REVIEW

Therapeutic Strategies for Mitigating Driving Risk in Patients with Narcolepsy

This article was published in the following Dove Press journal: Therapeutics and Clinical Risk Management

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Keywords: narcolepsy, cataplexy, driving, safety

Introduction

Narcolepsy is a lifelong disorder of hypersomnolence characterized by daily periods of irrepressible need to sleep, or frequent daytime lapses into sleep. The diagnosis typically requires a formal series of laboratory studies to demonstrate objective daytime sleepiness with the presence of two or more sleep-onset rapid eye movement (REM) periods during multiple sleep latency testing (MSLT).¹ Narcolepsy can only be diagnosed in the absence of other causes of hypersomnia, such as untreated obstructive sleep apnea, chronic insufficient sleep, and sedating medications or drugs. Some patients with narcolepsy also experience cataplexy, a phenomenon in which strong emotions precipitate bilateral loss of muscle tone with retained consciousness, and/or sleep paralysis, the complete inability to move after a partial awakening from REM sleep. Treatment of narcolepsy is generally symptomatic, and may include wakefulness-promoting medications such as stimulants, REM-suppressing medications for the treatment of cataplexy, and/or sodium oxybate (Xyrem[®]), a sodium salt of gamma-hydroxybutyric acid (GHB) that enhances sleep consolidation and reduces cataplexy.^{2,3}

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Therapeutics and Clinical Risk Management 2020:16 1099-1108

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Epidemiological and crash report data indicate a large proportion of narcolepsy patients experience sleepiness that interferes with driving (Table 1). It should be noted that few of these studies analyze accident risk separately for treated versus untreated patients with narcolepsy. One study of adults with narcolepsy found 66% reported falling asleep at the wheel, 29% experience cataplexy while driving, and 12% experience sleep paralysis while driving.⁴ Individuals with narcolepsy have a three- to four-fold increased risk of crashing compared to those without narcolepsy, with over a third reporting an accident due to sleepiness.^{5–7} Narcolepsy has also been found to confer greater risk for sleep-related accidents than other sleep disorders.^{8,9} In one study of patients with sleep apnea, narcolepsy, and other hypersomnia disorders, the proportion of patients with narcolepsy reporting sleep-related accidents was more than four times that of controls. Narcolepsy patients who reported having accidents were not more objectively sleepy on MSLT than those who did not have accidents, suggesting factors other than sleepiness contribute to accident risk.9 In January 2010, the Federal Motor Carrier Safety Administration's Medical Review Board concluded that even those narcolepsy patients who are treated still show abnormal levels of daytime sleepiness, and recommended all individuals with narcolepsy be ineligible for a commercial driver's license, even with treatment.¹⁰

Despite the evidence supporting the need for therapeutic risk reduction, monitoring, and mitigation of drowsy driving in those with narcolepsy, there is a relative paucity of studies investigating these strategies. This may be due to the fact that narcolepsy is a relatively rare disorder, occurring in only about 0.05% of the general population.^{11,12} In this paper, we review the evidence for evaluating and mitigating risk for sleep-related crashes in individuals with narcolepsy.

Evaluation of Crash Risk

There are currently no universally accepted guidelines for assessing risk of drowsy driving in narcolepsy patients. Research studies on crash risk in sleepy patients typically employ tests of real or simulated driving; however, these measures are not typically available to the clinician. In practice, evaluation of driving risk typically relies on selfreported sleepiness, in conjunction with objective measures of daytime sleepiness and sleep propensity. Of note, many studies examining measurements of sleepiness and driving risk include both patients with narcolepsy and those with other central nervous system (CNS) hypersomnia disorders, such as idiopathic hypersomnia (IH). Although IH is also defined as a disorder with pathologic sleepiness, it lacks features of narcolepsy, such as cataplexy, sleep paralysis, and sleep stage instability, that may increase risk of drowsy driving accidents.¹

Subjective measures of sleepiness include the Epworth Sleepiness Scale (ESS), a series of questions assessing how likely the respondent is to doze off in a variety of situations.¹³ The ESS is the most widely used tool for assessing sleep propensity in both research and clinical practice. Some studies have found that high scores at this scale seem to be clearly linked with accident risk;^{8,14-16} however, others have not found a clear correlation with real or simulated driving performance.^{17,18} Measures of self-reported sleepiness often do not reflect performance on cognitive or vigilance testing.¹⁹⁻²¹ Additionally, one's ability to rate their own sleepiness and impairment is negatively impacted by sleepiness, similar to those driving while intoxicated.^{22,23} Objective measures are therefore favored to accurately rate the risk of a drowsy driving accident.

The most frequently used objective measure of sleepiness for assessing safety to drive is the maintenance of wakefulness test (MWT).^{24,25} The MWT requires the patient to sit quietly in a dimly lit room without falling asleep, with a maximum duration of 40 minutes for each of 4 sessions. Mean sleep onset latencies (SOL) under 8 minutes are considered abnormal, but SOL between 8 and 40 minutes are of uncertain significance. The current American Academy of Sleep Medicine guideline discusses indications for the use of the MWT in assessing ability to stay awake, but cautions that its predictive value for assessing actual accident risk has not been established.²⁵ One study found MWT mean sleep latency

Study	N with Narcolepsy	N or % on Treatment	Pre/Post-Diagnosis Eval	Crash History/Odds Ratio (OR)
Aldrich, 1989 ⁹	25	None at the time of the sleep studies, otherwise not reported	Subjects were queried about lifetime crash history and underwent PSG/MLST	Percent of group with any lifetime crash due to sleepiness: Narcolepsy: 52% Control: 11%
Broughton et al, 1981 ⁴	180	Wakefulness-promoting medications: 98 REM-suppressing antidepressants: 61 Overlap of individual medications not reported.	Subjects with existing diagnoses were queried about lifetime crash history. The questionnaire did not differentiate crash history before/after diagnosis and treatment.	Fell asleep driving: Narcolepsy: 66.5% Controls: 6.2% Frequent near-accidents: Narcolepsy: 66.7% Controls: 0% Narcolepsy symptoms and/or sleepiness led to accidents: Narcolepsy: 36.8% Controls: 5.3% No analyses reported for treatment status.
Liu & Perez, 2018 ⁷	5	Not reported	Subjects with existing diagnoses were monitored using vehicle instrumentation for 1–2 years	OR for crash/near-crash, adjusted for gender, age, average trip duration, and self-reported frequency of sleepy driving: 10.24 (p < 0.1)
Philip et al, 2010 ⁸	48*	20.8%	Subjects with existing diagnoses were queried about near misses and crash history in the past year	OR of any crash: 3.16 (95% CI: 1.36–7.33) OR of a drowsy driving crash: 8.78 (95% CI 1.97–39.06) No difference was found between treated and untreated drivers.
Pizza et al, 2015 ⁶	129 NTI, 82 NT2, 71 IH	Not reported for narcolepsy. For all subjects with CNS hypersomnia disorders: 61.35%	Subjects with existing diagnoses were queried about 5-year crash history	OR of a crash, adjusted for gender, age, marital status, and coffee/energy drink consumption: NT1: 1.68 (95% CI: 0.97–2.91) NT2: 2.82 (95% CI: 1.60–4.96) CNS hypersomnia patients without treatment: 2.20 (95% CI: 1.29–3.73) CNS hypersomnia patients treated \leq 5 years: 2.68 (95% CI: 1.56–4.62) CNS hypersomnia patients treated \geq 5 years: 1.23 (95% CI: 0.56–2.69)

Table	I	Studies	Assessing	Crash	Risk in	Patients	with	Narcole	epsy
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Note: *Self-reported diagnosis of "narcolepsy/hypersomnia".

Abbreviations: Cl, confidence interval; NTI, narcolepsy type 1; NT2, narcolepsy type 2; IH, idiopathic hypersomnia.

correlated with the mean number of inappropriate lane changes for both untreated and treated (e.g., with modafinil) CNS hypersomnia disorder patients. However, the MWT did not correlate with deviation from the center of the lane in untreated or treated patients.²⁶ A study of MWT scores and driving simulator performance in CNS hypersomnia disorder patients found worse performance in the pathologically sleepy group (defined as mean SOL of 19 minutes or less). Although

those participants with intermediate sleepiness (mean SOL 20–33 minutes) had more inappropriate lane crossings, the difference between this group and the alert (mean SOL 34–40 minutes) and control (mean SOL >34 minutes) groups was statistically nonsignificant¹⁵ (Figure 1). Another study comparing the MWT to both simulated and real driving in CNS hypersomnia disorders found untreated patients had both shorter SOL on the MWT (median 20.8 minutes) and worse



Figure I Mean number of inappropriate lane crossings for individuals in different categories of Maintenance of Wakefulness score. Reprinted from Internat J Psychophys, 89, Philip P, Chaufton C, Taillard J, et al. Maintenance of Wakefulness Test scores and driving performance in sleep disorder patients and controls. 195–202, copyright (2013), with permission from Elsevier.¹⁵ *and **= statistically significant difference; NS = non-statistically significant difference.

simulated driving performance compared to treated patients. Treated patients had shorter SOL (median 34.9 minutes) than controls (median 40 minutes), but driving performance was identical.¹⁸ This suggests hypersomnia patients with MWT scores between 30 and 40 minutes may have appropriate driving performance. Indeed, based on current research, Ingram et al recommended to use a minimally acceptable MWT result of 30 minutes for narcolepsy patients, with the understanding that almost all patients with narcolepsy continue to have some degree of sleepiness even with effective pharmacologic therapy.²⁷

The multiple sleep latency test (MSLT), in contrast, has been found to have a relatively lower correlation with driving performance in patients with narcolepsy, or no correlation at all.^{6,18} The MSLT is a daytime test, typically performed the day after an overnight laboratory polysomnogram, that entails a series of 4–5 nap opportunities spread throughout the day. A patient is considered to have objective sleepiness if their mean sleep latency is ≤8 minutes. A diagnosis of narcolepsy also requires the occurrence of at least two REM periods within 15 minutes of sleep onset. The MSLT measures objective sleepiness for untreated patients in order to diagnose a hypersomnia disorder, and does not ask the patient to try to stay awake or alert. Accordingly, the MWT is considered more sensitive to changes to the ability to stay awake as a result of treatment.²⁸ The MWT and MSLT essentially measure different aspects of sleepiness, with the MWT evaluating sleep tendency plus the ability to maintain arousal, whereas the MSLT is a measure of sleep propensity alone. The MWT is therefore a closer approximation of driving alertness.¹⁸

As noted in previous sections, sleepiness may be only one facet of risk for drowsy driving accidents in patients with narcolepsy. Driving involves the ability to divide attention between stimuli, remain vigilant through monotonous driving scenarios, and react appropriately to sudden changes. One study tested whether neuropsychological testing of alertness, vigilance, and divided and continuous attention could be used to predict simulated driving performance, but found no correlation between these measures with high inter-participant differences.¹⁷ For patients with narcolepsy, sudden stress or emotional triggers may also present risk of accidents independently of sleepiness due to cataplexy. There is no test available to predict this risk. Some authors have also suggested individuals with narcolepsy have a perceptual-encoding deficit (dysfunctional processing of relevant stimulus properties leading to slower response time) that may affect performance, though without reported impairment in motor speed, vigilance, information processing speed or decision-making accuracy.29

The most accurate objective test of driving ability available is a real driving test. Most studies on driving performance hold

this as the gold standard when comparing other measures. Driving tests of patients with narcolepsy are typically performed in research settings and are not practically feasible from a clinical standpoint. As an alternative testing measure, simulated driving tests have been developed to test highway driving scenarios, measuring such events as inappropriate line crossings (ILC) and the standard deviation of lateral position (SDLP), which is a measure of the deviation of the vehicle from the center of the lane. In simulator studies, patients with narcolepsy demonstrated more SDLP, hit obstacles more frequently, and had a higher crash rate than controls.^{17,18,30} At least one study found similar results in simulated and real SDLP performance in CNS hypersonnia patients.¹⁸ The authors suggest using both simulated driving and the MWT may provide complementary measures for evaluating sleeprelated driving impairment.

One survey of 52 pediatric sleep providers on assessing readiness to drive for adolescents with narcolepsy found that the most important clinical factors included history of previous fall-asleep crashes or near-miss crashes, followed by subjective sleepiness as reported by the patient or caregiver, and then cataplexy as reported by the patient or caregiver.²⁷ Measures

such as the MWT and MSLT were given somewhat lower weight (Figure 2). Fifty-four percent of respondents were unsure whether their US state allows physicians to report a patient to the department of motor vehicles who has a condition that makes driving unsafe, and 46% of respondents practicing in a mandatory reporting state reported they were uncertain whether their state mandated reporting. In the US, six states require mandatory reporting of medical conditions that could impair driving (California, Delaware, Nevada, New Jersey, Oregon, and Pennsylvania) to licensing or public health authorities.²⁷ Each of these states has different procedures for communicating concerns for driving risk. Providers may be liable for negligence if they fail to report a patient with narcolepsy who is later involved in a motor vehicle accident. Other states allow reporting, or may request completion of a medical form after the driver's license applicant self-reports a condition that impairs driving. Driver's license applicants in the European Union and United Kingdom also require assessment of fitness to drive.³¹ These issues highlight the differences between measures in academic and research settings and the "real world" evaluation of sleep-related accident risk for patients with narcolepsy.



Factors Assessing Readiness to Drive

Figure 2 Factors considered important by pediatric sleep providers when assessing the readiness to drive safely in patients with narcolepsy. Reprinted by permission from Springer Nature, Springer, Sleep Breath, Assessing readiness to drive in adolescents with narcolepsy: what are providers doing? Ingram DG, Marciarille AM, Ehsan Z, Perry GV, Schneider T, Al-Shawwa B. Copyright (2019), 23(2):611-617.²⁷

Pharmacologic Treatments as Risk Mitigation

Wakefulness-Promoting Medications

The mainstay of treatment for CNS hypersonnia disorders such as narcolepsy are wakefulness-promoting medications and stimulants.³² These medications reduce excessive sleepiness in patients with narcolepsy; however, the ability of a patient with narcolepsy to stay awake is rarely comparable to normal controls even with treatment.^{32,33} The most commonly used medications are wakefulness-promoting agents (modafinil and armodafinil), but stimulants such as methylphenidate and amphetamine salts are also frequently used.³⁴ Two additional medications, solriamfetol and pitolisant, have also been recently approved for treating excessive daytime sleepiness in narcolepsy. Few studies have assessed how effective wakefulness-promoting medications and stimulants are for improving driving performance in narcolepsy patients. Two studies in narcolepsy patients found modafinil improved real driving performance relative to placebo, although it did not improve lane-keeping to the level of control drivers.^{18,26} In reports of real accident history, the use of modafinil or methylphenidate has been associated with lower risk of motor vehicle accident injury in drivers with narcolepsy.³⁵ Likewise, a study of self-reported crashes found that while untreated CNS hypersomnia patients reported more crashes over the past five years than controls, there was no difference in reported crashes between hypersomnolence patients treated with a psychostimulant medication for the past five years and controls.⁶

Although stimulants may improve clinical symptoms and reduce drowsy driving risk, they also have potential adverse effects. Non-stimulant wake-promoting medications such as modafinil and armodafinil generally have mild side effects including headache, nausea, dry mouth, and loss of appetite.³⁶ Stimulant drugs such as methylphenidate and amphetamine salts typically have more pronounced side effects including anxiety, arrhythmias, loss of appetite, nausea, insomnia, and psychosis.³⁷ Although abuse potential can be problematic in patients receiving stimulants, this issue is rare among individuals with a definitive narcolepsy diagnosis.³⁴

Sodium Oxybate

Sodium oxybate (Xyrem[®]) also improves sleepiness in narcolepsy. This medication is a $GABA_B$ receptor agonist and central nervous system depressant that is approved for the treatment of narcolepsy. The medication is taken in

two doses overnight, one at bedtime and the second 2.5 to 4 hours later. Sodium oxybate can treat cataplexy, improves subjective daytime sleepiness, increases ability to remain awake in maintenance of wakefulness test (MWT) performance, and reduces sleep attacks in those with narcolepsy.^{3,34} The mechanism by which excessive sleepiness is improved is likely related to decreased arousals, increased sleep efficiency, and increased slow wave sleep.³⁸ However, it may take as long as two months for patients to experience treatment response, with one study showing maximum effect after 106 days for excessive sleepiness and 213 days for cataplexy.³⁹ As a sodium salt of GHB, sodium oxybate can impair driving after being ingested due to profound sleepiness and reduced consciousness, and there have been reports of "sleep driving" in patients while taking it.^{40–45} However, sodium oxybate has a half-life of only 30-40 minutes, with rapid clearance, reducing the incidence of these medication-related parasomnias.⁴⁶ One study assessed driver simulator performance on sodium oxybate and found severe driving impairment one hour after dosing that was similar to drivers with breath alcohol concentrations of 0.08% to 0.1%, which is considered legally impaired for drivers in the US. However, driving performance returned to baseline after three and six hours, and no GHB was detected in the serum of participants after 6 hours.⁴⁰ Patients should be counseled regarding their dose times to ensure at least 6 hours have passed since their last dose before driving. (Xyrem product information, www.xyrem.com)

Other treatments for cataplexy include antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRIs) like venlafaxine, selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, and tricyclic antidepressants (TCAs) such as clomipramine.^{47,48} The mechanism of action for these agents is to suppress REM sleep by increasing brainstem monoamine levels. Another medication shown to have positive effect on both daytime sleepiness and cataplexy is pitolisant, a histamine H3 receptor inverse agonist.⁴⁹ Effects of these medications specifically on driving performance in narcolepsy patients have not been evaluated.

Behavioral Measures as Risk Mitigation

Regardless of the risk mitigation measures employed, all patients with narcolepsy should be counseled about the risk of crashes occurring as a result of sleepiness, cataplexy, and sleep paralysis. Symptoms of drowsy driving may include disconnected thoughts, difficulty focusing, daydreaming, heavy eyelids, frequent blinking, head nodding, difficulty remembering the last few miles drive, and lane drifting.^{50,51} Studies have consistently shown that the drowsy driver's ability to self-rate driving impairment is unreliable, thus drivers should plan ahead if sleepiness is anticipated.²³ Individuals with narcolepsy should also reduce risk of cataplexy by avoiding emotional triggers known to precipitate its occurrence, if possible.

Successful behavioral mitigation measures for reducing drowsy driving risk in narcolepsy patients also include scheduling naps before driving, keeping trips short, taking nap breaks during longer drives, and taking turns driving with another person.^{52,53} Avoiding nighttime shift work or driving at times when the individual might be especially sleepy (for example, late night or early morning) may also reduce the risk of a drowsy driving crash. Additional recommendations for timing of driving and lifestyle include avoiding driving after meals, consumption of simple sugars, alcohol (which may cause rebound cataplexy after metabolism), and medications that increase daytime sleepiness, such as anxiolytics, antihistamines, and long-acting hypnotics.⁵⁴

Adequate sleep is the only proven preventative measure against fall asleep crashes in the general population. In patients with narcolepsy, planned naps can be an effective therapeutic strategy and can mitigate the risk of drowsy driving.^{54,55} Studies on the effectiveness of naps in normal participants have shown a short 15-20 minute nap improves driving performance, with longer naps causing grogginess due to sleep inertia upon awakening.56,57 Drinking 1-2 cups of coffee and pulling over for a 20minute nap has also been shown to temporarily increase alertness in drowsy drivers, although again this was a study of normal adults.⁵⁸ One study of a repeated nap paradigm in narcolepsy with cataplexy patients found a single long nap, one-third the duration of nocturnal sleep (~2-3 hours) and occurring 12 hours after the nocturnal midsleep time, improved reaction time performance.⁵⁵ Naps may also improve performance on the MWT as a proxy measure of driving alertness.^{59,60}

Caffeine use has been well studied in non-narcoleptic subjects as a wakefulness-promoting substance that is widely used and easily obtained. A recent systematic review and meta-analysis of 45 studies found caffeine improved performance on tests of attention, executive function, response time, as well as measures of driving performance.⁶¹ In

patients with narcolepsy, caffeine has been found in limited research to improve sleepiness, but studies are lacking on its effectiveness to mitigate driving risk.⁶² Strategic dosing with caffeine or a prescribed stimulant medication prior to driving may be considered as an augmenting agent to further reduce risk of drowsy driving.

Other behavioral measures such as exercise, chewing gum, listening to music, opening car windows, talking to passengers, or talking on a cell phone are not beneficial for normal drivers, let alone those with narcolepsy, and may even increase risk of crashes due to distraction.^{63,64}

With appropriate driving precautions and effective treatment, patients with narcolepsy may be able to drive safely. Indeed, a case-control study focused on driving behavior and crash history found narcolepsy patients over 40 years old who adopted effective behavioral strategies such as napping, taking medications before driving, and pulling over for a nap when sleepy had even fewer crashes than controls.⁶⁵ There is little evidence that narcolepsy is continuously progressive. In fact, older patients with narcolepsy may be generally less sleepy than younger patients, and less likely to demonstrate REM sleep desynchrony, despite experiencing age-related decrements in sleep quality.⁶⁶ Worsening sleepiness in older patients with narcolepsy should prompt evaluation for comorbid sleep disorders such as obstructive sleep apnea. However, to our knowledge, studies on driving performance in patients with narcolepsy have not compared simulated or actual driving performance by age group.

Conclusion

Narcolepsy is a chronic CNS hypersomnia causing significant impairment in multiple aspects of life including driving performance. The disorder often arises in the adolescent and young adult years, when most people are beginning to drive. Patients with narcolepsy are at higher risk of sleep-related accidents than the normal population due to the propensity for sleep attacks, sleep paralysis, and cataplexy. Given the morbidity and mortality associated with drowsy driving, which kills over 6000 people per year in the United States, and the high risk of narcolepsy patients for sleep-related accidents, strategies to evaluate and modify driving risk are of high importance.⁶⁷ There are no established guidelines for determining appropriateness for driving in treated narcolepsy patients; additionally, many providers may not be aware of mandated reporting requirements in their region. When evaluating driving risk, the use of the MWT may be the most commonly used objective measure of alertness. Although caution should be used in applying MWT as a predictive measure for driving performance or risk, it can help establish the ability of the narcolepsy patient to resist sleep propensity. Use of the MWT should especially be considered for new or young drivers, patients with residual sleepiness, and those with prior history of fall-asleep crashes.

Narcolepsy treatments have demonstrated some efficacy in improving wakefulness and reducing cataplexy in patients with narcolepsy; however, few studies have evaluated whether these treatments improve driving safety. Modafinil may improve both MWT scores and driving performance in narcolepsy patients, though not to the level of normal drivers. Sodium oxybate (Xyrem) impairs driving after ingestion, but has a short half-life and improves next-day alertness. Other behavioral measures that may reduce driving risk include scheduled naps, driving only short distances at one time, and avoiding factors that may increase sleepiness, such as driving after heavy meals, simple carbohydrates, sedating medications, and alcohol intake.

Narcolepsy is a rare sleep disorder, but the impacts of unsafe driving in this population due to excessive sleepiness, cataplexy, and sleep paralysis are potentially farreaching. Additional research on the impacts of narcolepsy treatment on driving safety are warranted, especially for newer medications, caffeine, and behavioral strategies that are the cornerstones of current recommendations for safe driving in all sleepy patients. Clinical providers should also be educated on the risks of drowsy driving, how to screen for potentially unsafe driving, when to consider MWT, and whether reporting a diagnosis of narcolepsy to departments of public health or motor vehicles is required in their state or country. Providers should understand how to effectively counsel patients on safe driving practices, particularly for new drivers. With the appropriate treatment, counseling, precautions and limits, many narcolepsy patients may be able to drive safely during everyday life.

Disclosure

The authors report no conflicts of interest for this work.

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