Narcolepsy, Depression, and REM Suppressing Antidepressants: Comorbidity & Confound Impacts on Sleep Architecture and Diagnostic Sensitivity

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Abstract text

Introduction:
Systematic reviews and meta-analyses showed a 32%-57% prevalence of Depression or depression symptoms in patients with Narcolepsy disorders. MSLT protocols recommend a drug washout period of ≥14-days for antidepressants and other medications known to confound sleep architecture and REM sleep. Patient noncompliance with washout protocols for REM-suppressing antidepressants (REMS-AD) was found to reduce the incidence of SOREMP observations in MSLTs by ≥89% compared to washout-compliant patients. Prior studies demonstrated potential for improvements in Narcolepsy diagnostic sensitivity and reproducibility by exploiting more comprehensive analysis of full-night polysomnography (PSG) signals, through deep learning-based AI models (ROC-AUC 0.96) and algorithmic approaches. Prior research characterized Narcolepsy-specific microarchitectural sleep EEG abnormalities that manifest in Sleep Latency (SL), REM (Latency (REML), median/minimum duration, density, prevalence), N3 (time/prevalence), hypnodensity characteristics, and separately, Depression-specific state and trait EEG markers including low Delta Sleep Ratio (DSR), high/oscillatory Gamma, and high/asymmetric Alpha. Few works examine the extent of confounds to Narcolepsy diagnostic parameters from Depression comorbidity with and without the specific influence of REMS-ADs.

Materials and methods:
A nonrandomized, observational, de-identified cohort of N=282 PSGs were collected from subjects that underwent MSLT immediately following the PSG. Excluding subjects without drug-screen and/or medication questionnaire results, the final cohort (N=133) was composed of 59.6% Narcolepsy(+) subjects (N=35 NT1, N=44 NT2), and 40.4% Narcolepsy(-) Clinical Controls (CC) subjects. 47.9% of subjects had a documented Depression diagnosis, 52.1% with verified absence of Depression diagnostic history, and a 49.3% rate of comorbid Depression in Narcolepsy. The sample included N=39 subjects that were Narcolepsy(+)/Depression(+) for comparison to N=40 Narcolepsy(+)/Depression(-) subjects. Among Narcolepsy(+)/Depression(+), N=29 were REMS-AD(+) and N=10 REMS-AD (-). Mean latency, density, and prevalence were calculated for sleep stages (N1, N2, N3, REM, Wake, All-Stages), mean power spectral densities and ratios were calculated (Delta, Theta, Alpha, Beta, Gamma), then evaluated for differences and statistical significance in mean diagnostic parameter values based on two-sided 95% bootstrap median-percentile method Confidence Intervals (R=2,000).

Results:
In NT1, NT2, and CC, Mean REML was shortest in MDD(+)/REM-AD(-) subjects (NT1/NT2: 67mins (54mins, 77mins), CC: 118mins (97mins, 125mins)), the longest in MDD(+)/REM-AD(+) subjects (NT1/NT2: 156mins (115mins, 203mins), CC: 190mins (133mins, 247mins)), with MDD(-) subjects falling between (NT1/NT2: 108mins (93mins, 125mins), CC: 120mins (94mins, 152mins)). In both Narcolepsy and CC, Mean REM density was highest in MDD(+)/REM-AD(-) subjects (NT1/NT2: 111mins (88mins, 128mins), CC: 97mins (91mins, 105mins)), and substantially reduced in MDD(+)/REM-AD(+) subjects (NT1/NT2: 101mins (87mins, 113mins), CC: 82mins (62mins, 104mins)). Mean DSR was lowest in CC MDD(+)/REM-AD(-) subjects (CC: 0.96), and normalized in MDD(+)/REM-AD(+) (CC: 1.45) relative to MDD(-) (CC: 1.28). Mean DSR was lower in Narcolepsy MDD(+)/REM-AD(+) and MDD(+)/REM-AD(-) subjects than MDD(+)/REM-AD(+) and MDD(-) CCs (NT1/NT1: REM-AD(-): 1.19, REM-AD(+): 1.14, MDD(-): 1.39). Mean SOREMPs were lowest for MDD(+)/REM-AD(+) both in Narcolepsy (NT1/NT2: MDD(+)/REM-AD(+): 1.00, MDD(+)/REM-AD(-): 1.71, MDD(-): 1.50) and CCs (CC: MDD(+)/REM-AD(+): 0.21, MDD(+)/REM-AD(-): 0.33, MDD(-): 0.42).

Conclusions:
Comorbid Depression patients with and without REM-ADs showed substantial alterations in key Narcolepsy disorder diagnostic and sleep architecture parameters. Given significant rates of comorbidity, these findings highlight needs to better understand the interactions and impact of Depression on Narcolepsy diagnosis.

General

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