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# *An Evaluation of Orexin Receptor Agonists Versus Traditional Pharmacotherapy in Narcolepsy Type 1*

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***Abstract.*** Narcolepsy type 1 (NT1) is a chronic hypersomnia caused by autoimmune-mediated destruction of hypothalamic orexin (hypocretin) neurons, producing excessive daytime sleepiness (EDS), cataplexy (the loss of muscle control), and REM sleep intrusions. In the past 3 decades, the treatment has relied on symptomatic pharmacotherapy: wake-promoting agents for sleepiness, anti-cataplexy agents for REM-related symptoms, and traditional stimulants. However, neither restores orexin signaling itself. This paper reviews recent primary and secondary literature to compare traditional multi-drug regimens with the emerging class of orexin receptor 2 (OX2R) agonists, which act directly on the pathway the disease disables. It evaluates whether OX2R agonists represent a mechanistic advance over existing pharmacotherapy and what still limits their translation into standard care. Drawing on clinical trial data for 3 OX2R agonists (TAK-994, danavorexton and oveporexton) alongside pharmacotherapy reviews and diagnostic studies, the paper finds that OX2R agonists achieve single-agent efficacy for sleepiness and cataplexy but several issues, such as incomplete diagnostic criteria and persistent underdiagnosis, still constrain their clinical impact.

***Keywords:*** Narcolepsy Type 1, orexin receptor agonist, hypocretin, cataplexy, orexin

## 1. Introduction

Narcolepsy type 1 (NT1) is a rare and disabling sleep-wake disorder characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. Its defining lesion is the near-total loss of orexin-producing neurons in the lateral hypothalamus, a destruction understood to be autoimmune in origin and closely linked to the HLA-DQB1*06:02 allele [1]. Despite this mechanism, NT1 carries a diagnostic delay averaging 10 years, driven by symptom overlap with psychiatric and attention disorders and the unfamiliarity with its full symptom spectrum [2]. The historical treatments have been symptomatic: wake-promoting stimulants address sleepiness, and REM-suppressing agents address cataplexy, leaving the underlying orexin deficit untouched [3]. Over the past 5 years, a new drug class, orexin receptor 2 (OX2R) agonists, has entered clinical trials with the explicit goal of substituting for the missing neuropeptide. This paper compares the two treatment paradigms by asking how traditional pharmacotherapy and orexin receptor agonists differ in mechanism and measured efficacy, and whether either approach addresses the diagnostic and personalization gaps that still shape real-world NT1 care. This paper aims to evaluate whether

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mechanism-based therapy has meaningfully outperformed symptomatic management and where they still fall short.

## 2. The neurobiology of narcolepsy type 1

NT1 arises from the destruction of roughly 50,000-70,000 orexin (hypocretin) neurons normally present in the lateral hypothalamus, supported by postmortem studies that documented losses of up to 95% [4]. These neurons send widespread projections to the brain's monoaminergic and cholinergic arousal centers: the noradrenergic locus coeruleus, histaminergic tuberomammillary nucleus, serotonergic raphe nuclei, dopaminergic ventral tegmental area, and cholinergic basal forebrain. They help maintain sustained wakefulness and also inhibit the sleep-promoting ventrolateral preoptic area (VLPO), suppressing REM sleep outside of normal sleep periods [1]. This mutual inhibition between wake-promoting and sleep-promoting circuits acts as a bistable "flip-flop" switch. Orexin, in this case, plays the role of stabilizing whichever state the switch is in, which prevents the rapid, unwanted transitions between wake, NREM, and REM that are characteristic of NT1 [1]. Its loss destabilizes this boundary, so REM-associated phenomena, muscle atonia, hallucinations, and paralysis can intrude into wakefulness [1]. A 2026 postmortem study extended this picture and showed that narcolepsy with cataplexy also involves an average 46% loss of norepinephrine-producing neurons in the locus coeruleus, accompanied by microglial clustering around both the hypothalamic and brainstem lesions, indicating that hypocretin-neuron loss may not be driven only by neurodegenerative processes [5]. The cause of this neuronal loss is now recognized to be autoimmune. A study by Rauf R, Asif S, AlSaafeen A, et al. found that over 90% of NT1 patients carry the HLA-DQB1*06:02 allele, and genome-wide association studies have identified secondary risk loci in T-cell receptor genes, implicating antigen presentation by DQ0602 to CD4+ T cells and subsequent CD8+ T-cell-mediated destruction of hypocretin neurons [4]. Autoreactive, HLA-DR-restricted CD4+ T cells targeting multiple hypocretin-neuron antigens, along with hypocretin-specific CD8+ T cells, have been isolated directly from the blood and cerebrospinal fluid of NT1 patients [6]. A separate line of evidence links disease onset to molecular mimicry: cross-reactivity has been demonstrated between an amidated hypocretin epitope and a peptide from the 2009 pandemic influenza hemagglutinin protein, helping to explain the epidemiological clustering of NT1 onset after wild H1N1 infection and after vaccination with the AS03-adjuvanted vaccine Pandemrix [7]. Combined with the finding that over 90% of patients have cerebrospinal fluid orexin-A below 110 pg/mL, this cluster of biomarkers—low CSF orexin-A, HLA-DQB106:02 positivity, and detectable autoreactive T-cell responses—is specific enough to function as a near-diagnostic profile even before confirmatory polysomnography [4].

## 3. Traditional pharmacotherapy: symptomatic management

### 3.1. Wake-promoting agents

The first-line therapy for excessive daytime sleepiness consists of wake-promoting agents, principally modafinil, armodafinil (an enantiopure derivative of modafinil), solriamfetol, and pitolisant [3]. Modafinil acts as a weak inhibitor of dopamine reuptake and thus indirectly increases extracellular dopamine level in wake-promoting circuits without the broad monoamine-releasing effects of classic amphetamines. It reliably increases daytime sleep latency and remains the most widely prescribed option for NT1. However, its characteristic also suggests a favorable abuse-

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potential profile [3]. Additionally, it has no significant effect on cataplexy, and its safety data remains limited [3].

Solriamfetol, approved in 2019, is a dual-acting dopamine and norepinephrine reuptake inhibitor, and it also lacks the monoamine-releasing activity of amphetamines [8]. Across pivotal phase 3 trials (TONES: treatment of OSA and Narcolepsy excessive sleepiness program), 12 weeks of solriamfetol produced early and sustained reductions in daytime sleepiness and improved objective wakefulness relative to placebo, which offered an alternative mechanism for patients who reacted poorly to modafinil [8]. However, it has the same problem as modafinil does: it does not treat cataplexy well, and it must be paired with a separate agent if cataplexy is present in the patient.

Pitolisant, on the other hand, works through an entirely distinct mechanism that does not involve monoamine reuptake at all. As a histamine H3 receptor antagonist and inverse agonist, it blocks presynaptic H3 autoreceptors on histaminergic neurons in the tuberomammillary nucleus, increasing histamine release into the same arousal circuitry that orexin neurons normally drive [9]. Dauvilliers Y et al. have conducted a double-blind experiment, and in the placebo- and modafinil-controlled HARMONY-1 trial, pitolisant improved daytime sleepiness. It also improved cataplexy frequency among 80% of participants with a history of cataplexy, making it the only wake-promoting agent with meaningful anti-cataplectic activity.

### 3.2. Anti-cataplexy agents

Sodium oxybate, a form of gamma-hydroxybutyrate, is the only medication that was initially approved specifically for cataplexy in NT1. It also reduces the fragmentation of sleep at night and, in higher amounts, daytime sleepiness [3]. The drug is taken in two doses, once at bedtime and again 2.5 to 4 hours later. It is also thought to be a GABA-B receptor agonist, consolidating slow-wave sleep and decreasing the fragmentation of REM sleep, which may result in cataplexy the following day [3]. The use of the drug is limited by its high sodium content (around 1,000 to 1,500 mg each night) as well as by its abuse potential and the requirement that it be dispensed through a single central pharmacy [3]. In 2020, the FDA approved a version with less sodium, containing calcium, magnesium, potassium, and sodium oxybate. This new formulation has about 92% less sodium than the original. A phase 3 randomized, double-blind, placebo-controlled trial in 201 adults with NT1 found significant reductions in weekly cataplexy attacks and scores on the Epworth Sleepiness Scale compared to placebo in response to this drug, offering prescribers an option that is safer for cardiovascular health and similarly effective to the original product [10].

Another class of anti-cataplexy agents, REM-suppressing antidepressants, most often venlafaxine or fluoxetine, are commonly added off-label to control cataplexy by dampening the REM-sleep intrusions from which it originates, and tricyclic agents such as clomipramine remain a second-line option when SNRIs and SSRIs are insufficient [3].

Nevertheless, none of these agents, including sodium oxybate, act on orexin signaling itself, and because none is fully effective against both symptom domains alone, patients frequently require a combination of different agents. One wake-promoting agent from section 3.1 with sodium oxybate or an antidepressant is the typical way to control the full symptom tetrad. The following problem is evident: this layering will increase pill burden, drug interaction risk, and side effect exposure since it fails to address the root neuropeptide deficiency as mentioned in section 1.

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## 4. Orexin receptor agonists

### 4.1. Mechanism and clinical development

OX2R agonists are different from traditional agents, as the former are designed to bind directly to the remaining orexin receptors and signal downstream to the arousal-promoting neurons those receptors still innervate, and the latter compensate by acting through unrelated monoaminergic or GABAergic pathways. TAK-994 is the first oral OX2R agonist to be tested in clinical trials. It prevented cataplexy and had significant reductions in daytime sleepiness in an 8-week phase 2 trial, better than any single traditional agent alone [11].

Danavorexton (an intravenous OX2R-selective agonist) increased sleep latency on the Maintenance of Wakefulness Test (MWT) in dose-dependent ways up to the 40-minute limit and showed greater average improvement than modafinil in a 2024 multicenter trial [12].

Oveporexton (an oral OX2R-selective agonist) was studied in 4 dosing regimens in its phase 2 trial. At the most effective dose of 2 mg twice daily, the average MWT sleep latency improved by 25.4 minutes compared to placebo (a 1.2-minute decrease); Epworth Sleepiness Scores improved by 12.8 points; and weekly cataplexy rates were reduced to about a third of those in placebo patients, with a significant difference between oveporexton and placebo at all active doses [13]. Early in its phase 3 trials, FirstLight and RadiantLight were shown to meet all primary and secondary endpoints (for a variety of NT1 symptoms) at week 12, and the FDA approved Oveporexton's new drug application for priority review in February 2026, when the first trial is planned for the third quarter of 2026 [14].

All of the drugs mentioned above were able to control both of the major symptom areas that used to need separate drug classes. This surprising result shows that restoring receptor-level signaling might be a better strategy compared to managing symptoms downstream. On the whole, 20 minutes or more MWT sleep latency is normal, so oveporexton's 25.4 minutes improvement at its best dose took the average treated patient from pathological sleepiness to a generally normal range on this measure (Figure 1).

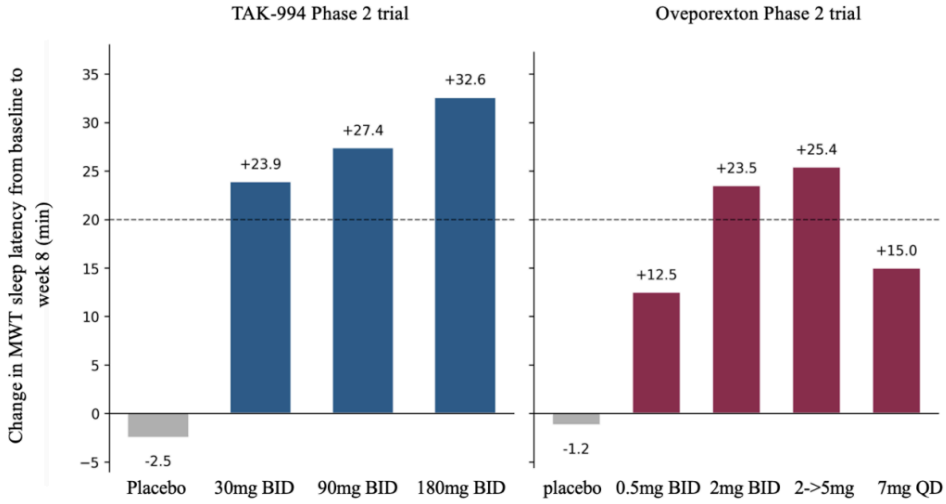



Figure 1. Change in Maintenance of Wakefulness Test (MWT) sleep latency at week 8

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### 4.2. Remaining limitations

The clinical promise of this class of drugs is influenced by a significant safety signal. The development of TAK-994 was terminated after 8 participants exceeded liver-enzyme thresholds for trial discontinuation, and 3 cases met the criteria for drug-induced liver injury. The leading hypothesis for this consequence attributes it to reactive metabolites specific to the TAK-994 molecule because orexin receptors are not expressed on hepatocytes [11]. Oveporexton's phase 2 trial reported no hepatotoxic effects, and this suggests that the liver signal may be compound-specific rather than a class effect. However, its most common adverse events, insomnia in roughly half of participants, urinary urgency, and urinary frequency, were substantially more frequent than in the placebo group, plausibly reflecting orexin receptor expression outside the central nervous system [13]. Because the class is new, and the long-term safety data comparable to the decades of post-marketing experience behind modafinil or sodium oxybate do not exist yet, oveporexton is under FDA priority review, with no compound in the class yet fully approved for routine prescribing [14].

Another point to consider is the cost and access. Since novel small-molecule agonists brought to market by a single manufacturer typically launch at price points well above generic stimulants such as modafinil, the cost factor is consequential for real-world applications. Trials to date have also enrolled adults with confirmed and severe orexin deficiency. However, whether OX2R agonists are similarly effective in patients with partial orexin-neuron loss, in narcolepsy type 2, or in children, for whom no narcolepsy pharmacotherapy currently carries FDA approval, is still unsure and unestablished, and none of the pivotal trials has yet reported data beyond roughly a year of continuous use [1].

## 5. Persisting gaps in diagnosis and treatment personalization

Neither approach addresses the diagnostic delay that precedes NT1 care. It is commonly years from symptom onset to diagnosis due to a lack of concordance between the classic symptom tetrad and the patients who actually present [2]. NT1 is diagnosed using a strict cutoff: CSF orexin-A below 110 pg/mL

will be diagnosed with NT1. But some patients diagnosed with NT2 or idiopathic hypersomnia also have abnormally low orexin-A, and other patients' orexin levels are not low enough to cross the line. This all-or-nothing cutoff makes these borderline patients harder to diagnose and shuts them out of orexin-targeted treatment. Currently, clinical approaches are based on cataplexy and polysomnographic data that do not represent this heterogeneity very well, and there remains a subset of hypersomnia patients for whom the path to diagnosis, and the applicability of OX2R agonists, is unclear [15]. An aspect worth mentioning is that children are particularly at risk, because neither traditional nor orexin-directed treatments are approved for pediatric NT1 by the FDA yet, and almost half of these patients are developing symptoms in their teenage years [1]. Even among those who are known to be NT1 patients, in trials, the clinical outcomes (sleep latency, Epworth score, cataplexy frequency) may not reflect the symptoms that the patients themselves consider most disruptive to daily life. In real life, orexin dysfunction has been considered to be associated with psychiatric disorders at rates far above those in the general population, with major depressive disorder occurring in about 40% of NT1 patients and anxiety disorders occurring in nearly 30% of NT1 patients, yet neither traditional nor orexin-directed trials are targeting the quality of life as a principal outcome [4]. A more mechanistically precise drug class is not sufficient to fill all these gaps: diagnostic criteria, trial design, and pediatric drug development are beyond pharmacology, and

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none of the three OX2R agonist programs reviewed here has yet considered patient-reported outcome measures as an endpoint.

## 6. A proposed experimental design

The evidence reviewed above leaves one question: does the degree of noradrenergic locus coeruleus (LC) degeneration found in NT1 [5] determine which patients achieve full cataplexy control on an OX2R agonist and which are left with residual symptoms? This proposed experimental design will test the hypothesis that patients with more severe LC degeneration will experience a smaller decrease in cataplexy frequency on OX2R agonist therapy than those whose LC integrity is relatively preserved, regardless of their baseline CSF orexin-A level or age.

To test this, a prospective multi-site, biomarker-stratified experiment would be conducted at 25 sleep neurobiology centers worldwide, enrolling 600 untreated patients with confirmed NT1 (a patient with CSF orexin-A below 110 pg/mL & HLA-DQB1*06:02 positive), including both adults and adolescents to address the current absence of pediatric data. First, each participant would have a PET scan to assess noradrenergic terminal density and therefore LC integrity at baseline. All participants would then start oveporexton at the phase 3 dose, which is 2 mg twice daily, and be followed for 24 weeks, keeping weekly cataplexy diaries. They would also have monthly MWT and Epworth scale assessments to measure sleepiness and alertness. At the end of week 24, a second PET scan would be performed to evaluate the treatment's effect on the LC signal.

The primary analysis would use mixed-effects regression to predict the percent reduction in weekly cataplexy rate at week 24 based on baseline PET-measured LC integrity. A secondary analysis would then stratify participants into quartiles of LC integrity to examine a possible dose-response relationship. An interaction term for pediatric versus adult participants would be included to test whether the LC response relationship varies by age.

## 7. Conclusion

Comparing traditional therapy to OX2R agonists, the evidence supports a clear mechanistic and efficacy advantage for the latter over the former. Across 3 independent compounds, a single agent achieved control of both EDS and cataplexy by restoring signaling at the receptor pathway, while traditional regimens require multiple drug classes to approximate this. This constitutes a shift from symptomatic to mechanistic treatment, the first of its kind for NT1.

But that advance is not yet unconditional. The hepatotoxicity signal of TAK-994 shows that targeting the right receptor is not sufficient to guarantee a good safety profile, and even oveporexton still includes adverse events too frequently and with a general lack of long-term real-world safety data to warrant caution before this class is considered a settled first-line therapy. Traditional pharmacotherapy continues to be important because it offers decades of real-world safety experience and lower generic cost than OX2R agonists' costs; it is the necessary fallback and the default for patients diagnosed under current criteria while OX2R agonists are still being reviewed by regulatory authorities.

In real-world cases, a lot of patients who could benefit from either treatment do not have access to it, regardless of which drug class is more effective. Both of those paradigms are more sequential and complementary than competitive. The proposed study in Section 6, which examines whether locus coeruleus integrity predicts residual cataplexy, is a particularly important step toward understanding why even OX2R agonist dosing is not enough for some patients. Thus, long-term

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post-marketing safety monitoring needs to focus on diagnostic criteria that include the whole orexin-deficiency spectrum.

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