of Family Medicine, Jefferson Health Northeast, Philadelphia, PA, USA.

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***Corresponding Author: Edward J. Modestino**
Brain & Behavior Laboratory, Department of Psychology, Curry College, Milton, MA, USA.
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While there are 6,935 articles listed on PubMed (as of 12-30-24), as penned by Bob Dylan, “how does it feel -to be on your own- with no direction home -like a complete unknown- like a rolling stone” (narcolepsy struggling for more answers), those struggling need novel genetic and epigenetic answers.

A study by Modestino and Winchester[1] revealed a significant link between childhood ADHD symptoms and subsequent development of narcolepsy, suggesting that a subtype of ADHD may be an early stage of a progressive neurological condition that eventually manifests as hypersomnia or narcolepsy. Supporting this hypothesis, earlier studies[2] observed the same hypovigilance and pupilographic instabilities in individuals with ADHD and narcolepsy, while Weinberg and Harper[3] identified a new syndrome combining both, coining the term "Primary Disorder of Vigilance." Sultan et al.[4] introduced "Syndrome Z," encompassing ADHD, narcolepsy, and other related symptoms, highlighting a potential narcolepsy spectrum. Ohayon further demonstrated a significantly higher prevalence of childhood ADHD among narcoleptics compared to controls.

While similarities between ADHD and hypersomnia/narcolepsy raise concerns about diagnostic confusion, the historical stereotypes of ADHD as hyperactivity in children and narcolepsy as sleepiness in adults may have hindered recognition of a genuine connection.[7] Emerging research challenges traditional symptom-based classifications, advocating for a cause-driven nosology that reflects the overlapping genetic and neurobiological mechanisms underlying conditions like ADHD and narcolepsy. This shift is supported by findings of shared therapeutic response to medication among ADHD, narcolepsy, and other disorders within the Affective Spectrum Disorder (ASD) framework and by initiatives like the Research Domain Criteria (RDoC) project, which promote comprehensive analysis of brain disorders through behavioral, neurobiological, and genetic measures.[7]

Additionally, Reward Deficiency Syndrome (RDS) integrates addictive, compulsive, and impulsive behaviors, including ADHD, under a shared framework of dopamine dysregulation.[7] This neurochemical disruption spans multiple pathways, including those involving hypocretin/orexin modulation of dopamine, linking narcolepsy to ADHD within the broader context of RDS.[7] These findings underscore the importance of reexamining rigid diagnostic boundaries to better understand the interconnected nature of these conditions.

Narcolepsy, while closely associated with HLA-DQB1*0602, appears to be polygenic, influenced by interactions among multiple genes and environmental factors.[5-7] Genes linked to Reward Deficiency Syndrome (RDS) and ADHD, such as the Taq A1 allele variant of the D2 dopamine receptor, have also been associated with narcolepsy, along with genetic factors related to COMT, GABA, and serotonin as well as proposed neurobiological mechanisms.[6-8] Specifically, orexin neurons regulate sleep-wake behavior, and the consequences of the loss of orexin neurons seem sound. Additionally, there is evidence that narcolepsy is an autoimmune disorder that may be caused by a T cell-mediated attack on the orexin neurons.[8] These findings align with evidence supporting polygenic conditions and pleiotropy[9] and frameworks like the Research Domain Criteria (RDoC), which promote cause-based rather than symptom-based classifications.[10,11]

We propose that hypersomnias, including narcolepsy, could evolve from an ADHD history within the broader framework of RDS. This hypothesis suggests that dopaminergic deficits observed in ADHD/RDS may worsen with the onset of narcolepsy.[7] KB220Z™, a nutraceutical complex extensively studied in pre-clinical and clinical trials, has shown potential in addressing dopamine dysregulation associated with RDS. Studies indicate that KB220Z™ enhances dopamine production, reduces substance cravings, alleviates withdrawal symptoms, and improves behavioral and emotional well-being.[12] Furthermore, its effects on the anterior cingulate cortex and nucleus accumbens demonstrate its role in modulating neural networks tied to addiction and reward systems.[13]

Incorporating genetic assessments, such as the Genetic Addiction Risk Score (GARS), into treatment models could enhance early identification of dopamine dysregulation risks. This approach advocates for achieving dopamine homeostasis through genetically informed nutraceutical interventions like KB220Z.[13] These findings provide a framework for exploring shared genetic underpinnings of ADHD and narcolepsy within RDS, addressing both psychological and biological factors in terms of predisposition and possibly even preaddiction.[14]

Narcolepsy type 1 and narcolepsy type 2 are central disorders of hypersomnolence. Narcolepsy type 1 is characterized by excessive daytime sleepiness and cataplexy and is associated with hypocretin-1 deficiency.[16] On the other hand, in narcolepsy type 2, cerebrospinal fluid hypocretin-1 levels are normal, and cataplexy is absent.[16] However, despite

major advances in our understanding of narcolepsy mechanisms, its current management is only symptomatic, awaiting more neurogenetic and neurobiological answers.

Treatment options may vary from a single drug that targets several symptoms or multiple medications that each treat a specific symptom. Currently, narcolepsy treatment has changed with the widespread use of modafinil/armodafinil for daytime sleepiness, antidepressants (selective serotonin and dual serotonin and noradrenalin reuptake inhibitors) for cataplexy, and sodium oxybate for both symptoms.[16] Other psychostimulants can also be used, such as methylphenidate, pitolisant, and rarely amphetamines, as third-line therapy.[16]

Interestingly, a low level of hypocretin-1/orexin-A in the cerebrospinal fluid is sufficient to diagnose narcolepsy type 1, being a highly specific and sensitive biomarker, and the irreversible loss of hypocretin neurons is responsible for the main symptoms of the disease: sleepiness, cataplexy, sleep-related hallucinations, and paralysis, and disrupted nocturnal sleep.[15]

Importantly, clinically relevant subjective and objective measures of daytime sleepiness are required to monitor the treatment safety and efficacy and to provide guidance on whether the treatment goals are achieved. Associated symptoms and comorbid conditions, such as hypnagogic/hypnopompic hallucinations (potentially with comorbid schizophrenia in rare cases)[16], sleep paralysis, disturbed nighttime sleep, unpleasant dreams, REM- and non-REM-related parasomnias, depressive symptoms, overweight/obesity, and obstructive sleep apnea should also be considered.[17] In the future, the efficacy of new wake-promoting drugs, anticataleptic agents, hypocretin replacement therapy, and immunotherapy at the early stages of the disease may also be developed.

Based on this evidence, we theorize that ADHD and narcolepsy may share a genetic background within the context of RDS and GARS, a premise which needs to be explored.

AUTHOR CONTRIBUTION

The initial manuscript was developed by KB, EJM, KUL AND APLL and all co-authors approved.

CONFLICT OF INTEREST

KB is the owner of all domestic and foreign patents related to both GARS and kb220.

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