https://doi.org/10.5664/jcsm.8884

JCSM | Journal of Clinical Sleep Medicine

COMMENTARY

# Twice is nice? Test-retest reliability of the Multiple Sleep Latency Test in the central disorders of hypersomnolence

Commentary on Trotti LM, Staab BA, Rye DB. Test-retest reliability of the Multiple Sleep Latency Test in narcolepsy without cataplexy and idiopathic hypersomnia. *J Clin Sleep Med.* 2013;9(8):789–795. doi:10.5664/jcsm.2922

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In 2013, the current author and colleagues reported poor Multiple Sleep Latency Test (MSLT) test-retest reliability in people with noncataplectic hypersomnia disorders (NCHD).[1] Half of our participants' MSLT-based diagnoses changed between MSLTs, driven by changes across the 8-minute sleep latency threshold used to define sleepiness and the 2 sleep-onset REM period (SOREM) threshold used to identify narcolepsy. Before our report, there were concerns about the MSLT,[2] but the existing literature suggested adequate MSLT retest reliability in people with narcolepsy (mostly with cataplexy, ie, narcolepsy type 1 [NT1]).[3,4]

Subsequently, studies have confirmed that MSLT retest reliability is poor in NCHD compared to NT1. Combining data across published studies, repeat MSLT confirms NT1 diagnosis in 91% (68/75) of patients[4–6] but only in 45% (26/58) of patients with narcolepsy type 2 (NT2)[1,4–7] and in 49% (21/43) of patients with idiopathic hypersomnia.[1,5,7] Seventy percent of patients with self-reported sleepiness and a normal first MSLT have a normal second MSLT,[1,5,7] and 60% have a normal second MSLT if excluding MSLTs on consecutive days. In patients with NT1, the 8-minute threshold is crossed on only 7% (7/107) of repeat tests, the 2-SOREM threshold on only 10% (12/121) of repeat tests, and both are crossed on 7% (7/107) of repeat tests.[4–6,8] For NCHD, the 8-minute threshold is crossed on 35% (63/182) of repeat tests, the 2-SOREM threshold on 28% (66/235) of repeat tests, and both on 24% (41/170) of repeat tests.[1,4–9]

What explains low retest reliability? Broadly, the possibilities are (1) inadvertent bias introduced by study design, (2) MSLT variability despite stable disease phenotype over time, and (3) disease phenotype variability over time. Many studies of repeat MSLT, including ours,[1] were retrospective clinical analyses. Testing may have been repeated because initial results were somehow clinically discordant, leading to a selection bias for repeat testing. However, even when repeat testing is performed routinely, nearly 1 in 5 people with NT2 cross the 2-SOREM threshold at 5 years, significantly more than those with NT1.[9]

The MSLT has some inherent retest variability because it requires strict adherence to specific protocols[2] that are challenging in practice.[10] Numerous factors affect the MSLT, not limited to age, sleep during the days and weeks before testing, physical activity, medications, nonprescription substances, and momentary state. This finding may explain the improved retest reliability with shorter retest intervals, eg, consecutive days vs months or years, even in the same patients.[7] However, across longer intervals, retest reliability remains poor even when excluding medication changes,[1,6] and these other sources of variability should not disproportionately affect those with NCHD.

Finally, these diseases may evolve differently over time. In NT1, once hypocretin cell loss is maximal, symptoms (and the MSLT results) would be expected to remain relatively stable. Because the cause or causes of NCHD remain unknown, it is possible that their underlying pathology shows more fluctuation. Epworth Sleepiness Scale scores vary somewhat more over time in patients with NT2 than in those with NT1.[9] It is possible that both sleepiness and REM propensity are fluctuating features of NCHD, making poor retest reliability of these measures inevitable.

Poor MSLT test-retest reliability for NCHD has negative consequences for patients, providers, and health care systems. MSLTs are expensive, in both dollars and time, and repeat tests doubly so. Uncertainty about diagnoses impacts patients' ability to understand and cope with their chronic disease, stymies clinical research, and undermines disease classification that heavily emphasizes the MSLT. Notably, because treatment may only be approved or covered for those with specific diagnoses, especially NT1 and NT2, the lack of MSLT stability can have profound effects on patient access to medications. If only a single MSLT is performed, then it can feel like a roll of the dice—if ≥ 2 SOREMs appear, then the patient can be treated, otherwise not. Yet idiopathic hypersomnia and NT2 cannot be otherwise distinguished on clinical grounds, making this withholding of medications scientifically unjustifiable.[11]

The MSLT remains a good, if technically difficult, diagnostic test for NT1, but new paradigms are clearly needed for NCHD. Whether this initiative will involve a change in MSLT analysis parameters,[12] novel polysomnography measures,[13] cognitive

testing,[14] or ultimately mechanistic biomarkers, attention to the test-retest reliability of these measures is critical.

## CITATION

Trotti LM. Twice is nice? Test-retest reliability of the Multiple Sleep Latency Test in the central disorders of hypersomnolence. *J Clin Sleep Med.* 2020;16(suppl_1):17S–18S.

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## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication October 9, 2020**
**Submitted in final revised form October 9, 2020**
**Accepted for publication October 9, 2020**
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## DISCLOSURE STATEMENT

Work for this study was supported by the National Institutes of Health (R01 NS111280). This work is solely the responsibility of the author and does not necessarily represent the official views of the funding agency. The author reports no conflicts of interest.