Review

Shedding new light on anorexia nervosa: The therapeutic promise of the orexin system

Nadzieje związane z układem oreksynowym w terapii jadłowstrętu psychicznego

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Abstract

Anorexia nervosa (AN) is a severe psychiatric disorder associated with high morbidity and mortality. Despite decades of research, pharmacological treatments remain largely ineffective. Increasing evidence suggests that the orexin (hypocretin) system, which regulates arousal, motivation, feeding behavior, and stress responses, may play an important role in the pathophysiology of AN.

The present review aims to summarize current evidence regarding the involvement of the orexin system in AN, including its neurobiological mechanisms, interactions with dopaminergic and serotonergic pathways, and the therapeutic potential of orexin receptor modulators.

A literature review was conducted using the PubMed®, Scopus and Web of Science databases. Studies using animal models (activity-based anorexia (ABA)) and clinical investigations were included to assess orexin expression, signaling and modulation in AN. Preclinical findings indicate that orexin contributes to hyperactivity, disrupted reward processing and altered feeding behavior in anorexia models. Both orexin receptor type 1 (OX1R) and type 2 (OX2R) appear to play distinct but complementary roles. Pharmacological modulation, particularly via antagonists such as suvorexant and tebideutorexant (JNJ-61393215), shows promise for reducing hyperarousal and maladaptive motivation. However, clinical evidence remains limited and inconclusive. Human studies have reported inconsistent concentrations of orexin A (OXA) in AN, possibly due to methodological heterogeneity.

The orexin system represents a promising but underexplored target in AN. Further clinical trials are urgently needed to clarify its therapeutic potential and safety profile in malnourished populations. Incorporating orexin modulators into multimodal treatment strategies may provide novel approaches to addressing the biological complexity of AN.

Keywords: anorexia nervosa, orexin system, orexin receptors, reward processing, neuropharmacology

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Streszczenie

Przegląd ma na celu podsumowanie wiedzy o roli układu oreksynowego w jadłowstręcie psychicznym (grec. *anorexia nervosa* - AN), w tym w mechanizmach neurobiologicznych, interakcjach z układami dopaminergicznym i serotoninergicznym oraz potencjale terapeutycznym modulatorów receptorów oreksynowych. Jadłowstręt psychiczny jest ciężkim zaburzeniem psychicznym o wysokiej śmiertelności. Pomimo licznych badań leczenie farmakologiczne pozostaje w dużej mierze nieskuteczne. Coraz więcej dowodów wskazuje na to, że układ oreksynowy (hipokretynowy), regulujący pobudzenie, motywację, zachowania żywieniowe i reakcje na stres, może odgrywać rolę w patofizjologii AN.

Przeprowadzono przegląd literatury w bazach PubMed® i Scopus obejmujący badania przedkliniczne (np. *activity-based anorexia*) oraz badania kliniczne analizujące ekspresję, sygnalizację i modulację oreksyny w AN. Wyniki badań przedklinicznych wskazują, że oreksyna przyczynia się do nadpobudliwości, zaburzeń układu nagrody i zmian w zachowaniach żywieniowych w modelach jadłowstrętu psychicznego. Receptory oreksynowe 1 (OX1R) i 2 (OX2R) mają odrębne, ale wzajemnie uzupełniające się funkcje. Farmakologiczna modulacja układu oreksynowego, szczególnie za pomocą antagonistów, takich jak suworeksant i JNJ-61393215 (tebideutorexant), wykazuje potencjał w redukcji nadmiernego pobudzenia i nieadaptacyjnych stanów motywacyjnych. Jednak dane kliniczne pozostają ograniczone i niejednoznaczne. Wyniki badań poziomu oreksyny A przeprowadzone u osób cierpiących na AN są niespójne, co prawdopodobnie jest spowodowane heterogennością metodologiczną oraz różnicami w stadium choroby i stanie odżywienia pacjentów.

Układ oreksynowy stanowi obiecujący, lecz wciąż słabo zbadany cel terapeutyczny w jadłowstręcie psychicznym. Niezbędne są dobrze zaprojektowane badania kliniczne, które pozwolą określić skuteczność i bezpieczeństwo interwencji ukierunkowanych na oreksynę, szczególnie w populacjach osób niedożywionych. Włączenie modulatorów oreksynowych do wielomodalnych strategii terapeutycznych może zaoferować nowe podejście do leczenia AN, które będzie uwzględniać jej złożoną neurobiologię.

Słowa kluczowe: *anorexia nervosa*, jadłowstręt psychiczny, układ nagrody, układ oreksynowy, receptory oreksyny, leczenie jadłowstrętu psychicznego

Introduction

Anorexia nervosa (AN), which is characterized by restrictive food intake, is considered one of the most severe and complex psychiatric disorders. Individuals with AN commonly experience an intense fear of weight gain and a distorted perception of their body image (Resmark *et al*., 2019). The highest incidence of AN is observed among adolescents aged 15–19 years. Recent studies from European countries have reported an increasing incidence of AN among girls aged 10–14 years and even younger children (Holland *et al*., 2016; Reas and Rø, 2018; Udo and Grilo, 2022; van Eeden *et al*., 2023). Research published in 2022 estimated that eating disorders affect approx. 0.91% of the population over a lifetime, whereas AN occurred in 0.16% of the population (Qian *et al*., 2022). More recently, a study published in 2024 reported a marked increase in the incidence of AN among children and adolescents following the coronavirus disease 2019 (COVID-19) pandemic (Datta *et al*., 2024).

The development of AN is associated with numerous mental and physical health issues, including depression, anxiety, hormonal problems, and obsessive-compulsive disorder (Resmark *et al*., 2019). Despite advances in the treatment of AN, no pharmacological therapy has yet demonstrated clinical efficacy (Datta *et al*., 2024). Furthermore, the neurobiological mechanisms underlying the characteristic features of AN, such as reduced appetite, anxiety, and sleep disturbances associated with excessive arousal and physical activity, remain incompletely understood (Charrat *et al*., 2023; Datta *et al*., 2024). These observations suggest the involvement of neurobiological systems regulating feeding behavior, stress, arousal, and reward processing. The orexin system regulates mechanisms of reward, motivation, arousal, eating behavior, and the stress response (Sakurai *et al*., 2021).

Although behavioral and physiological abnormalities in AN have been well documented, the mechanisms underlying these alterations remain incompletely understood due to limitations and inconsistencies in the available evidence.

The role of orexin receptor agonists and antagonists has not been fully established in the context of AN. Current evidence regarding the role of the orexin system is inconsistent and inconclusive, highlighting the need for further clinical research.

The orexin system serves as a critical interface between metabolic information and reward processing, motivational responses, and arousal regulation within the central nervous system (Katzman and Katzman, 2022).

The disruption of orexin signaling pathways, which are linked to dopaminergic and serotonergic systems, may result in appetite problems and reward system abnormalities, as well as hyperactivity and increased anxiety in AN (Mavanji *et al*., 2022; Sakurai *et al*., 2021; Schéle *et al*., 2023).

Despite growing interest in these mechanisms, research supporting pharmacological interventions targeting the orexin system remains limited (Miskovic-Wheatley *et al*., 2023). The evidence supporting the involvement of the orexin system in AN is scarce as only preclinical models have been used and no consistent results have been found in clinical studies (Schéle *et al*., 2023). Consequently, a comprehensive review of the current literature is necessary to clarify the potential role of orexin system regulation as a therapeutic approach in AN (Datta *et al*., 2024).

The present review summarizes current evidence regarding the involvement of the orexin system in the pathogenesis of AN by integrating findings from both animal and human studies. In addition, it proposes novel therapeutic strategies for psychiatric conditions, including AN.

Material and methods

This narrative review was conducted following the SANRA (Scale for the Assessment of Narrative Review Articles) scale to ensure methodological rigor, transparency, and coherence. Although not a systematic review, a structured and reproducible approach was employed, including predefined search terms, the inclusion of multiple databases, clear selection criteria, and critical evaluation of study quality.

A literature search was conducted in the PubMed®, Scopus and Web of Science databases, covering the period from 2000 to 2025. Additional databases such as ClinicalTrials.gov were searched for registered trials on orexin modulators. The following keywords and their combinations were used: "orexin"; "hypocretin"; "anorexia nervosa"; "eating disorders"; "OX1R"; "OX2R"; "orexin receptor antagonists"; "orexin receptor agonists"; "activity-based anorexia"; "suvorexant"; "JNJ-61393215"; "orexin signaling"; "dopaminergic system"; and "serotonergic system".

The inclusion criteria were as follows: (1) preclinical or clinical studies involving orexin receptor modulators in the context of AN, feeding behavior, motivation, stress, or hyperarousal; (2) research presenting neurobiological, molecular, behavioral, or clinical endpoints related to orexin signaling; (3) clinical trials or animal model studies including activity-based anorexia (ABA) models.

The exclusion criteria encompassed the following: (1) studies with low methodological quality or unclear outcomes; (2) non-original publications, e.g., opinion pieces, commentaries, editorials, or duplicate reports; (3) studies focused exclusively on sleep disorders, addiction, or metabolic conditions not relevant to eating disorders, anorexia or the orexin system; (4) studies for which the full text was unavailable or conference abstracts without peer-reviewed data.

A total of 121 peer-reviewed English-language articles (original research and reviews) were initially identified. Duplicates were removed, and full texts were reviewed for eligibility by 2 independent reviewers. The quality of the studies was assessed by 2 investigators on a scale from 0 to 2, where: 2 – fully addressing at least one of the 3 aims of the article; 1 – partially addressing the aims; 0 – not addressing the aims. Discrepancies were resolved through discussion and consensus.

The obtained data were extracted into standardized fields:

- study type (preclinical/clinical);
- model (human, animal, etc.);
- intervention (compound target/receptor target);
- endpoints assessed (e.g., orexin expression, brain-derived neurotrophic factor (BDNF) levels, anxiety behaviors, hyperactivity, feeding regulation, reward processing);
- key findings and author conclusions.

All included studies were grouped thematically into 4 major domains: (1) feeding regulation and energy homeostasis; (2) hyperactivity and arousal; (3) anxiety, stress and affective processes; and (4) reward processing and motivational mechanisms.

Additionally, the discussion addressed methodological limitations, translational gaps, and clinical implications based on the extracted evidence.

Neurobiological foundations of the orexin system

The orexin system was first described in 1998 by 2 independent research groups (de Lecea *et al*., 1998; Sakurai *et al*., 1998). Sakurai *et al*. (1998), using chromatography, identified an appetite-enhancing neuropeptide. In parallel, another research team used molecular techniques to discover the same hypothalamic peptide, which they named hypocretin (de Lecea *et al*., 1998). Orexin (also known as hypocretin) was originally thought to play a key role in the regulation of sleep and wakefulness, reward processing, motivation, and appetite (Xia *et al*., 2023). Recent studies have demonstrated that orexin influences additional functions, including physiological processes such as circadian rhythms. Furthermore, environmental factors, such as food restriction, have been shown to influence the activity of the orexin system (Zink *et al*., 2014).

The system consists of 2 peptides secreted by hypothalamic neurons: orexin A (OXA), which is highly conserved among mammals, suggesting a crucial role in physiological regulation; and orexin B (OXB), which exhibits greater interspecies variability and may have more diverse functions (Grady *et al*., 2022; Wong *et al*., 2011). Both peptides are formed through the enzymatic cleavage of a common precursor protein, prepro-orexin (Chieffi *et al*., 2017).

Orexin A is composed of 33 amino acids and contains 2 disulfide bridges, while OXB consists of 28 amino acids (Ten-Blanco *et al*., 2023). Studies have shown that orexin-producing neurons are located primarily in the lateral hypothalamus (LH) and adjacent brain regions, including the periventricular area, dorsal hypothalamus, and posterior hypothalamus. From these regions, orexin neurons regulate feeding behavior, energy expenditure, reward processing, sleep, and stress responses (Chatterjee *et al*., 2023; Xiao *et al*., 2025). More recent studies have emphasized the role of orexin in the regulation of circadian rhythms and its potential utility as a therapeutic target in sleep and metabolic disorders (Mohammadkhani *et al*., 2024).

Two G protein-coupled orexin receptors have been identified: orexin receptor type 1 (OX1R), which is found only in mammals and exhibits a higher affinity for OXA; and

orexin receptor type 2 (OX2R), which is present in all vertebrates and displays similar affinity for both OXA and OXB (Soya and Sakurai, 2020). OX1R is predominantly expressed within the midbrain dopaminergic system, including the ventral tegmental area (VTA) and substantia nigra (SN), whereas OX2R plays a major role in the obligatory regulation of sleep and wakefulness and is highly expressed in the tuberomammillary nucleus, posterior subthalamic nuclei, and selected thalamic nuclei (Soya and Sakurai, 2020).

Once stimulated, these receptors initiate multiple intracellular signaling pathways, including Gq-phospholipase C signaling, Ca^{2+} signaling, and mitogen-activated protein kinase (MAPK) signaling (Couvineau *et al.*, 2022). These pathways influence neurotransmitter excitability and gene expression, thereby contributing to the broad physiological effects of orexin (Chatterjee *et al.*, 2023).

Interplay between the orexin, dopaminergic and serotonergic systems

Orexin activates and modulates both dopaminergic and serotonergic pathways, enabling the organism to respond effectively to rewarding stimuli (Katzman and Katzman, 2022).

The dopaminergic and orexin systems are interconnected, particularly in the regulation of motivation, reward processing and arousal (Calipari and España, 2012). Moreover, both systems contribute to the regulation of food intake and energy expenditure. Orexins have been shown to influence the axonal network of the VTA and SN, which together contain the majority of dopaminergic neurons in both humans and rodents (Fadel and Deutch, 2002; Hrabovszky *et al.*, 2013). Stimulation of the orexin system within the VTA and nucleus accumbens leads to dopamine release, thereby reinforcing behaviors associated with the introduced stimuli or rewards (Kukkonen *et al.*, 2024). Furthermore, activation of OX1R receptors on dopaminergic neurons modulates neuronal activity, influencing learning processes and the development of addictive behaviors (Aston-Jones *et al.*, 2009). The orexin system also suppresses GABAergic neurotransmission, resulting in enhanced dopaminergic activity (Baimel *et al.*, 2015; Tung *et al.*, 2016). The interaction between these systems is bidirectional, as dopamine can influence the activity of the orexin system through D1 and D2 receptors (Bubser *et al.*, 2005; Li *et al.*, 2025). These systems maintain a two-way relationship because dopamine activates orexin system neurons through its binding to D1 and D2 receptors (Bubser *et al.*, 2005; Li *et al.*, 2025). Coordinated signaling between the orexin and dopaminergic systems is essential for the regulation of reward-based behaviors, motivational responses, and arousal levels, while dysregulation of these pathways has been implicated in eating disorders, sleep disorders, and addictive behaviors (Tsujino and Sakurai, 2009). Excessive activation of the orexin system may lead to heightened motivation but has also been associated with addiction, eating disorders, and mood disturbances. Conversely, reduced orexin activity may contribute to diminished motivation and depressive symptoms (Mohammadkhani *et al.*, 2024).

The serotonergic and orexin systems interact closely in the regulation of sleep–wake cycles, physical movement, and feeding behavior (Narayanan *et al.*, 2010). In addition to their role in appetite regulation, both systems influence glucose processing, body thermoregulation and autonomic nervous system function (Xiao *et al.*, 2021). Their coordinated activity contributes to the maintenance of normal sleep architecture and helps prevent excessive daytime sleepiness and disrupted sleep patterns (Hasegawa *et al.*, 2014; Tabuchi *et al.*, 2013). The orexin and serotonergic systems also participate in the regulation of mood and stress responses and may therefore prevent the development of depressive disorders (Staton *et al.*, 2018; Zhang *et al.*, 2022). The serotonergic system in the dorsal raphe nucleus receives stimulation from orexin neurons, which may result in increased dopaminergic activity (Brown *et al.*, 2001; Hasegawa *et al.*, 2014). The orexin system receives inhibitory signals from serotonergic neurons through activation of 5-HT1A receptors, forming a negative feedback mechanism that contributes to sleep stabilization (Sakurai *et al.*, 2005; Tabuchi *et al.*, 2013).

Orexins and anorexia: Evidence from animal studies

Research investigating the role of the orexin system and its receptors, OX1R and OX2R, in AN is ongoing, with some studies suggesting their therapeutic potential while highlighting the complexity of orexin-mediated mechanisms (Xia *et al.*, 2023).

The OX1R is primarily associated with motivation- and reward-related aspects of feeding behavior, whereas OX2R is more closely involved in the regulation of activity levels, energy expenditure and, according to animal studies, meat production (Kukkonen *et al.*, 2024; Mohammadkhani *et al.*, 2024).

Animal studies have demonstrated that selective OX2R agonists, such as YNT-18, attenuated chemotherapy-induced anorexia in mice (Xia *et al.*, 2023). However, the use of OX1R receptor agonists has shown limited efficacy, suggesting that simultaneous activation of both orexin receptors may be more effective in the treatment of AN (Xia *et al.*, 2023).

Activity-based anorexia is a well-established animal model that replicates core features of AN (Foldi, 2023; Gutierrez, 2013; Spadini *et al.*, 2021). In this model, rodents are provided with free access to a running wheel while food availability is restricted, resulting in a paradoxical combination of excessive physical activity and reduced food intake that ultimately leads to rapid and severe weight loss

(Gutierrez, 2013; Schalla and Stengel, 2019; Skowron *et al*., 2021; Spadini *et al*., 2021). Originally developed in the late 1960s, the ABA model remains the most valid and extensively used preclinical paradigm for investigating the neurobiological, hormonal, and behavioral mechanisms underlying AN (Beeler and Burghardt, 2021; Gutierrez, 2013; Schalla and Stengel, 2019).

The ABA model reliably induces alterations in homeostatic systems, including changes in neuropeptide expression, neural circuitry, hormonal profiles, and immune function, thereby reproducing many of the physiological and behavioral abnormalities observed in patients with AN (Chowdhury *et al*., 2015; Gutierrez, 2013; Schalla and Stengel, 2019; Spadini *et al*., 2021).

Importantly, the severity and progression of ABA are influenced by factors such as age, sex, genetic background, and specific protocol details (e.g., duration and timing of food access, wheel adaptation). These variables must be carefully controlled to ensure reproducibility and translational relevance of the model (Gutierrez, 2013; Miletta and Horvath, 2023; Schalla and Stengel, 2019; Spadini *et al*., 2021).

Despite certain limitations, including its acute rather than chronic nature and its inability to fully capture the complexity of human AN, the ABA model remains a valuable tool for investigating vulnerability, resilience, and potential therapeutic interventions for eating disorders (Beeler *et al*., 2020; Foldi, 2023; Gutierrez, 2013; Schalla and Stengel, 2019; Spadini *et al*., 2021).

Given its established role in the regulation of arousal, feeding behavior, and energy expenditure, the orexin system has emerged as a promising candidate for involvement in ABA (Jászberényi *et al*., 2024; Pinos *et al*., 2022; Schéle *et al*., 2023; Xia *et al*., 2023). Recent studies have investigated changes in the expression of orexin in ABA and examined how pharmacological or genetic manipulation of the orexin system influences the ABA phenotype (Pinos *et al*., 2022; Schéle *et al*., 2023; Xia *et al*., 2023). Furthermore, evidence from ABA models suggests that pharmacological antagonism of orexin receptors can reduce hyperactivity, supporting the hypothesis that the orexin system may represent a promising therapeutic target for the treatment of hyperactivity and energy dysregulation associated with AN (Jászberényi *et al*., 2024; Pinos *et al*., 2022; Schéle *et al*., 2023; Xia *et al*., 2023).

Recent studies using the ABA mouse model have demonstrated that a large population of hypothalamic orexin neurons becomes highly activated during the severe anorectic state. This activation was visualized using the Fos-TRAP2 technique, which captures active neurons, and was subsequently confirmed by immunohistochemistry. The increased activity of orexin neurons was associated with enhanced food anticipatory activity and hyperactivity. According to the researchers, pharmacological antagonism of orexin receptors (e.g., with suvorexant) reduces hyperactivity, supporting a functional role of orexin in driving excessive activity during ABA (Schéle *et al*., 2023).

In rats, the capacity to upregulate orexin expression in response to ABA depends on stress-coping style and prenatal stress exposure. Vulnerable animals, characterized by passive coping behavior and prenatal stress exposure, did not exhibit an increase in orexin expression in the LH during ABA. This impaired response was associated with greater weight loss and reduced food intake. In contrast, resilient animals exhibited increased orexin expression, suggesting that orexin upregulation is an adaptive response to starvation and stress (Boersma *et al*., 2016)

Moreover, in male rats, the number of OXA-immunoreactive cells in the LH decreases significantly at the end of the ABA protocol, particularly when food restriction is combined with increased physical activity. This reduction is more pronounced than that observed following either food restriction or increased activity, suggesting that the combination of severe energy deficit and hyperactivity suppresses orexin expression in the LH (Pinos *et al*., 2022; Pinos *et al*., 2023). This decline may represent an adaptive response to prolonged energy deficiency, similar to changes observed during long-term fasting (Pinos *et al*., 2023).

Some studies report no significant changes in prepro-orexin mRNA expression in the LH during the development of ABA, even as other neuropeptides (e.g., agouti-related peptide (AgRP) and neuropeptide Y (NPY)) are robustly regulated. These findings suggest that orexin expression may not always be directly responsive to negative energy balance or may be regulated by additional factors (de Rijke *et al*., 2005; Hillebrand *et al*., 2007).

Human studies investigating anorexia nervosa and orexin signaling

The role of the orexin system in patients with AN remains insufficiently understood, and further studies are required to clarify the specific roles of orexin receptors in the complex pathogenesis of this disorder.

Preliminary studies investigating the role of OXA in AN and its association with cognitive function, sleep, and appetite regulation have yielded inconclusive results (Mogavero *et al*., 2023; Xia *et al*., 2023). In a study by Steward *et al*. (2019), involving 51 adult women with AN and 51 age- and education-matched controls, plasma OXA concentrations were significantly lower in patients with AN than in the control group. Participants completed neuropsychological tests for the assessment of cognitive functions, including the Wisconsin Card Sorting Test (WCST) and the Iowa Gambling Task (IGT). Patients with AN demonstrated poorer performance on both tests than the control group. The authors suggested that reduced OXA concentrations may be associated with cognitive impairment in AN, indicating a possible relationship between orexin

signaling and cognitive dysfunction in this disorder (Steward *et al.*, 2019).

The study by Sauchelli *et al.* (2016) investigated the relationship between OXA concentration, sleep quality, and treatment outcomes in 48 patients with AN and 98 healthy women who served as controls. Although the mean concentration of OXA did not differ between the 2 groups, in patients with AN, higher concentrations of OXA were correlated with reduced sleep quality, which, in turn, was associated with a poorer therapeutic response to treatment (Sauchelli *et al.*, 2016).

Janas-Kozik *et al.* (2011) examined plasma levels of leptin, a hormone involved in satiety regulation, and OXA, a neuropeptide associated with appetite regulation, in patients with the restrictive subtype of AN. The research focused on analyzing the hormonal disturbances accompanying this disorder. Because both leptin and OXA play important roles in the regulation of appetite and feeding behavior, alterations in their circulating concentrations may contribute to the development or progression of AN. The researchers reported decreased levels of periodin A and leptin in patients with restrictive type of AN compared to the control group. With increasing body weight in AN patients, the concentration of OXA decreased whereas leptin concentration increased, leading the authors to conclude that the regulation of the orexin system in restrictive AN is independent of body weight (Janas-Kozik *et al.*, 2011).

Recent publications from 2020 to 2025 highlight the limited clinical evidence regarding the role of the orexin system in patients with AN (Mohammadkhani *et al.*, 2024; Toor *et al.*, 2021). Further analysis of human orexin studies is needed, particularly to clarify the role of the orexin system in the pathogenesis of AN (Nigro *et al.*, 2025; Toor *et al.*, 2021).

Mechanisms of OX2R agonism and OX1R antagonism in the regulation of body weight and motivation

Increased OX2R expression has been shown to protect against high-fat diet-induced obesity by enhancing the metabolic rate and improving leptin sensitivity, rather than by directly suppressing appetite (Funato *et al.*, 2009).

Long-term administration of a selective OX2R agonist to mice fed a high-fat diet inhibited weight gain and protected against the development of obesity. While short-term orexin activity may stimulate appetite, chronic stimulation of OX2R receptors, particularly in the context of a high-fat diet, has been shown to increase the metabolic rate and prevent obesity (Funato *et al.*, 2009). OX2R may therefore represent a promising target for regulating energy balance and body weight. However, there is no clear evidence that OX2R activation leads to weight gain, particularly in humans. On the contrary, numerous studies indicate that OX2R may be involved in mechanisms that protect against the development of obesity (Chieffi *et al.*, 2017; Funato *et al.*, 2009; Perez-Leighton *et al.*, 2013).

Orexin receptors influence glutamatergic neurotransmission and may affect motivational mechanisms related to food intake and reward processing (Borgland *et al.*, 2008). OX2R is more closely associated with the regulation of wakefulness and arousal, whereas OX1R has a greater impact on reward-related motivation. However, both receptors appear to play complementary roles in these processes (Gozzi *et al.*, 2011; Hopf, 2020; Mohammadkhani *et al.*, 2024).

The orexin system is intricately connected with multiple aspects of metabolism, including hunger, energy status, and stress. Through its actions on hypothalamic–mesolimbic structures, the orexin system influences behaviors such as increased activity, heightened vigilance, and social interactions (Mohammadkhani *et al.*, 2024).

Reduced activity of this system may lead to decreased motivation to eat, diminished interest in pleasurable activities, and indifference, which are symptoms commonly observed in AN and depression (Mohammadkhani *et al.*, 2024; Wang *et al.*, 2018). However, in AN, increased orexin activity may lead to heightened arousal, hyperactivity, and anxiety. Rather than promoting food intake, this elevated activity may unexpectedly reinforce restrictive eating behaviors (Mohammadkhani *et al.*, 2024). Conversely, the overactivation of the orexin system can lead to excessive motivation to seek rewards, which plays a significant role in addictions and compulsive overeating (Mehr *et al.*, 2021).

As discussed above, modulation of the orexin system appears to be a promising therapeutic approach; nevertheless, its clinical application requires careful consideration due to the multifunctional nature of this system and the potential adverse effects associated with its manipulation.

Steiner *et al.* (2024) described the first selective OX1R antagonist, SB-334867, which demonstrated markedly greater affinity for ORX1R than for OX2R. This discovery represented an important advance in defining the specific role of OX1R antagonism.

OX1R antagonists are the subject of active investigation as promising pharmacological agents for the treatment of various mental conditions. They are being extensively studied as a potential strategy for reducing hyperactivity, anxiety, stress, and impulsive behavior (Fagan *et al.*, 2023; Williams *et al.*, 2024).

Previous studies indicate that pharmacological blockade of OX1R receptors reduces arousal and anxiety in both animal models and humans (Salvadore *et al.*, 2020).

In studies evaluating the selective OX1R antagonist tebideutorexant (JNJ-61393215), researchers observed a reduction in lactam- and CO_2-induced panic attacks in rodents, confirming the important role of OX1R

in regulating anxiety and memory responses. Notably, the antagonist did not affect motor activity or sleep (Salvadore *et al*., 2020).

In a clinical study involving patients with anxiety disorders, researchers demonstrated that this compound reduced both the subjective and somatic symptoms of panic. OX1R blockade decreased excessive neuronal activity without inducing sedation, distinguishing it from traditional sedative medications. Additionally, OX1R stimulated the serotonergic, dopaminergic, and noradrenergic systems, leading to increased wakefulness, heightened arousal, faster responses, and difficulty returning to a calm physiological state (Salvadore *et al*., 2020).

High OX1R activity intensifies the stress response by increasing the secretion of corticotropin-releasing hormone (CRH), stimulating the amygdala, and elevating autonomic arousal. This heightened activity results in excessive sensitivity to stimuli, leading to a stronger stress response and somatic manifestations such as tachycardia and hyperactivity (Salvadore *et al*., 2020).

In contrast, blockade of OX1R exerts anxiolytic effects by reducing excessive stimulation and normalizing behavior (Merlo Pich and Melotto, 2014; Salvadore *et al*., 2020).

In stress-free and anxiety-free conditions, OX1R blockade did not produce any changes in motor activity. Similarly, studies evaluating tebideutorexant in healthy individuals demonstrated no significant alterations in motor function (Brooks *et al*., 2023).

The publication by Williams *et al*. (2024) describes the development of nivasorexant (ACT-539313), the first selective OX1R antagonist to advance into later-stage clinical trials. The researchers provide a detailed account of the compound discovery process, including the identification of an OX1R-selective compound and the assessment of its pharmacokinetic properties and safety profile. Selective blockade of OX1R inhibited responses associated with stress, emotional arousal, and reward-seeking behavior (Williams *et al*., 2024).

Nivasorexant is considered a promising therapeutic option due to its favorable pharmacological profile and lack of sedative effects, supporting its potential use in the treatment of disorders characterized by excessive stress responses and compulsive behaviors (Williams *et al*., 2024).

OX1R antagonists may represent a promising therapeutic option, particularly under conditions of heightened stress and motivation rather than during periods of rest (Bonaventure *et al*., 2015).

Importance of further research

The integration of orexin modulators into multimodal treatment strategies for AN represents a promising but still emerging field. Preclinical and early clinical evidence supports the role of orexin in the regulation of appetite, reward processing, and sleep, all of which are disrupted in patients with AN (Beckenstrom *et al*., 2023; Kukkonen and Leonard, 2014; Mehr *et al*., 2021; Reichelt *et al*., 2015). However, direct clinical trials in AN are lacking, and most evidence is extrapolated from related disorders or animal models (Beckenstrom *et al*., 2023; McElroy *et al*., 2019; Mehr *et al*., 2021; Reichelt *et al*., 2015). The combination of pharmacotherapy targeting the orexin, dopamine, or glutamate systems with psychotherapy (enhanced cognitive behavioral therapy (CBT-E)) is theoretically well justified, given the complex neurobiology of AN. Nevertheless, robust clinical data are needed (Frank and Shott, 2016; Lewis *et al*., 2024; Mitchell *et al*., 2023).

The quality of the available evidence varies considerably. While mechanistic studies and animal models provide substantial support for the involvement of the orexin system, clinical trials remain limited, and no orexin-targeted pharmacological agents have been approved for the treatment of AN (Beckenstrom *et al*., 2023; Muratore and Attia, 2022). Progress in this field is further hindered by the heterogeneity of AN, small sample sizes, and the challenges associated with translating neurobiological insights into effective therapeutic interventions (Frank and Shott, 2016; Lewis *et al*., 2024).

Orexin receptor antagonists and agonists: Risks and safety profile

Both orexin receptor antagonists and agonists have been investigated as therapeutic agents for the treatment of sleep disorders, including insomnia and narcolepsy (Hartman *et al*., 2025; Na *et al*., 2024; Xue *et al*., 2021).

A well-characterized representative of selective orexin receptor antagonists (SORAs) is seltorexant, a selective orexin 2 receptor antagonist (2-SORA) (Ziemichód *et al*., 2023), under investigation for insomnia disorder and major depressive disorder (MDD) (Mesens *et al*., 2025; Savitz and Saoud, 2020; Recourt *et al*., 2019). It has demonstrated efficacy in the treatment of insomnia and MDD, with a favorable safety and tolerability profile in clinical trials; however, it has not yet been approved for clinical use. The most frequently reported adverse effects included somnolence, fatigue, headache, dizziness, abdominal discomfort, and nightmares (Recourt *et al*., 2019).

Among orexin receptor antagonists, dual orexin receptor antagonists (DORAs), including lemborexant, suvorexant, and daridorexant, have been extensively studied and approved for the treatment for insomnia (Kukkonen *et al*., 2024; Xue *et al*., 2021; Ziemichód *et al*., 2022). These DORAs have been reported to consistently improve sleep onset and sleep maintenance in adults with insomnia, with benefits sustained for up to 12 months (Kunz *et al*., 2023; Michelson *et al*., 2014; Yardley *et al*., 2021). Nonetheless, they have also been associated with a greater incidence of adverse effects compared to placebo (Na *et al*., 2024). Despite their effectiveness, DORAs may cause excessive

daytime sleepiness, sleep paralysis (Na *et al.*, 2024), as well as somnolence, abnormal dreams, fatigue, and xerostomia (Xue *et al.*, 2021). No significant differences in safety have been reported between suvorexant, lemborexant, and daridorexant (Xue *et al.*, 2021). However, among these DORAs, suvorexant has been reported to be associated with the highest relative risk of excessive daytime sleepiness compared with placebo (Na *et al.*, 2024).

Furthermore, several compounds with orexin receptor agonistic activity have also been studied for their potential to promote wakefulness, particularly in patients with narcolepsy. These include oveporexton (TAK-861) (Dauvilliers *et al.*, 2025) and firazorexton (TAK-994) (Dauvilliers *et al.*, 2023). Novel OX2R agonists, such as ORX750, investigated in phase 1 study for the treatment of narcolepsy and idiopathic hypersomnia, have shown a favorable safety profile, with only transient and mild adverse events reported in healthy volunteers (Hartman *et al.*, 2025). In contrast, the OX2R agonist TAK-994 was evaluated in a phase 2, randomized, placebo-controlled trial in patients with narcolepsy type 1. Although the drug demonstrated robust improvements in sleep latency, daytime sleepiness, and cataplexy compared with placebo, its safety profile raised significant concerns. TAK-994 was associated with a high rate of adverse events, most notably serious liver toxicity, which led to the premature termination of the clinical trial (Dauvilliers *et al.*, 2023).

Overall, while sedation and sleep disturbances are the most commonly reported risks, serious metabolic effects and drug interactions are rare or have not yet been reported, especially for OX2R agonists. Additional longitudinal and real-world studies are needed to provide a more comprehensive characterization of their safety profile (Hartman *et al.*, 2025; Na *et al.*, 2024; Ufer *et al.*, 2021; Xue *et al.*, 2021).

Orexin modulators: Registered studies and evidence transfer to anorexia nervosa

Current research on orexin receptor modulators (agonists and antagonists) is most advanced in sleep disorders, particularly narcolepsy, with emerging studies on depression and addiction. However, to date, there are no active or registered interventional studies directly targeting orexin pathways in AN or other eating disorders. Table 1 summarizes key registered studies investigating orexin modulators in narcolepsy, depression, and related conditions, together with their current status and key findings.

Preclinical studies have linked orexin signaling to food-seeking behavior and binge-like eating, and altered orexin levels have been observed during caloric deprivation and in animal models of eating disorders (Beckenstrom *et al.*, 2023; Carpi *et al.*, 2024; Kukkonen *et al.*, 2024). Orexin modulators are being actively investigated for narcolepsy, insomnia, depression, and addiction, but no clinical trials have evaluated these agents in patients with AN (Carpi *et al.*, 2024). Moreover, pathophysiological differences between narcolepsy, depression, addiction, and AN limit the direct evidence transfer. Consequently, the safety and efficacy of orexin modulators in malnourished patients with AN remain unknown (Beckenstrom *et al.*, 2023; Carpi *et al.*, 2024). Although preclinical and mechanistic studies suggest considerable translational potential, dedicated clinical trials are needed. At present, evidence transfer to AN is speculative and highlights a significant research gap.

Knowledge gaps and recommendations for the future

The following section outlines the current state of knowledge regarding the role of the orexin system in AN, identifies key research gaps, and proposes priorities for future investigation.

What we know

Clinical studies examining OXA levels in patients with AN have yielded relevant but inconsistent findings. Steward *et al.* (2019) reported reduced OXA levels in individuals with AN, a finding supported by Janas-Kozik *et al.* (2011). Furthermore, Steward *et al.* stated that reduced orexin levels were associated with cognitive impairment. In contrast, Bronsky *et al.* (2011) documented both increases and decreases in OXA concentrations during an eight-week refeeding period. Moreover, Sauchelli *et al.* (2016) found no significant differences in OXA concentrations between patients with AN and healthy controls, although higher orexin levels within the AN group were associated with poorer sleep quality. Collectively, these discrepancies highlight the limited nature of the current evidence and the considerable heterogeneity of study populations and methodologies.

In summary, the presence of orexin in the brain, together with findings from behavioral and animal studies, suggests that the orexin system may represent a potential therapeutic target in AN. However, the evidence remains mixed, and further studies are needed to elucidate the underlying mechanisms and assess the translational potential of orexin-modulated interventions.

What we do not know

To advance the field, future studies should be rigorously designed to assess both OXA and OXB across different stages of the disorder while distinguishing between the restrictive and binge–purge subtypes of anorexia. Given the complex physiological roles of orexins, it is essential to control for key confounding variables, including age,

Table 1. Summary of key registered and completed clinical studies evaluating orexin receptor modulators

Topic	Study	Indication	Drug (NCT/Ref)	Summary	Status
Narcolepsy and sleep disorders	Dauvilliers *et al.*, 2025	narcolepsy type 1	oveporexton (TAK-861, NCT05687903)	Phase 2 RCT in patients with narcolepsy type 1; oral OX2R agonist significantly improved wakefulness and reduced daytime sleepiness and cataplexy over 8 weeks. The most common side effects were insomnia and urinary symptoms, and no hepatotoxicity was observed.	completed
	Dauvilliers *et al.*, 2023	narcolepsy type 1	firazorexton (TAK-994, NCT04096560, NCT04820842)	Phase 2 RCT in patients with narcolepsy type 1; oral OX2R agonist improved sleep latency and reduced cataplexy but was associated with liver toxicity, leading to early termination of the trial.	terminated
	Hartman *et al.*, 2025	narcolepsy, hypersomnia	cleminorexton (ORX750)	Phase 1 in healthy volunteers; oral OX2R agonist demonstrated dose-dependent wake-promoting effects and was well tolerated, with only mild, transient side effects.	ongoing
	Grunstein *et al.*, 2025	narcolepsy, hypersomnia	alixorexton (ALKS 2680)	Phase 1b study in patients with narcolepsy and idiopathic hypersomnia; OX2R agonist improved wakefulness in a dose-dependent manner and demonstrated a favorable safety profile, with only mild side effects and no serious safety concerns.	completed
	Na *et al.*, 2024; Mieda and Sakurai, 2013	insomnia	DORAs (suvorexant, lemborexant, daridorexant)	Multiple RCTs and meta-analyses in patients with insomnia; DORAs improved sleep onset and sleep maintenance but increased the risk of mild narcolepsy-like adverse events, including sleep paralysis and daytime sleepiness.	approved/ completed
Depression	Meshkat *et al.*, 2025	MDD	seltorexant	Several RCTs in patients with MDD; OX2R antagonist (20 mg) reduced depressive symptoms in some studies, especially when used as adjunctive therapy, although findings remain inconsistent.	completed
	Fagan *et al.*, 2022; Meshkat *et al.*, 2025	MDD	filorexant	RCT in patients with MDD; filorexant did not demonstrate significant improvement in depressive symptoms compared with placebo.	completed
	Schmidt *et al.*, 2025	MDD with anxious distress	tebideutorexant (JNJ-61393215, NCT04080752)	Phase 2a in patients with MDD with anxious distress; OX1R antagonist did not significantly improve depression or anxiety scores compared to placebo but demonstrated an acceptable safety profile.	completed

DORAs – dual orexin receptor antagonists; MDD – major depressive disorder; NCT – National Clinical Trial number; RCT – randomized controlled trial; OX2R – orexin receptor type 2.

sleep quality, comorbid psychiatric conditions, and substance use. In addition, the interplay between the orexin system and other systems that may affect the patient's condition should be carefully considered.

Although the ABA model has been instrumental in elucidating orexin-related mechanisms, it exhibits critical translational limitations. Activity-based anorexia reflects an acute, short-term state of malnutrition, whereas human AN is a chronic, relapsing disorder driven by psychological and sociocultural factors. Moreover, interspecies differences limit the applicability of pharmacological findings from rodent models to clinical settings. Consequently, findings derived from the ABA model should be interpreted with appropriate caution when extrapolated to human disease. There is therefore a need for refined or alternative preclinical models that more accurately reproduce the chronic course and psychosocial complexity of AN, for example through protocols incorporating prolonged food restriction, stress exposure, or repeated relapse cycles.

Another important research gap is the absence of clinical trials directly evaluating orexin modulators in individuals with AN. Although preclinical and mechanistic studies provide a rationale for their potential use, differences in pathophysiology and the particular vulnerability of malnourished patients necessitate dedicated investigations of the pharmacodynamics, pharmacokinetics, and safety profiles of these compounds in this population. Therefore, the extrapolation of evidence from other disorders to AN remains speculative and highlights a significant research gap.

Additionally, inconsistencies in the current literature may reflect methodological differences across studies, including the assessment of mRNA vs. protein expression, differences in the timing of tissue collection, and variation in the hypothalamic subregions analyzed. For instance, some studies focus solely on the LH, whereas others include broader hypothalamic areas, contributing to variability in the reported changes in orexin expression (Boersma *et al.*, 2016; de Rijke *et al.*, 2005; Hillebrand *et al.*, 2007; Mavanji *et al.*, 2024; Schéle *et al.*, 2023).

What should be investigated

Multimodal treatment approaches integrating pharmacotherapy (e.g., orexin modulators, dopamine agents, or NMDA antagonists) with psychotherapy, such as CBT-E, represent a promising but still underexplored direction in the treatment of AN (Beckenstrom *et al.*, 2023; Frank

and Shott, 2016; Lewis *et al*., 2024; Mitchell *et al*., 2023). Ketamine and zinc have been proposed as agents targeting the dysregulation of excitatory and inhibitory neurotransmission, potentially enhancing the effects of psychotherapy (Lewis *et al*., 2024; Mitchell *et al*., 2023), while dopamine modulation may facilitate fear extinction and reduce eating-related distress (Baik, 2020; Frank and Shott, 2016).

Sleep dysregulation is common in eating disorders and may exacerbate compulsive eating through hyperactivity of the orexin system (Beckenstrom *et al*., 2023; Mehr *et al*., 2021). Therefore, pharmacological interventions that normalize orexin signaling could improve both sleep quality and eating behaviors. Dual orexin receptor antagonists, which are already being investigated for sleep disorders and substance use, may also have therapeutic potential in eating disorders such as binge eating disorder (BED) (Mehr *et al*., 2021). Animal studies suggest that chronic binge eating may induce plasticity and hyperactivity within the orexin system, contributing to both compulsive eating and sleep disturbances. Furthermore, stress and chronic undernutrition can disrupt dopamine-mediated reward processing, further contributing to the pathophysiology of AN (Baik, 2020; Frank and Shott, 2016; Kukkonen and Leonard, 2014).

The integration of orexin modulators into multimodal treatment strategies for AN remains a promising but emerging field. Although mechanistic studies and animal models provide valuable insights, clinical trials remain limited, and no orexin-targeted drugs have been approved for the treatment of AN (Beckenstrom *et al*., 2023; Muratore and Attia, 2022). Progress in this area is further limited by the clinical heterogeneity of AN, small sample sizes, and the difficulty of translating neurobiological findings into effective therapeutic interventions.

In conclusion, although preclinical evidence provides a compelling rationale for targeting orexin pathways in AN, well-designed clinical trials are urgently needed to evaluate the safety, efficacy, and potential integration of orexin-targeted therapies into individualized treatment frameworks.

Conclusions

Although the number of published studies investigating the role of the orexin system in the behavioral and physiological abnormalities associated with AN is increasing, the available evidence remains inconsistent, and the underlying mechanisms have not yet been fully elucidated. The orexin system represents a promising but underexplored therapeutic target in AN. Since the role of orexin receptor agonists and antagonists has not been fully evaluated in patients with AN or other eating disorders, further clinical trials are urgently needed to clarify their therapeutic potential and safety profile in malnourished populations.

Although evidence from experimental animal studies indicates that the orexin system plays an important role in hyperactivity and energy dysregulation in model ABA, its contribution appears to be context-dependent rather than exclusive. The variability observed across experimental models highlights the influence of genetic and environmental factors, while the complexity of orexin system regulation warrants further investigation. Additional studies are required to clarify the precise roles of orexin and its therapeutic potential in AN. Moreover, translational research bridging findings from animal models to human AN remains limited. Despite significant advances, important knowledge gaps persist, including the need to investigate sex-specific differences, the long-term effects of orexin manipulation, and the translation of animal findings into clinical practice.

Based on the available sources, there are no active or registered clinical trials directly targeting orexin pathways in AN or other restrictive eating disorders, making this a promising yet unvalidated therapeutic approach. Evidence from clinical trials in other neuropsychiatric disorders suggest that orexin modulation may influence appetite regulation and reward processing; however, its clinical translation to AN remains untested and speculative.

Orexin modulators represent a novel and biologically plausible therapeutic strategy for AN, particularly when incorporated into multimodal treatment approaches that combine pharmacotherapy targeting reward, sleep, and neurohormonal pathways with psychotherapy to address the complex neurobiology of the disorder. Such integrated approaches may provide novel opportunities to improve treatment outcomes, particularly in patients with severe, chronic, or comorbid forms of AN. However, clinical evidence remains preliminary, and further research is essential to establish the efficacy and safety of orexin-targeted therapies in this patient population.

Modulation of sleep and reward systems is central to both the pathophysiology and potential treatment of AN. Interventions targeting these systems, including orexin modulators and dopaminergic agents, are under active investigation and may offer new therapeutic options for patients who do not respond adequately to standard treatment. Ultimately, personalized, multimodal treatment strategies tailored to an individual's neurobiology and clinical presentation are likely to play an important role in the management of AN. Future studies should therefore focus on establishing the efficacy and safety of these integrated strategies.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Use of AI and AI-assisted technologies

Not applicable.

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