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DOI: 10.5582/ddt.2026.01056

Oveporexton: The first-in-class orexin receptor 2 (OX2R) agonist approved for treatment of narcolepsy type 1 (NT1)

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SUMMARY: Narcolepsy type 1 (NT1) is a chronic neurological disorder caused by selective loss of orexin-producing neurons, resulting in unstable sleep-wake regulation and characteristic symptoms including excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, hypnagogic or hypnopompic hallucinations, and disrupted nocturnal sleep. Current treatments mainly provide partial symptomatic relief and do not correct the underlying orexin deficiency, highlighting the need for mechanism-based therapies. Oveporexton (TAK-861), an orally administered selective orexin receptor 2 (OX2R) agonist developed by Takeda Pharmaceuticals, represents the first approved therapy targeting the orexin pathway in NT1. By activating preserved OX2R signaling, oveporexton restores wakefulness regulation and alleviates multiple core symptoms of NT1. Its approval was aided by two global phase 3 trials which demonstrated significant improvements in wakefulness and cataplexy compared with placebo. Although its long-term safety, accessibility, and real-world efficacy need to be evaluated further, oveporexton represents a major advance toward disease mechanism-based treatment for NT1.

Keywords: narcolepsy, NT1, orexin, OX2R, EDS, cataplexy

1. Narcolepsy and disease burden

Narcolepsy is a chronic neurological disorder characterized by impaired stability of the sleep–wake state and dysregulation of rapid eye movement (REM) sleep (*1*). According to the International Classification of Sleep Disorders (ICSD), narcolepsy is mainly classified into narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2). NT1 accounts for approximately 70% of all narcolepsy cases, and its core pathological feature is the selective loss of orexin (also known as hypocretin)-producing neurons in the lateral hypothalamus, resulting in markedly reduced orexin levels in cerebrospinal fluid (*2-4*).

Patients with NT1 typically present with excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, hypnagogic or hypnopompic hallucinations, and disrupted nocturnal sleep (*1*). Among these symptoms, cataplexy is the key clinical feature distinguishing NT1 from NT2 and is considered to result from the abnormal intrusion of REM sleep-associated muscle atonia mechanisms into wakefulness (*1,5*). In contrast, NT2 is primarily characterized by EDS without typical cataplexy, and orexin levels in cerebrospinal fluid are generally normal. The underlying pathophysiological mechanisms of NT2 still have yet to be fully understood (*1,5*).

Although NT1 has a relatively low prevalence, it imposes a substantial disease burden. Epidemiological studies in the United States have reported a prevalence of approximately 0.025–0.05%, although estimates vary among different studies (*6*). In China, the true prevalence of narcolepsy remains unclear due to the lack of large-scale population-based studies; however, available surveillance data indicate that narcolepsy cases continue to be identified, with NT1 representing a substantial proportion of cases (*7*). Persistent daytime sleepiness and cataplexy significantly impair patients' academic performance, occupational ability, and social functioning. In addition, they increase the risk of traffic accidents and occupational injuries and are associated with depression, anxiety, obesity, and cardiometabolic abnormalities (*1,5*).

2. Current treatment landscape and the unmet clinical need for treatment of NT1

Current management of NT1 mainly includes behavioral interventions and pharmacological therapies. The major therapeutic goals are to alleviate EDS, reduce cataplexy episodes, optimize nocturnal sleep, and help patients regain normal social functioning (*8,9*). Pharmacological treatment remains a cornerstone of disease management.

Commonly used medications for EDS include modafinil, armodafinil, sodium oxybate, pitolisant, and solriamfetol. Modafinil has long been considered a first-line wake-promoting medication for many patients due to its established efficacy and favorable safety profile. Sodium oxybate can alleviate both EDS and cataplexy and it remains an important therapeutic option for NT1. Pitolisant and solriamfetol are newer medications developed primarily for the management of EDS (*8,9*). For cataplexy, sodium oxybate and certain antidepressants, including tricyclic antidepressants and serotonin reuptake inhibitors, can effectively reduce the frequency of attacks (*8,9*).

However, current treatments mainly act by enhancing wake-promoting pathways or modulating monoaminergic neurotransmission and cannot correct the fundamental pathological defect of orexin deficiency in NT1. Therefore, existing therapies only provide partial symptomatic relief, and many patients continue to experience residual sleepiness, cataplexy episodes, and impaired nocturnal sleep quality. Moreover, some medications are associated with limitations, including the potential risk of dependence, cardiovascular adverse effects, or insufficient evidence regarding long-term safety. Therefore, the development of mechanism-based therapies targeting the orexin pathway represents an important unmet clinical need.

3. Mechanism of action and approval status of oveporexton

Oveporexton (TAK-861; trade name ORZEYFUL) is an orally administered, highly selective orexin receptor 2 (OX2R) agonist developed by Takeda Pharmaceuticals. The orexin system plays a critical role in maintaining wakefulness stability, regulating sleep–wake transitions, and preventing inappropriate intrusion of REM sleep characteristics into wakefulness (*3*). Although patients with NT1 exhibit extensive loss of orexin-producing neurons, downstream OX2R signaling pathways remain preserved. Therefore, direct activation of OX2R represents a therapeutic strategy that bypasses neuronal loss and restores wakefulness regulation.

On July 23, 2026, the National Medical Products Administration (NMPA) of China announced that oveporexton tablets have been approved for the treatment of NT1 in adolescents and adults age 16 years and older, making it the first approved oral OX2R agonist globally (*10,11*). On August 5, 2026, the U.S. Food and Drug Administration (FDA) approved oveporexton tablets for the treatment of adult patients with NT1 (*12*). The approved indications differ between the two countries: China includes patients age ≥16 years, whereas in the U.S. the current indication is limited to adults. Compared to conventional wake-promoting medications, oveporexton directly restores orexin signaling and theoretically has the potential to alleviate multiple core symptoms of NT1, including EDS, cataplexy, and sleep–wake instability. Therefore, it represents an important transition from symptomatic management towards disease mechanism-based therapy.

4. Clinical evidence

The approval of oveporexton was primarily aided by two global phase 3 randomized, double-blind, placebo-controlled clinical trials. The FirstLight study (TAK-861-3001; NCT06470828) enrolled 168 patients with NT1 and evaluated the efficacy and safety of oveporexton at doses of 1 mg twice daily and 2 mg twice daily compared to a placebo over 12 weeks (*13*). Both doses significantly improved sleep latency in the Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS) scores, and the weekly cataplexy rate (WCR). All primary and key secondary endpoints were met with significant improvement. At week 12, both oveporexton 1 mg and 2 mg twice daily significantly reduced the WCR, with an incidence ratio versus a placebo of 0.34 (95% CI, 0.20–0.57) and 0.38 (95% CI, 0.23–0.61), respectively (*13*).

The RadiantLight study (TAK-861-3002; NCT06505031) further evaluated the efficacy of oveporexton at 2 mg twice daily (*13*). This study enrolled 105 patients with NT1 who were randomized at a ratio of 2:1 to receive oveporexton or a placebo. Compared to a placebo, at week 12 the oveporexton group showed a 20.1-minute increase in MWT sleep latency, a 9.5-point greater reduction in ESS scores, and a significantly lower risk of cataplexy events (rate ratio, 0.25). All major efficacy outcomes were significant (*13*). The most frequently reported adverse events included insomnia, increased urinary frequency, urgency to urinate, and increased saliva production.

5. Clinical significance and future perspectives

The approval of oveporexton represents a major advance in the treatment of narcolepsy. Over the past several decades, NT1 management has relied primarily on wake-promoting agents and symptomatic therapies. Oveporexton is the first pharmacological intervention specifically targeting the core pathological defect of NT1, an orexin deficiency, and it represents an important breakthrough in mechanism-based treatment for sleep disorders.

Nevertheless, the long-term clinical value of oveporexton needs to be evaluated further. Orexin neuron loss in NT1 is generally irreversible, so whether OX2R activation can fully restore physiological sleep–wake regulation remains to be determined through long-term follow-up studies. In addition, further study needs to be performed to clarify the long-term safety, tolerability, and real-world efficacy of oveporexton and differences in treatment response among patients of different ages

and disease stages. Drug cost and accessibility may also influence its widespread clinical adoption.

Overall, oveporexton provides a novel therapeutic option for patients with NT1 based on disease mechanisms. Its approval represents a significant shift in the therapeutic paradigm of narcolepsy; however, its long-term clinical benefits need to be further assessed in clinical practice.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received August 12, 2026; Accepted August 16, 2026.

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Released online in J-STAGE as advance publication August 19, 2026.