Sleep Medicine 148 (2026) 109216

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Sleep disruption and neuropsychiatric features in Angelman syndrome: insights into underlying neurobiology

Gaetano Terrone [a,*], Maria Giuseppina Miano [b], Marco Carotenuto [c], Maria Francesca Fiorile [a], Salvatore Aiello [a], Carmela Bravaccio [a], Ennio Del Giudice [a]

[a] Child Neurology and Psychiatry Unit, Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy
[b] Institute of Genetics and Biophysics "Adriano Buzzati-Traverso", CNR, Naples, Italy
[c] Clinic of Child and Adolescent Neuropsychiatry, Department of Mental Health, Physical and Preventive-Medicine, University of Campania "Luigi Vanvitelli", Caserta, Italy

ARTICLE INFO

Keywords:
Angelman syndrome
Sleep disorders
UBE3A
Circadian rhythms
Epilepsy
Behavioral disorders

ABSTRACT

Sleep disorders are a core feature of Angelman syndrome (AS), affecting approximately 80% of individuals. They typically manifest as insomnia and disrupted sleep–wake cycles and contribute substantially to the burden experienced by affected individuals and their families. AS is caused by loss of function of the ubiquitin protein ligase E3A (*UBE3A*) gene, which encodes the E3 ubiquitin ligase E6AP, a protein essential for synaptic development and function. In individuals with a maternal 15q11–q13 deletion, concomitant deletion of neighboring non-imprinted genes, including *GABRB3, GABRA5, GABRG3, ATP10A,* and *HERC2*, may also contribute to the phenotype.

Evidence from animal models further indicates that *UBE3A* plays a key role in sleep homeostasis and circadian rhythm regulation, including through interactions with core clock genes such as *BMAL1*.

In this narrative review, we examine the role of *UBE3A* in sleep regulation and outline the principal sleep disturbances observed in AS, integrating findings from both preclinical models and human studies, while also considering genotype–phenotype correlations for the main clinical manifestations.

The available evidence suggests that sleep disruption may be closely linked to the core neurological and behavioral features of AS, particularly epilepsy and behavioral abnormalities, through shared pathophysiological mechanisms related to *UBE3A* deficiency.

Early identification and management of sleep disturbances may therefore represent a potentially modifiable factor for improving behavioral outcomes, seizure control, and overall quality of life in individuals with AS. In addition, sleep measures should be considered as potentially relevant clinical endpoints in ongoing trials of emerging therapeutic strategies.

1. Introduction

Angelman Syndrome (AS) is a rare neurogenetic disorder with a prevalence of ~1:12,000–20,000 caused by the loss of function of the maternal *UBE3A* gene located on chromosome 15q11-q13 [1–3]. This gene exhibits genomic imprinting, meaning its expression is parent-of-origin specific. In most somatic tissues, both the maternal and paternal alleles of *UBE3A* are active. However, in neurons, the paternal *UBE3A* allele is silenced by a long non-coding antisense transcript called UBE3A-ATS, leaving only the maternal allele actively expressed [4]. Several distinct genetic mechanisms can lead to the loss of maternal *UBE3A* function, accounting for nearly all cases of AS. The most common cause, occurring in approximately 65-70% of individuals with AS, is a deletion of the maternal 15q11-q13 chromosomal region, which includes the *UBE3A* gene. Paternal uniparental disomy (UPD) of chromosome 15, where an individual inherits two copies of chromosome 15 from the father and none from the mother, accounts for about 2-3% of AS cases. In this scenario, both *UBE3A* alleles are paternally derived and thus silenced in neurons. Imprinting center defects (ICD), which affect the epigenetic marks controlling the parent-of-origin specific expression of genes in the 15q11-q13 region, including *UBE3A*, are responsible for approximately 3-5% of cases [1,2]. Finally, pathogenic mutations within

* Corresponding author.
E-mail address: gaetano.terrone@unina.it (G. Terrone).

https://doi.org/10.1016/j.sleep.2026.109216
Received 27 April 2026; Received in revised form 12 August 2026; Accepted 12 August 2026
Available online 14 August 2026
1389-9457/© 2026 Elsevier B.V. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

the maternal *UBE3A* gene itself, leading to a non-functional protein, occur in about 5-11% of individuals with AS. Rare instances of translocation or other rearrangements of chromosome 15 have also been reported (<2%) [1,2].

Functionally, the absence of functional UBE3A protein, a key E3 ubiquitin ligase critical for synaptic development and function, leads to severe neurodevelopmental sequelae [5]. The classic phenotype includes profound intellectual disability, minimal expressive speech, ataxia, tremor, stereotypies, a characteristic happy demeanor with frequent laughter, and a high prevalence of epilepsy and severe sleep disturbances [6,7]. One of the core symptoms of AS is sleep disturbance which affects approximately 80% of individuals with AS. These disturbances are characterized by difficulties with sleep initiation and maintenance, reduced total sleep time (TST), and abnormal sleep architecture [8,9].

Importantly, the clinical phenotype varies according to the underlying molecular subtype, and genotype–phenotype correlations appear to be domain-specific rather than reflecting a single severity hierarchy across all clinical manifestations of AS. Sleep disturbances are common across molecular subtypes and available evidence does not demonstrate a consistent difference in their prevalence according to genotype. This contrasts with other clinical domains, such as epilepsy and developmental performances, in which more robust genotype–phenotype associations have been demonstrated. In particular, individuals with a maternal 15q11–q13 deletion generally exhibit a more severe phenotype, particularly with respect to epilepsy. This greater phenotypic severity may result, at least in part, from the concomitant deletion of neighboring non-imprinted genes within the 15q11–q13 region, including *GABRB3, GABRA5, GABRG3, ATP10A,* and *HERC2* [10]

Sleep disruption may itself exacerbate epilepsy and behavioral phenotype by increasing hyperactivity and anxiety, as well as reducing attention span [11].

Importantly, studies carried out in animal models for AS proved that *UBE3A* plays a key role in sleep homeostasis and regulation of circadian clocks [12–15].

This narrative review integrates current evidence on the role of *UBE3A* in sleep regulation and provides an overview of the sleep characteristics observed in AS, while also considering genotype–phenotype correlations for the main clinical manifestations.

Finally, we hypothesize a potential pathophysiological interplay among disrupted sleep patterns, epilepsy, and behavioral dysregulation in AS, highlighting shared mechanisms that may represent promising targets for novel therapeutic strategies (see Fig. 1)

2. Methods

This narrative review provides a comprehensive overview of the current evidence on the pathophysiological mechanisms underlying sleep disorders in AS, with particular emphasis on the role of *UBE3A* deficiency and insights derived from preclinical models. A non-systematic literature search was conducted in PubMed, Scopus, Embase, and the Cochrane Library. The search included combinations of the following keywords: “Angelman syndrome,” “UBE3A,” “sleep,” “sleep-wake disorders,” “insomnia,” “sleep architecture,” “animal model,” “epilepsy,” “seizures,” “EEG,” “behavior,” “self-injurious behavior,” “irritability,” “attention,” “treatment,” and “antisense oligonucleotide” (ASO). The literature search was last updated in January 2026. The reference lists of relevant articles were also examined to identify additional pertinent publications.

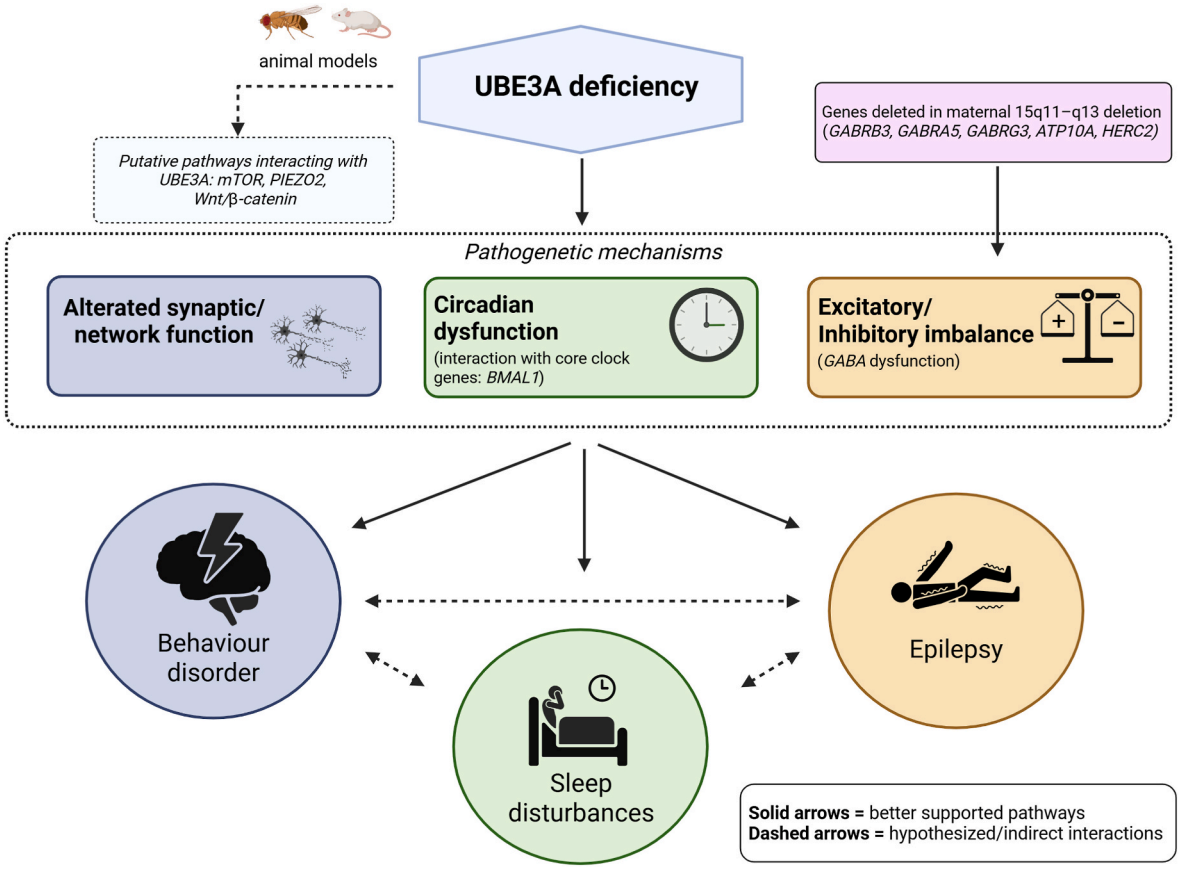


Fig. 1. *UBE3A* deficiency and pathogenetic mechanisms in Angelman Syndrome: a conceptual model of the interactions among sleep disturbances, epilepsy, and behavior disorder (created in https://BioRender.com).

3. Pathophysiological mechanisms of sleep disruption in preclinical models of as

3.1. UBE3A deficiency and dysregulation of sleep pattern

Since the human and mouse *UBE3A* gene homologues are located on the same chromosome and imprinted in the same way, different animal models of AS have been generated to study efficiently abnormal sleep pattern [12–16]. (Table 1). Sleep–wake architecture has been examined in the AS mouse model *Ube3a*$^{m-/p+}$ (also termed *Ube3a*-del) harboring a maternal *Ube3a* deletion [13]. This is a null AS model because the maternal deletion abolishes UBE3A protein expression in the brain, and the paternal allele is epigenetically silenced in most neurons. *Ube3a*$^{m-/p+}$ mice display reduced sleep efficiency, accompanied by fragmentation of both wakefulness and slow-wave sleep, reflecting the disrupted sleep patterns commonly reported in patients with AS [23,24]. Subsequent studies further showed that *Ube3a*$^{m-/p+}$ mice have impaired sleep homeostasis, with a markedly reduced ability to build sleep pressure during their active phase and in response to enforced sleep deprivation [16].

Copping & Silverman described that *Ube3a*$^{m-/p+}$ mice displayed reduced sleep spindle generation, which significantly correlates with delta rhythm activity [12]. Of note, sleep spindle production is a key indicator of memory consolidation during sleep, and its disruptions have been associated with intellectual disability, childhood epilepsies, and autism spectrum disorders (ASD) [25]. In addition, the authors showed that *Ube3a*-del mice exhibit reduced total sleep duration, decreased mean rapid eye movement (REM) sleep and a trend toward reduced slow-wave sleep compared with wild-type animals [12]. Noteworthy, in a new mouse model termed *Ube3a*$^{m\Delta e6/p+}$ (also reported as *Ud6*-$^{m-/p+}$) that harbor a larger deletion of *Ube3a*′s exon 6 generated with CRISPR/Cas9 (a 1247 nt deletion that confers a frame shift), it has been observed that these animals have 30% less REM sleep amount during the subjective day of constant darkness (with access to a running wheel), most likely due to shorter bouts of REM sleep [20]. More recently, it has been shown that lowering Ube3a-ATS levels by using antisense oligonucleotides in juvenile or adult *Ube3a*$^{m-/p+}$ mice can restore Ube3a protein expression. Remarkably, this rescue is paralleled by a recovery of abnormal EEG activity and sleep disturbances, underscoring the value of EEG power spectra and sleep parameters as meaningful functional readouts of therapeutic efficacy [21].

Table 1
Sleep and circadian alterations in preclinical models of AS.

Animal model	Sleep/circadian alterations	Ref.
Ube3a$^{m-/p+}$ mouse (classical maternal knockout)	• Reduced and fragmentated SWS • ↓ REM sleep with prolonged latency • Abnormal sleep–wake architecture • ↓ Sleep pressure during wakefulness • ↓ TST • ↓ Total spindle count • ↑ Spindle density relative to TST • ↓ Circadian robustness with longer circadian period • ↓ Rhythm amplitude • Altered light–dark phase relationship • Faster re-entrainment after phase shift • Weaker rebound sleep after sleep deprivation • Attenuated imprinting of paternal *Ube3a* within the SCN • Ube3a colocalization with AVP and PER2 and BMAL1	[13, 16, 17]
dube3a-null *Drosophila melanogaster*	• ↑ Arrhythmicity • ↓ Strength of circadian rest–activity rhythms	[18]
dube3a-RNAi knockdown (*Drosophila*) PER2:Luc mouse	• Conserved role of UBE3A in regulating the molecular circadian clock through BMAL1 ubiquitination and degradation • Altered UBE3A expression disrupts molecular and behavioral circadian rhythmicity	[19]
UG (1.6-Mb deletion from *Ube3a* to *Gabrb3*)$^{m-/p+}$ mouse	• ↓ Circadian robustness with longer circadian period • ↓ Rhythm amplitude • Altered light–dark phase relationship • Faster re-entrainment after phase shift	[14]
Ube3a$^{m\Delta e6/p+}$ mouse (also reported as *Ud6*-$^{m-/p+}$)	• Loss of the late dark-phase siesta • ↓ REM sleep • Disturbed sleep architecture in juvenile and adult mice	[20, 21]
Neuron-specific *Ube3a* deletion (glutamatergic or GABAergic neurons)	• Altered sleep–wake organization • ↓ REM sleep • Sleep fragmentation	[22]

Abbreviations: AVP, arginine vasopressin; LD, light–dark cycle; REM, rapid eye movement; SCN, suprachiasmatic nucleus; SWS, slow-wave sleep; TST, total sleep time.

3.2. Role ofUBE3A in circadian regulation and relationship with core clock genes

The timing of sleep is generally regulated by the circadian clock [26]. In a *Drosophila* model for AS based on a null mutation of the fly counterpart to *Ube3a* (*dube3a*), circadian rhythmicity and activity/rest cycles are abnormal [18]. Gossan et al. showed that BMAL1 (ARNTL in humans), a clock protein that is a central component of the mammalian circadian clock, is an ubiquitination target of E6AP, the protein product of *Ube3a* gene [19]. In AS mice with UBE3A deficiency, it has been observed a reduced activity in the light with longer circadian periods [14,20]. In contrast, *Ube3a* transgenic mice carrying an additional copy of the *Ube3a* gene run more on wheels during the light/day phase of light-dark cycle a period when mice are normally inactive or asleep [20]. Persistent UBE3A expression has been observed in the suprachiasmatic nucleus (SCN) of the hypothalamus—the principal circadian pacemaker in the mammalian brain—in *Ube3a*$^{m-/p+}$ mice. This finding reveals a previously unrecognized region in the adult brain where the typical maternal expression bias of *Ube3a* is partially relaxed [16]. Extending this study, Jones et al. report on paternal *Ube3a* expression occurs in neurons throughout the SCN in adult mice. The authors showed that paternal UBE3A-positive cells partially co-localize with clock proteins (PER2 and BMAL1) [17].

Together, these findings suggest that UBE3A regulates the circadian clock, at least in part through ubiquitination and turnover of BMAL1, with downstream effects on PER2 rhythms, providing a plausible molecular link between UBE3A deficiency and the circadian abnormalities observed in AS.

3.3. Putative pathways interacting with UBE3A: mTOR, PIEZO2, and Wnt/β-catenin

Several studies have shown that the ubiquitin ligase activity of UBE3A is involved in the proteasome-dependent degradation of multiple cellular substrates, suggesting that dysregulation of these targets may contribute to the development of AS [27–29]. By regulating the stability of synaptic proteins, ion channels, and circadian-related factors, UBE3A indirectly modulates neuronal excitability and network synchronization—processes that are essential for proper circadian clock function and sleep architecture. These roles are consistent with the broad pleiotropic activity of UBE3A, as demonstrated by multiple studies [29]. Because of Ube3A deficiency, a connection between UBE3A and the mechanosensitive ion channel PIEZO2 has been established [30]. The authors showed that in AS mice *Ube3a*$^{m-/p+}$ and human AS cell lines there is a decreased PIEZO2 activity and protein expression that can be rescued by fatty acid administration [30]. Although there is

currently no direct evidence linking PIEZO2 to sleep regulation in AS, recent studies have shown that polymorphisms in the *Piezo* gene are associated with sleep latency in *Drosophila* [31]. Given the conserved homology between the drosophila *Piezo* gene and mammalian *Piezo1* and *Piezo2*, further studies are warranted to determine whether these orthologues contribute to sleep regulation in mammals [32].

Thus, the potential involvement of *PIEZO2* in sleep disturbances in AS remains hypothetical and requires direct experimental investigation.

Alterations in mTOR signaling have also been reported in AS models. In particular, increased activity of mTORC1 and its downstream effector S6K1 has been reported in *Ube3a*$^{m-/p+}$ mice [28].

This study proposed that the hyperactivation of the mTORC1–S6K1 pathway contributes to the learning deficits observed in the AS mice [28]. More recent studies indicate that mTOR signaling also regulates key features of circadian clocks, including period length, entrainment, and synchronization [33]. Although these findings provide a biologically plausible link between mTOR signaling and circadian regulation, a direct role of mTOR dysregulation in sleep disturbances in AS has not yet been established.

Additional evidence comes from transcriptomic studies of *Ube3a* rat models. Lopez et al. identified gene networks associated with developmental age and genotype, with enrichment of pathways involved in Wnt/β-catenin signaling, epigenetic regulation, synaptic processes, imprinting, neurogenesis and gliogenesis, circadian entrainment, ubiquitin activity, mTOR signaling, and splicing [34]. In addition, loss of UBE3A has been shown to reduce β-catenin levels in both human iPSC-derived neurons and *Ube3a* $^{m-/p+}$ mice [35]. Mechanistically, UBE3A has been reported to stabilize β-catenin by inhibiting GSK3β, thereby preventing its degradation *via* the canonical Wnt pathway [35]. Thus, in AS mice *UBE3A* deficiency may lead to enhanced β-catenin degradation with increased activity of the destruction complex and interfere with circadian regulation, however, the relevance of this pathway to sleep regulation in AS remains indirect.

Indeed, disruption of the circadian clock has been reported to exacerbate autistic-like behaviors and dysregulate Wnt/β-catenin signaling in ASD mice lacking the *Bmal1* gene [36]. Notably, BMAL1 itself is a target of UBE3A-mediated ubiquitination [19], suggesting a convergence of UBE3A, Wnt signaling, and circadian clock mechanisms in the regulation of brain functioning. Collectively, these findings identify mTOR, PIEZO2, and Wnt/β-catenin signaling as biologically plausible pathways that may interact with UBE3A deficiency. However, unlike the evidence directly linking UBE3A to circadian regulation, their specific contribution to sleep disturbances in AS remains speculative and requires further investigation.

4. Clinical evidence

4.1. Sleep disorders in individuals with AS

Sleep problems represent a core feature of AS and are included in the diagnostic criteria affecting approximately 80% of individuals [1,37]. These disturbances mainly consist of insomnia and abnormal sleep–wake cycles, followed by sleep-disordered breathing, sleep-related movement disorders, and excessive daytime sleepiness [1]. Sleep architecture may be further disrupted by other factors, including nocturnal seizures, the effects of antiseizure medications (ASMs), scoliosis and gastrointestinal symptoms (i.e. gastro-esophageal reflux, constipation) [8,11]. In a recent systematic review by O'Rourke, aggregating seven studies (n = 266), reduced total sleep duration (M = 538 min), longer night-awakenings (M = 67 min) and reduced sleep efficiency (78%), was demonstrated in individuals with AS compared with typically developing peers [38].

Assessment of sleep disorders in AS has been performed using both parental reports and objective measures such as polysomnography (PSG) and actigraphy, a non-invasive method for monitoring sleep–wake patterns over extended periods in the home environment. Survey studies on caregivers highlight difficulties with sleep onset and frequent nocturnal awakenings [39,40]. On the other hand, PSG studies provide direct evidence that individuals with AS show a reduction in TST (often <7 h in childhood), prolonged sleep onset latency (SOL >30 min), low sleep efficiency (<80%), and frequent or prolonged nocturnal awakenings, reflected by increased wake after sleep onset (WASO >60 min). Sleep tends to be highly fragmented, with an increased frequency of awakenings and transitions between sleep stages, along with a reduction in the deepest stages of non-rapid eye movement (NREM) sleep, despite no clear reduction in the total amount of NREM sleep [24,25,41]. During NREM sleep, both the number and duration of sleep spindles appear to be significantly reduced, suggesting a potential direct relationship between poor sleep quality and memory difficulties [42]. A reduction in REM sleep has also been observed, likely due to inefficient progression through the NREM three stages required to reach REM sleep [23,24,41]. These sleep disturbances often begin in infancy, peak in early childhood, and persist in more than 60% of adults. Comparative studies using PSG and actigraphy in children and adolescents with AS and their parents demonstrate considerable variability in sleep parameters, particularly in PSG-measured WASO, and consistently higher levels of wakefulness and sleep fragmentation in individuals with AS compared with their parents. Actigraphy data also show that parents of children with AS experience substantial sleep disruption themselves, with more than 1 h of wake time after sleep onset and fragmented sleep, highlighting the significant familial impact of sleep problems in AS [43].

To date, direct comparisons between specific genotypes (maternal 15q11–q13 deletion versus other molecular subtypes, including *UBE3A* pathogenic variants, UPD, ICDs, and other rare molecular mechanisms) and the severity of the sleep phenotype remain limited, and genotype–phenotype correlations have been largely inferred from studies on epilepsy rather than sleep-specific investigations [10].

In a large cohort of 695 Chinese children with AS, Du et al. reported a high prevalence of sleep disturbances in both the deletion and non-deletion groups (89.08% vs. 83.90%, respectively). The non-deletion group included individuals with pathogenic *UBE3A* variants (9.35% of the total cohort), UPD (4.46%), ICDs (1.44%), and unclassified molecular subtypes (1.58%) [44]. These findings indicate that sleep problems are common across molecular subtypes, although they appeared slightly more frequent in individuals with the deletion subtype.

In patients with deletion AS, the contribution of co-deleted non-imprinted genes to the pathophysiology of sleep disorders remains poorly understood. Nevertheless, indirect evidence suggests that the *GABRB3–GABRA5–GABRG3* gene cluster may play a role in sleep regulation. In particular, a population-based genetic association study identified variants within these GABA receptor genes as candidate loci associated with sleep duration, supporting their potential involvement in the sleep phenotype observed in deletion AS [45].

4.1.1. Relation between sleep dysregulation and epilepsy

Epilepsy is a highly prevalent and clinically significant feature of AS, affecting approximately 80-90% of individuals, with onset typically occurring between 18 and 36 months of age. Individuals with larger 15q11-q13 region deletions may have an earlier onset, higher prevalence and most severe epileptic phenotype as compared to those with other genetic mechanisms like UPD or ICD [46,47]. In a cohort of 265 children with AS, Cassater et al. reported a significantly higher prevalence of epilepsy in individuals carrying a 15q11-q13 deletion compared with non-deletion genotypes (91% vs. 61%), along with an earlier median age at seizure onset (24 vs. 57 months) and higher hospitalization rates [10]. This greater severity of epilepsy is likely attributable not only to the loss of *UBE3A* but also to the concomitant haploinsufficiency of other genes located within the deleted region, particularly those encoding GABA receptor subunits, including *GABRB3*, *GABRA5*, and *GABRG3*. These genes play essential role in inhibitory neurotransmission and neuronal network maturation, and pathogenic variants affecting GABAergic signaling have been consistently linked to epilepsy

and other neurodevelopmental disorders [48]. Consequently, the combined loss of *UBE3A* and neighboring GABA receptor genes may contribute to the increased seizure susceptibility and more severe epileptic phenotype characteristic of deletion AS.

Regarding seizure semiology in AS, common seizure types include atypical absence (65-85%), myoclonic (50-75%) and tonic-clonic (40-60%) seizures, and focal seizures with impaired consciousness (30-50%) [49–53]. Cortical myoclonus (rhythmic or arrhythmic symmetric and asymmetric jerks involving limbs, trunk, and face) and non-convulsive status epilepticus (NCSE) are also reported in 35–85% of individuals [49,50].

The EEG is typically characterized by three specific patterns, found across different genotypes, including.

1) runs of high amplitude (200 to 500 μV) rhythmic delta (2 to 3 Hz) activity, more often observed in the frontal regions, present in wakefulness and increasing in voltage during drowsiness and sleep; this pattern may be also present as so called notched-delta pattern, a variant in which spikes are superimposed on the ascending or the descending phase of the slow wave giving it a notched appearance [51,52]. In adolescence and adulthood this pattern may be characterized by a triphasic activity (anterior sharp slow-waves complexes) [50,52,53].
2) persistent rhythmic theta (4- to 6-Hz) high-amplitude (200 μV) activity with a centro-temporal predominance, disappearing with increasing age [50];
3) spikes mixed 3- to 4-Hz high-amplitude rhythmic activity (greater than 200 μV), mainly found in the posterior regions, and facilitated by eye closure, more prominent during drowsiness and sleep [53–55]. Sporadic focal or generalized interictal discharges may be present [53].

Interestingly, Sidorov et al. demonstrated that elevated power and rhythmic organization in the delta frequency range on EEG during wakefulness and sleep is a conserved feature of AS in both children and mouse models, supporting its use as a reliable translational EEG biomarker for preclinical and clinical therapeutic studies [56].

Although the precise pathological mechanism underlying epileptogenesis in AS is not completely clear, epilepsy is thought to originate from an imbalance between local excitatory-inhibitory circuits that results in a generalized circuit hyperexcitability. Judson et al. demonstrated that in conditional *Ube3a*$^{m-/p+}$ mice with selective maternal deletion of *Ube3a* in cortical GABAergic neurons there are circuit hyperexcitability, increased seizure severity, and EEG abnormalities [57]. Thus, the authors hypothesize that GABAergic, but not glutamatergic, *Ube3a* loss is responsible for mediating the EEG abnormalities and seizures that affect individuals with AS [57]. Moreover, Mandel-Brehm et al. showed that the seizure-like activity observed in *Ube3a*$^{m-/p+}$ young mice can be attenuated by genetically reducing the expression level of the activity-regulated cytoskeleton-associated protein, Arc [58]. This is a synaptic protein that is ubiquitinated by UBE3A and thus degraded [59]. In the absence of Ube3A, the authors showed that elevated levels of Arc were accumulated in neurons of *Ube3A* knockout mice resulting in the excessive internalization of AMPA receptors at synapses causing an impaired synaptic function [59].

The co-occurrence of epilepsy and sleep disorder in AS suggests shared pathophysiological pathways, with the loss of *UBE3A* function serving as a common upstream cause able to create a neurobiological landscape where sleep disruption and epileptogenesis are intertwined, each potentially exacerbating the other [37,60]. The disruption of epilepsy–sleep circuits emerges as a consistent feature in murine models of AS. Previous studies have shown that *Ube3a*$^{m-/p+}$ mice display characteristic paroxysmal EEG discharges accompanied by alterations in slow-wave sleep architecture [13]. More recent work further supports this link, demonstrating that *Ube3a* deletion models exhibit concurrent electrophysiological abnormalities and impairments in sleep–wake regulation [11]. Together, these findings suggest that aberrant network excitability and sleep dysfunction are tightly interconnected in AS, raising the possibility that shared circuit-level mechanisms underlie both phenotypes. This interplay may have important implications for understanding disease progression and for developing therapeutic strategies targeting sleep-dependent neural homeostasis.

In individuals with AS, available evidence suggests a bidirectional relationship between epilepsy and sleep disruption. In particular, sleep deprivation and poor sleep quality (reduced TST, increased WASO) may lower seizure thresholds, facilitate cortical hyperexcitability and increase seizure frequency [43,61,62]. Circadian dysregulation and melatonin deficiency in AS, may also contribute to both sleep instability and reduced seizure threshold [63].

On the other hand, seizures particularly during NREM can significantly disrupt normal sleep architecture, interrupt sleep continuity, reducing SWS duration and quality, and increasing WASO and stage shifts, independent of overt seizures [42,64,65]. Nocturnal seizures, even if brief, can cause arousals and awakenings, leading to sleep fragmentation and reduced sleep efficiency [66].

4.1.2. Relation between sleep dysregulation and behavioral issues

Behavioral abnormalities are a core feature of AS, characterized by frequent laughter, smiling, excitability, hyperactivity, and motor stereotypies [1,67]. Although similar traits occur in other severe intellectual disabilities, their combination with a persistently cheerful demeanor constitutes a distinctive behavioral signature of AS [68]. [64] Despite this apparent positivity, emotional and behavioral dysregulation represents a major clinical challenge, significantly impacting quality of life and caregiver burden [6,69]. Laughter in AS is context-dependent, increasing not only during positive interactions but also in stressful situations, suggesting a role as a marker of emotional dysregulation rather than purely positive affect [70]. While its frequency may decrease in adulthood [71], hyperactivity remains prominent and often coexists with aggression, which can worsen over time [72,73]. Self-injurious behaviors (SIB), affecting up to 70% of individuals, are among the most severe manifestations and are typically triggered by frustration, anxiety, sensory dysregulation, and sleep disturbances [8,73,74]. Autistic-like traits, including social communication deficits and repetitive behaviors, are common but appear largely influenced by cognitive and communicative impairments rather than representing primary autism [75]. Anxiety and separation distress are increasingly recognized as key contributors to behavioral dysregulation, often underlying irritability and agitation [76–78]. Genotype plays a significant role, with individuals carrying maternal 15q11.2–q13 deletions showing more severe hyperactivity, self-injurious behavior (SIB), and developmental impairment than those with other genetic subtypes [44,79]. In a recent genotype–phenotype correlation study involving a large cohort of Chinese children with AS, Du et al. demonstrated that the deletion group exhibited more pronounced food-related behavioral abnormalities and hyperactivity, whereas individuals in the non-deletion group showed greater autonomy in adaptive functioning [44]. Conversely, Keute et al. demonstrated that individuals with UPD were more severely impaired than those with other non-deletion genotypes, including individuals carrying missense or truncating *UBE3A* variants and those with ICDs [79]. This observation is particularly interesting because truncating *UBE3A* variants are generally expected to result in substantial loss of *UBE3A* function, suggesting that phenotypic severity may not be determined solely by the extent of UBE3A functional impairment. These data raise the hypothesis that UPD may represent a distinct non-deletion molecular subtype, with a phenotype that, for some developmental domains, may be intermediate between non-deletion genotypes and maternal 15q11.2–q13 deletion.

In AS, sleep disturbances are associated with behavioral problems. In particular, poor sleep quality—characterized by reduced TST and increased fragmentation—is associated with increased hyperactivity, impulsivity, irritability, anxiety, and SIB [80,81]. Sleep fragmentation

likely contributes to impaired prefrontal regulation of emotion and behavior [82]. Additionally, sleep disturbances correlate with higher anxiety levels and may exacerbate aggressive behaviors, particularly in adults [76,83]. Importantly, hyperactivity in AS is not solely a consequence of sleep disruption but represents an intrinsic feature of the syndrome [84]. Conversely, behavioral dysregulation can further disrupt sleep by interfering with sleep initiation and maintenance [85,86]. Moving to animal models, several studies confirm that sleep dysregulation and behavioral abnormalities co-occur in AS mice. In addition to abnormalities in siesta and sleep–wake behavior, *Ube3a*-deficient AS mice display altered performance in rotarod and marble-burying tests compared with wild-type littermates [20]. In a recent study Ringelberg et al. observed deficits in numerous motor and innate behaviors in conditional mice with glutamatergic *Ube3a* deletion, and relatively few consequences in conditional mice with GABAergic *Ube3a* deletion [22]. However, by testing sleep parameters, the authors proposed that glutamatergic *Ube3a* deletion causes altered sleep–wake behavior, while GABAergic *Ube3a* deletion induces sleep fragmentation phenotype. These results suggest that Ube3a may have a specific role in regulating motor and innate behaviors in AS model mice, independent of the circuits responsible for seizures and EEG abnormalities.

5. Therapeutic considerations and management strategies

5.1. Current approaches to managing sleep disorders

Managing sleep disturbances in AS requires a multifaceted approach that integrates behavioral strategies, environmental modifications, and pharmacological interventions. A cornerstone of management is the establishment of consistent sleep hygiene practices, supported by targeted behavioral interventions [87]. When behavioral approaches are insufficient, pharmacological treatments are often required.

Melatonin is commonly used as a first-line treatment for sleep disturbances in AS. It can be titrated across a range of doses, from low-dose regimens (0.3 mg/day) to higher doses (2.5 mg/day for children younger than 6 years and 5 mg/day for children aged 6 years or older) [88,89]. In addition to improving sleep, melatonin has also been associated with reductions in hyperactivity and irritability in individuals with AS [90–92].

However, despite the widespread use of pharmacological treatments for insomnia and other sleep disorders, there is a lack of well-designed, controlled studies evaluating the efficacy, tolerability, optimal dosing, and safety of hypnotic medications in patients with AS. Consequently, current therapeutic approaches have largely been extrapolated from studies conducted in adults or in individuals with other neurodevelopmental disorders, particularly ASD. Mirtazapine has been evaluated in a small case series of patients with AS, where it was associated with improvements in sleep onset and reductions in nighttime awakenings [93]. The most commonly reported adverse effects included weight gain, hyperphagia, and hyperactivity [93].

Additional pharmacological options, commonly used in patients with neurodevelopmental disorders according to their comorbidities, include α-adrenergic agonists (e.g., clonidine and guanfacine, particularly in individuals with co-occurring ADHD symptomatology), benzodiazepines (e.g., clonazepam, especially in patients with epilepsy), gabapentinoids (e.g., gabapentin and pregabalin, particularly if present restless legs syndrome or epilepsy), antihistamines (e.g., promethazine and diphenhydramine), antidepressants (e.g., trazodone), and, in selected refractory cases, atypical antipsychotics (e.g., quetiapine) [94,95]. Most of the listed agents are used off-label for insomnia in AS population and are not supported by specific controlled studies.

The adverse effects of these medications vary according to drug class and may be for a-Adrenergic agonists: drowsiness, transient sedation, headache, dizziness, fatigue, hypotension, bradycardia, and, less commonly, insomnia; for benzodiazepine: sedation, tolerance, and dependence, and occasionally paradoxical reactions, including agitation; for gabapentinoids: dizziness and ataxia, whereas for antihistamines daytime sedation and anticholinergic effects. Trazodone may cause daytime drowsiness, orthostatic hypotension, and, rarely, priapism. Quetiapine is associated with metabolic adverse effects, including weight gain, dyslipidemia, and glucose dysregulation, as well as sedation [95].

5.2. Current antiseizure therapeutic strategies

The management of epilepsy in AS remains a central clinical challenge, often necessitating a personalized approach to optimize ASM regimens and minimizing treatment-related adverse effects. Common first-line ASMs include valproate, levetiracetam, clobazam, topiramate, lamotrigine, and ethosuximide, chosen based on seizure type and individual patient characteristics [9,96]. It is crucial to monitor for both efficacy in seizure control and any adverse effects on sleep and behavior. For instance, some ASMs (i.e. clonazepam) can cause sedation, which might be perceived as beneficial for sleep but can also lead to daytime drowsiness and worsening cognitive function or behavior. Valproic acid can worsen ataxia and decline in gross and fine motor skills. Conversely, other ASMs (i.e. topiramate) can cause insomnia and produce cognitive side effects [9,96]. Notwithstanding its GABAergic properties, vigabatrin is generally contraindicated in AS due to the risk of exacerbating seizures or causing neurological worsening [49,97]. Anecdotal reports exist about effectiveness of cannabidiol in particular in NCSE [98], but a rigorous randomized clinical trial has not been performed in this population. For individuals with drug-resistant epilepsy, non-pharmacological options such as the ketogenic diet or vagus nerve stimulation may be considered and have shown promise in some cases [9,96].

5.3. Current therapeutic approaches for behavioral problems

Behavioral interventions play a crucial role in managing the behavioral phenotype of AS. These interventions are typically tailored to the individual's specific needs, developmental level, and communication abilities [70]' [99]. [66]' [95] Applied Behavior Analysis principles are often used to teach new skills, increase adaptive behaviors, and reduce challenging behaviors. This can involve breaking down complex skills into smaller, manageable steps, using positive reinforcement to encourage desired behaviors, and implementing strategies to address specific issues like tantrums or aggression. Communication training is also a key component of behavioral intervention, as improving an individual's ability to express their needs and wants can reduce frustration and associated behavioral problems. This often involves the use of augmentative and alternative communication methods, such as picture exchange systems or speech-generating devices. The efficacy of behavioral interventions often depends on early implementation, intensity, and the consistency of application across different settings (home, school, therapy) [100].

5.4. Emerging targeted therapies and their potential impact

The landscape of therapeutic development for AS is rapidly evolving, with several targeted strategies showing promise in preclinical studies (Table 2) and early-phase clinical trials. These approaches primarily aim to restore functional expression of the maternally deficient *UBE3A* in the brain. In this context, Milazzo et al. demonstrated that antisense oligonucleotide (ASO)-mediated reduction of *UBE3A-ATS* robustly reinstates paternal *UBE3A* expression in a mouse model, resulting in partial rescue of multiple phenotypes, including motor, cognitive, and electrophysiological deficits, although not all abnormalities were fully corrected [101]. Lee et al. extended these findings by showing that ASO treatment can normalize cortical EEG abnormalities—particularly elevated delta power—and improve sleep disturbances in both juvenile and adult mice, indicating that key circuit-level dysfunctions retain a degree of

Table 2
Therapeutic strategies and disease-related phenotype rescue in preclinical models of AS.

Animal model	Treatment	Rescue outcome	Ref.
Ube3a$^{m-/p+}$ mouse	THIP (gaboxadol; extrasynaptic $GABA_A$ receptor agonist)	Partial rescue of motor deficits	60
Ube3a$^{m-/p+}$ juvenile mouse	Genetic reduction of *Arc*	Normalization of seizure-like phenotype and EEG abnormalities	58
Ube3a$^{m-/p+}$ mouse (ASO rescue model)	ASO-mediated unsilencing of paternal *Ube3a*	Reduced audiogenic seizure susceptibility	101
Ube3a$^{m-/p+}$ mouse	(S)-PHA533533 (CDK2 inhibitor)	Unsilencing of paternal *Ube3a* and partial rescue of AS–associated phenotypes (including improvements in motor deficits, seizure susceptibility, and behavioral abnormalities)	102
Ube3a $^{m\Delta e6/p+}$ mouse	ICV Ube3a-targeting ASO	Normalization of cortical EEG activity and rescue of sleep abnormalities	21
Neuron-specific *Ube3a* deletion (glutamatergic or GABAergic neurons)	Glutamatergic Ube3a reinstatement	Restoration of REM sleep	22

Abbreviations: ARC, Activity Regulated Cytoskeleton Associated Protein; ASO, antisense oligonucleotide; AVP, arginine vasopressin; EEG, electroencephalogram; ICV, intracerebroventricular; LD, light–dark cycle; REM, rapid eye movement, THIP: 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol.

reversibility beyond early developmental stages [21].

More recently, Vihma et al. identified the cyclin-dependent kinase inhibitor (S)-PHA533533 through a high-content chemogenetic screen [102]. This compound selectively inhibits CDK2 and was shown to induce unsilencing of the paternal *Ube3a* allele in vivo following systemic administration in *Ube3a*$^{m-/p+}$ mice. Furthermore, treatment with (S)-PHA533533 increased paternal *UBE3A* mRNA levels in induced pluripotent stem cell (iPSC)-derived neurons from individuals with AS. Collectively, these findings suggest that (S)-PHA533533 represents a promising tool compound for non-invasive, brain-penetrant reactivation of paternal *UBE3A* expression. However, further studies are needed to define the extent, specificity, and long-term functional consequences of *UBE3A* restoration in vivo.

Recently, a screening of a library of locked nucleic acid (LNA)-modified ASOs in AS patient-derived neurons led to the identification of rugonersen (RO7248824), which selectively and potently reduces UBE3A-ATS and upregulates UBE3A mRNA and protein in neurons derived from neurotypical humans, AS patients, and cynomolgus monkeys. In vivo studies with rugonersen in wild-type and AS mice, and cynomolgus monkeys revealed a steep relationship between Ube3a-ats knock-down and UBE3A mRNA/protein upregulation, requiring ~90% knock-down for 50% upregulation. Two studies of up to three lumbar intrathecal rugonersen doses in monkeys showed no adverse effects and produced long-lasting paternal UBE3A mRNA/protein reactivation in key brain regions [103].

Based on this evidence, recently, a multicenter clinical phase 1 trial with rugonersen (ClinicalTrials.gov registration: NCT04428281) was completed in humans. The study was a phase 1, multicenter, open-label, multiple-ascending-dose trial with a long-term extension to investigate the safety and tolerability (primary) and pharmacokinetics (secondary) of rugonersen in children aged 1–12 years with AS. Rugonersen showed acceptable safety and tolerability profile, led to a dose-dependent partial normalization of the AS-associated EEG abnormality and revealed signals of clinical improvement in core AS symptom domains tested by Bayley Scales and Vineland Adaptive Behavior Scales [104]. Notably, although sleep was not a predefined primary or secondary endpoint, it was evaluated as part of the Symptoms of Angelman Syndrome–Clinician Global Impression (SAS-CGI) scale, which includes a specific sleep subdomain among its nine clinician-rated symptom domains. Improvements in sleep subdomain were observed following rugonersen treatment [104].

To date, there are other clinical trials ongoing in individuals with AS:

In particular a i) phase 3 trial (ClinicalTrials.gov ID NCT06914609) in children and adults with AS evaluating the efficacy of ION582 (80 mg ION582 vs placebo), an ASO designed to inhibit the *UBE3A-ATS* transcript, allowing for the activation of the silent paternal *UBE3A* gene. Among the secondary outcome measures, the trial includes the Symptoms of Angelman Syndrome–Clinician Global Impression of Change (SAS-CGI-C) for sleep problems, assessed from baseline to Week 52.

Ii) a phase 2 open-label, basket study (ClinicalTrials.gov ID NCT07157254), investigating the safety and efficacy of GTX-102 in adult and pediatric subjects with deletion- or nondeletion-type AS. Notably, sleep is a key efficacy outcome in this trial: the Angelman Severity Assessment (ASA) Sleep score is included as a component of the Multidomain Responder Index (MDRI) net response, which is the primary outcome for subprotocols B/D; while the change from baseline to day 338 in the ASA Sleep Rating as a standalone measure is a secondary outcome; iii) a phase 3 efficacy and safety study (ClinicalTrials.gov ID NCT06617429) evaluating the effect of GTX-102 in cognitive function in individuals with deletion-type AS; notably, change from baseline to Day 338 in the ASA Sleep Rating Raw Score is included among the secondary outcome measures.

and iv) a phase 1/2 study (ClinicalTrials.gov ID NCT07181837), evaluating the safety and efficacy of MVX-220 gene therapy, delivering a functional copy of the *UBE3A* gene directly to neurons by injection into the cisterna magna in children and adults with AS with UBE3A gene deletion, UPD, or imprinting center defect genotypes. Change from baseline to Week 104 in caregiver-reported sleep diary parameters is included as a secondary outcome measure.

The impact of such therapies could be transformative, moving beyond symptomatic management to address the underlying neurobiological deficits in AS.

6. Conclusion

Deficiency of UBE3A represents a key pathophysiological mechanism in AS, affecting not only neurodevelopment but also sleep architecture and circadian regulation, partly through interactions with core clock genes. Preclinical studies have been instrumental in elucidating these mechanisms, highlighting the role of UBE3A in circadian rhythm regulation, synaptic plasticity, and neural circuit development, particularly in GABAergic neurons. Remarkably, several findings in murine models show substantial translational relevance to individuals with AS. In particular, the reduced sleep efficiency, sleep fragmentation, impaired sleep homeostasis and REM sleep abnormalities observed in *Ube3a*-deficient mice closely mirror the high prevalence of insomnia, frequent nocturnal awakenings, reduced sleep duration and altered sleep architecture reported in clinical cohorts of patients with AS.

Overall, converging evidence from animal models and clinical observations support a bidirectional relationship among sleep disturbances, epilepsy, and behavioral dysfunction. We further propose that these manifestations may participate in a self-reinforcing cycle that amplifies their cumulative impact on neurodevelopmental outcomes and overall quality of life. Although this conceptual framework is biologically plausible, it remains hypothetical, as causal relationships have not yet been established and no study has demonstrated that treating sleep disturbances alone is sufficient to interrupt this cycle and subsequently improve epilepsy or behavioral outcomes. Future longitudinal and interventional studies are needed to test this hypothesis and clarify whether targeting sleep may provide broader therapeutic benefits in AS.

Over the past decade, substantial translational progress has led to the development of novel therapeutic strategies aimed at restoring UBE3A function. While the effects of these emerging therapies on sleep and circadian dysfunction remain to be fully characterized, early recognition and appropriate management of sleep disturbances may represent a modifiable component of care with the potential to improve quality of life and possibly contribute to better behavioral and seizure outcomes. Consequently, standardized sleep assessments and sleep-related outcome measures should be incorporated as clinically meaningful endpoints in future natural history studies and clinical trials evaluating disease-modifying therapies for AS.

CRediT authorship contribution statement

Gaetano Terrone: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Maria Giuseppina Miano:** Conceptualization, Writing – review & editing. **Marco Carotenuto:** Writing – review & editing. **Maria Francesca Fiorile:** Data curation. **Salvatore Aiello:** Writing – review & editing. **Carmela Bravaccio:** Writing – review & editing. **Ennio Del Giudice:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interests

All authors declare no conflict of interest.

References

[1] Williams CA, Beaudet AL, Clayton-Smith J, et al. Angelman syndrome 2005: updated consensus for diagnostic criteria. Am J Med Genet 2006;140(5):413–8. https://doi.org/10.1002/ajmg.a.31074.

[2] Dagli AI, Mathews J, Williams CA. Angelman syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1998 Sep 15. p. 1993–2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1144/. [Accessed 2 November 2023].

[3] Laan LA, v Haeringen A, Brouwer OF. Angelman syndrome: a review of clinical and genetic aspects. Clin Neurol Neurosurg 1999 Sep;101(3):161–70. https://doi.org/10.1016/s0303-8467(99)00030-x.

[4] Vu TH, Hoffman AR. Imprinting of the Angelman syndrome gene, UBE3A, is restricted to brain. Nat Genet 1997 Sep;17(1):12–3. https://doi.org/10.1038/ng0997-12.

[5] Judson MC, Sosa-Pagan JO, Del Cid WA, Han JE, Philpot BD. Allelic specificity of Ube3a expression in the mouse brain during postnatal development. J Comp Neurol 2014;522(8):1874–96. https://doi.org/10.1002/cne.23507.

[6] Wheeler AC, Sacco P, Cabo R. Unmet clinical needs and burden in Angelman syndrome: a review of the literature. Orphanet J Rare Dis 2017;12(1):164. https://doi.org/10.1186/s13023-017-0716-z.

[7] Williams CA, Zori RT, Hendrickson J, Stalker H, Marum T, Whidden E, Driscoll DJ. Angelman syndrome. Curr Probl Pediatr 1995 Aug;25(7):216–31. https://doi.org/10.1016/s0045-9380(06)80036-8.

[8] Pelc K, Cheron G, Boyd SG, Dan B. Are there distinctive sleep problems in Angelman syndrome? Sleep Med 2008;9(4):434–41. https://doi.org/10.1016/j.sleep.2007.07.001.

[9] Duis J, Nespeca M, Summers J, Bird L, et al. A multidisciplinary approach and consensus statement to establish standards of care for Angelman syndrome. Mol Genet Genom Med 2022 Mar;10(3):e1843. https://doi.org/10.1002/mgg3.1843.

[10] Cassater D, Bustamante M, Sach-Peltason L, Rotenberg A, Nespeca M, Tan WH, Bird LM, Hipp JF. Clinical characterization of epilepsy in children with angelman syndrome. Pediatr Neurol 2021 Nov;124:42–50.

[11] Conant KD, Thibert RL, Thiele EA. Epilepsy and the sleep-wake patterns found in Angelman syndrome. Epilepsia 2009;50(11):2497–500. https://doi.org/10.1111/j.1528-1167.2009.02109.x.

[12] Copping NA, Silverman JL. Abnormal electrophysiological phenotypes and sleep deficits in a mouse model of Angelman Syndrome. Mol Autism 2021;12(1):9. https://doi.org/10.1186/s13229-021-00416-y.

[13] Colas D, Wagstaff J, Fort P, Salvert D, Sarda N. Sleep disturbances in UBE3A maternal-deficient mice modeling Angelman syndrome. Neurobiol Dis 2005;20:471–8. https://doi.org/10.1016/j.nbd.2005.04.003.

[14] Shi SQ, Bichell TJ, Ihrie RA, Johnson CH. Ube3a imprinting impairs circadian robustness in Angelman syndrome models. Curr Biol 2015 Mar 2;25(5):537–45. https://doi.org/10.1016/j.cub.2014.12.047. Epub 2015 Feb 5. PMID: 25660546; PMCID: PMC4348236.

[15] Rotaru DC, Mientjes EJ, Elgersma Y. Angelman syndrome: from mouse models to therapy. Neuroscience 2020;445:172–89. https://doi.org/10.1016/j.neuroscience.2020.02.017.

[16] Ehlen JC, Jones KA, Pinckney L, Gray CL, Burette S, Weinberg RJ, Evans JA, Brager AJ, Zylka MJ, Paul KN, Philpot BD, DeBruyne JP. Maternal Ube3a loss disrupts sleep homeostasis but leaves circadian rhythmicity largely intact. J Neurosci 2015;35:13587–98. https://doi.org/10.1523/JNEUROSCI.2194-15.2015.

[17] Jones KA, Han JE, DeBruyne JP, Philpot BD. Persistent neuronal Ube3a expression in the suprachiasmatic nucleus of Angelman syndrome model mice. Sci Rep 2016;6:28238. https://doi.org/10.1038/srep28238.

[18] Wu Y, Bolduc FV, Bell K, Tully T, Fang Y, Sehgal A, Fischer JA. A drosophila model for Angelman syndrome. Proc Natl Acad Sci USA 2008 Aug 26;105(34):12399–404.

[19] Gossan NC, Zhang F, Guo B, Jin D, Yoshitane H, Yao A, Glossop N, Zhang YQ, Fukada Y, Meng QJ. The E3 ubiquitin ligase UBE3A is an integral component of the molecular circadian clock through regulating the BMAL1 transcription factor. Nucleic Acids Res 2014 May;42(9):5765–75. https://doi.org/10.1093/nar/gku225.

[20] Shi SQ, Mahoney CE, Houdek P, Zhao W, Anderson MP, Zhuo X, Beaudet A, Sumova A, Scammell TE, Johnson CH. Circadian rhythms and sleep are dependent upon expression levels of key ubiquitin ligase Ube3a. Front Behav Neurosci 2022 Mar 23;16:837523. https://doi.org/10.3389/fnbeh.2022.837523. PMID: 35401134; PMCID: PMC8989470.

[21] Lee D, Chen W, Kaku HN, Zhuo X, Chao ES, Soriano A, Kuncheria A, Flores S, Kim JH, Rivera A, Rigo F, Jafar-Nejad P, Beaudet AL, Caudill MS, Xue M. Antisense oligonucleotide therapy rescues disturbed brain rhythms and sleep in juvenile and adult mouse models of Angelman syndrome. eLife 2023;12:e81892. https://doi.org/10.7554/eLife.81892.

[22] Ringelberg NW, Mayfield RE, Lord JS, Diering GH, Burette AC, Philpot BD. Cell type-specific contributions of UBE3A to Angelman syndrome behavioral phenotypes. eNeuro 2025 Sep 29;12(9). https://doi.org/10.1523/ENEURO.0453-24.2025. ENEURO.0453-24.2025.

[23] Miano S, Bruni O, Leuzzi V, Elia M, Verrillo E, Ferri R. Sleep polygraphy in Angelman syndrome. Clin Neurophysiol 2004 Apr;115(4):938–45. https://doi.org/10.1016/j.clinph.2003.11.004.

[24] Miano S, Bruni O, Elia M, et al. Sleep breathing and periodic leg movement pattern in Angelman syndrome: a polysomnographic study. Clin Neurophysiol 2005;116(11):2685–92. https://doi.org/10.1016/j.clinph.2005.08.006.

[25] Herrera CG, Tarokh L. A thalamocortical perspective on sleep spindle alterations in neurodevelopmental disorders. Curr Sleep Med Rep 2024;10(2):103–18. https://doi.org/10.1007/s40675-024-00284-x. Epub 2024 Mar 11. PMID: 38764858; PMCID: PMC11096120.

[26] Meyer N, Harvey AG, Lockley SW, Dijk DJ. Circadian rhythms and disorders of the timing of sleep. Lancet 2022;400(10357):1061–78.

[27] Tomaić V, Banks L. Angelman syndrome-associated ubiquitin ligase UBE3A/E6AP mutants interfere with the proteolytic activity of the proteasome. Cell Death Dis 2015 Jan 29;6(1):e1625. https://doi.org/10.1038/cddis.2014.572. PMID: 25633294; PMCID: PMC4669770.

[28] Sun J, Liu Y, Tran J, O'Neal P, Baudry M, Bi X. mTORC1-S6K1 inhibition or mTORC2 activation improves hippocampal synaptic plasticity and learning in Angelman syndrome mice. Cell Mol Life Sci 2016 Nov;73(22):4303–14. https://doi.org/10.1007/s00018-016-2269-z. Epub 2016 May 12. PMID: 27173058; PMCID: PMC5056144.

[29] Biagioni M, Baronchelli F, Fossati M. Multiscale spatio-temporal dynamics of UBE3A gene in brain physiology and neurodevelopmental disorders. Neurobiol Dis 2024;201:106669. https://doi.org/10.1016/j.nbd.2024.106669.

[30] Romero LO, Caires R, Kaitlyn Victor A, Ramirez J, Sierra-Valdez FJ, Walsh P, Truong V, Lee J, Mayor U, Reiter LT, Vásquez V, Cordero-Morales JF. Linoleic acid improves PIEZO2 dysfunction in a mouse model of Angelman syndrome. Nat Commun 2023;14(1):1167. https://doi.org/10.1038/s41467-023-36818-0.

[31] Eiman MN, Kumar S, Serrano Negron YL, Tansey TR, Harbison ST. Genome-wide association in drosophila identifies a role for piezo and Proc-R in sleep latency. Sci Rep 2024 Jan 2;14(1):260. https://doi.org/10.1038/s41598-023-50552-z.

[32] Wu J, Lewis AH, Grandl J. Touch, tension, and transduction - the function and regulation of piezo ion channels. Trends Biochem Sci 2017 Jan;42(1):57–71. https://doi.org/10.1016/j.tibs.2016.09.004.

[33] Singla R, Mishra A, Cao R. The trilateral interactions between mammalian target of rapamycin (mTOR) signaling, the circadian clock, and psychiatric disorders: an emerging model. Transl Psychiatry 2022;12(1):355. https://doi.org/10.1038/s41398-022-02120-8.

[34] Lopez SJ, Laufer BI, Beitnere U, Berg EL, Silverman JL, O'Geen H, Segal DJ, LaSalle JM. Imprinting effects of UBE3A loss on synaptic gene networks and Wnt signaling pathways. Hum Mol Genet 2019 Nov 15;28(22):3842–52. https://doi.org/10.1093/hmg/ddz221.

[35] Yang X, Huang YA, Marshall J. UBE3A stabilization of β-catenin preserves synaptic proteins essential for motor and cognitive functions in Angelman syndrome. Mol Autism 2025 Nov 27;16(1):60. https://doi.org/10.1186/s13229-025-00690-0.

[36] Zhang Y, Chen Y, Li W, Tang L, Wang G, Li J, Feng X. Circadian clock dysfunction exacerbate autistic-like behaviour and Wnt/β-Catenin signalling dysregulation in ASD mice and treatment of melatonin. J Cell Mol Med 2026 Jan;30(1):e70991. https://doi.org/10.1111/jcmm.70991.

[37] Qu S, Wang J, Guan X, Song C, Wang Y. Sleep disturbance in Angelman syndrome patients. Orphanet J Rare Dis 2024 Apr 5;19(1):146. https://doi.org/10.1186/s13023-024-03154-5.

[38] O'Rourke N, Haverty R, Mannion A, et al. Characterization of sleep problems in angelman syndrome: a systematic review. Rev J Autism Dev Disord 2024. https://doi.org/10.1007/s40489-024-00458-x.

[39] Walz NC, Beebe D, Byars K. Sleep in individuals with Angelman syndrome: parent perceptions of patterns and problems. Am J Ment Retard 2005;110(4):243–52. https://doi.org/10.1352/0895-8017(2005)110[243:SIIWAS]2.0.CO;2.

[40] Didden R, Korzilius H, Smits MG, Curfs LM. Sleep problems in individuals with Angelman syndrome. Am J Ment Retard 2004 Jul;109(4):275–84. https://doi.org/10.1352/0895-8017(2004)109<275:SPIIWS>2.0.CO;2. PMID: 15176919.

[41] Bruni O, Ferri R, D'Agostino G, Miano S, Roccella M, Elia M. Sleep disturbances in Angelman syndrome: a questionnaire study. Brain Dev 2004;26(4):233–40. https://doi.org/10.1016/S0387-7604(03)00160-8.

[42] den Bakker H, Sidorov MS, Fan Z, et al. Abnormal coherence and sleep composition in children with Angelman syndrome: a retrospective EEG study. Mol Autism 2018;9:32. https://doi.org/10.1186/s13229-018-0214-8.

[43] Goldman SE, Bichell TJ, Surdyka K, et al. Sleep in adolescents and young adults with Angelman syndrome: association with parent sleep and stress. J Intellect Disabil Res 2012;56(6):600–8. https://doi.org/10.1111/j.1365-2788.2011.01499.x.

[44] Du X, Wang J, Li S, Ma Y, Wang T, Wu B, Zhou Y, Yu L, Wang Y. An analysis of phenotype and genotype in a large cohort of Chinese children with angelman syndrome. Genes 2022 Aug 14;13(8):1447. https://doi.org/10.3390/genes13081447. PMID: 36011358; PMCID: PMC9408022.

[45] Hou SJ, Tsai SJ, Kuo PH, Lin WY, Liu YL, Yang AC, Lin E, Lan TH. An association study in the Taiwan Biobank elicits the GABAA receptor genes GABRB3, GABRA5, and GABRG3 as candidate loci for sleep duration in the Taiwanese population. BMC Med Genom 2021 Sep 16;14(1):223.

[46] Luk HM, Lo IF. Angelman syndrome in Hong Kong Chinese: a 20 years' experience. Eur J Med Genet 2016 Jun;59(6–7):315–9. https://doi.org/10.1016/j.ejmg.2016.05.003.

[47] Lossie AC, Whitney MM, Amidon D, et al. Distinct phenotypes distinguish the molecular classes of Angelman syndrome. J Med Genet 2001;38(12):834–45. https://doi.org/10.1136/jmg.38.12.834.

[48] Hernandez CC, Macdonald RL. A structural look at $GABA_A$ receptor mutations linked to epilepsy syndromes. Brain Res 2019 Jul 1;1714:234–47.

[49] Valente KD, Koiffmann CP, Fridman C, et al. Epilepsy in patients with Angelman syndrome caused by deletion of the chromosome 15q11-13. Arch Neurol 2006;63(1):122–8. https://doi.org/10.1001/archneur.63.1.122.

[50] Laan LA, Renier WO, Arts WF, Buntinx IM, vd Burgt IJ, Stroink H. Evolution of epilepsy and EEG findings in Angelman syndrome. Epilepsia 1997;38(2):195–9. https://doi.org/10.1111/j.1528-1157.1997.tb01097.x.

[51] Valente KD, Andrade JQ, Grossmann RM, Kok F, Fridman C, Koiffmann CP, Marques-Dias MJ. Angelman syndrome: difficulties in EEG pattern recognition and possible misinterpretations. Epilepsia 2003 Aug;44(8):1051–63. https://doi.org/10.1046/j.1528-1157.2003.66502.x.

[52] Minassian BA, DeLorey TM, Olsen RW, Philippart M, Bronstein Y, Zhang Q, Guerrini R, Van Ness P, Livet MO, Delgado-Escueta AV. Angelman syndrome: correlations between epilepsy phenotypes and genotypes. Ann Neurol 1998 Apr;43(4):485–93. https://doi.org/10.1002/ana.410430412. PMID: 9546330.

[53] Dan B, Boyd SG. Angelman syndrome reviewed from a neurophysiological perspective. The UBE3A-GABRB3 hypothesis. Neuropediatrics 2003;34(4):169–76. https://doi.org/10.1055/s-2003-42208.

[54] Ganji S, Duncan MC. Angelman's (happy puppet) syndrome: clinical, CT scan and serial electroencephalographic study. Clin Electroencephalogr 1989 Apr;20(2):128–40. https://doi.org/10.1177/155005948902000210. PMID: 2706791.

[55] Boyd SG, Harden A, Patton MA. The EEG in early diagnosis of the Angelman (happy puppet) syndrome. Eur J Pediatr 1988 Jun;147(5):508–13. https://doi.org/10.1007/BF00441976. PMID: 3409926.

[56] Sidorov MS, Deck GM, Dolatshahi M, Thibert RL, Bird LM, Chu CJ, Philpot BD. Delta rhythmicity is a reliable EEG biomarker in Angelman syndrome: a parallel mouse and human analysis. J Neurodev Disord 2017 May 8;9:17. https://doi.org/10.1186/s11689-017-9195-8.

[57] Judson MC, Wallace ML, Sidorov MS, et al. GABAergic neuron-specific loss of Ube3a causes angelman syndrome-like EEG abnormalities and enhances seizure susceptibility. Neuron 2016;90(1):56–69. https://doi.org/10.1016/j.neuron.2016.02.040.

[58] Mandel-Brehm C, Salogiannis J, Dhamne SC, Rotenberg A, Greenberg ME. Seizure-like activity in a juvenile Angelman syndrome mouse model is attenuated by reducing Arc expression. Proc Natl Acad Sci U S A 2015 Apr 21;112(16):5129–34. https://doi.org/10.1073/pnas.1504809112. Epub 2015 Apr 6. PMID: 25848016; PMCID: PMC4413330.

[59] Greer PL, Hanayama R, Bloodgood BL, Mardinly AR, Lipton DM, Flavell SW, Kim TK, Griffith EC, Waldon Z, Maehr R, Ploegh HL, Chowdhury S, Worley PF, Steen J, Greenberg ME. The Angelman syndrome protein Ube3A regulates synapse development by ubiquitinating arc. Cell 2010 Mar 5;140(5):704–16. https://doi.org/10.1016/j.cell.2010.01.026. PMID: 20211139; PMCID: PMC2843143.

[60] Egawa K, Kitagawa K, Inoue K, Takayama M, Takayama C, Saitoh S, Kishino T, Kitagawa M, Fukuda A. Decreased tonic inhibition in cerebellar granule cells causes motor dysfunction in a mouse model of Angelman syndrome. Sci Transl Med 2012 Dec 5;4(163):163ra157. https://doi.org/10.1126/scitranslmed.3004655. PMID: 23220633.

[61] Wang PJ, Lee WT, Hwu WL, et al. The controversy regarding diagnostic criteria for early myoclonic encephalopathy. Brain Dev 1998;20(7):530–5. https://doi.org/10.1016/s0387-7604(98)00040-0.

[62] Badawy RA, Curatolo JM, Newton M, Berkovic SF, Macdonell RA. Sleep deprivation increases cortical excitability in epilepsy: syndrome-specific effects. Neurology 2006;67(6):1018–22. https://doi.org/10.1212/01.wnl.0000237392.64230.f7.

[63] Tomažič T, Kovačič L, Trebušak Podkrajšek K, Battelino T, Grošelj U. The role of UBE3A in the hypothalamus and its potential link with sleep disturbance in Angelman syndrome. Front Neurosci 2024;18:1343642. https://doi.org/10.3389/fnins.2024.1343642.

[64] Halász P. How sleep activates epileptic networks? Epilepsy Res Treat 2013;2013:425697. https://doi.org/10.1155/2013/425697.

[65] Vendrame M, Kothare SV. Epileptiform discharges and sleep fragmentation in children. J Child Neurol 2011;26(9):1193–7. https://doi.org/10.1177/0883073811408428.

[66] Jain SV, Kothare SV. Sleep and epilepsy. Semin Pediatr Neurol 2015;22(2):86–92. https://doi.org/10.1016/j.spen.2015.03.005.

[67] Williams CA. The behavioral phenotype of the Angelman syndrome. Am J Med Genet C Semin Med Genet 2010 Nov 15;154C(4):432–7. https://doi.org/10.1002/ajmg.c.30278. PMID: 20981772.

[68] Summers JA, Allison DB, Lynch PS, Sandler L. Behaviour problems in Angelman syndrome. J Intellect Disabil Res 1995;39(Pt 2):97–106. https://doi.org/10.1111/j.1365-2788.1995.tb00476.x.

[69] Pfarrer P, von Hagen C, Borggraefe I, Manssen L, Makowski C. Significance of behavioural problems on family impact in angelman syndrome: a prospective cross-sectional Study. J Autism Dev Disord 2025 Jun 25. https://doi.org/10.1007/s10803-025-06939-0.

[70] Oliver C, Demetriades L, Hall S. Effects of environmental events on smiling and laughing behavior in Angelman syndrome. Am J Ment Retard 2002;107(3):194–200. https://doi.org/10.1352/0895-8017(2002)107<0194:EOEEOS>2.0.CO;2.

[71] Adams D, Horsler K, Mount R, Oliver C. Brief report: a longitudinal study of excessive smiling and laughing in children with Angelman syndrome. J Autism Dev Disord 2015;45(8):2624–7. https://doi.org/10.1007/s10803-015-2404-y.

[72] Barry RJ, Leitner RP, Clarke AR, Einfeld SL. Behavioral aspects of Angelman syndrome: a case control study. Am J Med Genet 2005 Jan 1;132A(1):8–12. https://doi.org/10.1002/ajmg.a.30154. Erratum in: Am J Med Genet A. 2005 Jul 1;136(1):111. Berry, Raymond J [corrected to Barry, Raymond J]. PMID: 15578589).

[73] Sadhwani A, Willen JM, LaVallee N, Stepanians M, Miller H, Peters SU, Barbieri-Welge RL, Horowitz LT, Noll LM, Hundley RJ, Bird LM, Tan WH. Maladaptive behaviors in individuals with Angelman syndrome. Am J Med Genet 2019 Jun;179(6):983–92. https://doi.org/10.1002/ajmg.a.61140.

[74] Arron K, Oliver C, Moss J, Berg K, Burbidge C. The prevalence and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. J Intellect Disabil Res 2011;55(2):109–20. https://doi.org/10.1111/j.1365-2788.2010.01337.x.

[75] Wink LK, Fitzpatrick S, Shaffer R, Melnyk S, Begtrup AH, Fox E, Schaefer TL, Mathieu-Frasier L, Ray B, Lahiri D, Horn PA, Erickson CA. The neurobehavioral and molecular phenotype of Angelman syndrome. Am J Med Genet 2015 Nov;167A(11):2623–8.

[76] Wheeler AC, Okoniewski KC, Wylie A, DeRamus M, Hiruma LS, Sacco P. Anxiety and mood problems in individuals with Angelman syndrome and mothers: correlations with parenting stress. J Intellect Disabil Res 2020;64(8):593–606. https://doi.org/10.1111/jir.12735.

[77] Grebe SC, Limon DL, McNeel MM, Guzick A, Peters SU, Tan WH, Sadhwani A, Bacino CA, Bird LM, Samaco RC, Berry LN, Goodman WK, Schneider SC, Storch EA. Anxiety in angelman syndrome. Am J Intellect Dev Disabil 2022 Jan 1;127(1):1–10. https://doi.org/10.1352/1944-7558-127.1.1. PMID: 34979033; PMCID: PMC8803540.

[78] Keary CJ, Mullett JE, Nowinski L, Wagner K, Walsh B, Saro HK, Erhabor G, Thibert RL, McDougle CJ, Ravichandran CT. Parent description of anxiety in Angelman syndrome. J Autism Dev Disord 2022 Aug;52(8):3612–25.

[79] Keute M, Miller MT, Krishnan ML, Sadhwani A, Chamberlain S, Thibert RL, Tan WH, Bird LM, Hipp JF. Angelman syndrome genotypes manifest varying degrees of clinical severity and developmental impairment. Mol Psychiatry 2021 Jul;26(7):3625–33. https://doi.org/10.1038/s41380-020-0858-6.

[80] Richdale AL, Wiggs L. Behavioural approaches to the treatment of sleep problems in children with developmental disorders. What is the state of the art? Int J Behav Consult Ther (IJBCT) 2005;1(3):165–90. https://doi.org/10.1037/h0100737.

[81] Wiggs L, Stores G. Severe sleep disturbance and daytime challenging behaviour in children with severe learning disabilities. J Intellect Disabil Res 1996;40(Pt 6):518–28. https://doi.org/10.1111/j.1365-2788.1996.tb00663.x.

[82] Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. Pediatr Clin North Am 2011;58(3):649–65. https://doi.org/10.1016/j.pcl.2011.03.002.

[83] Coleman H, Mannion A, Whelan S, Tones M, Heussler H, Bellgard M, Leader G. Association between challenging behaviour and sleep problems in adults enrolled in the global Angelman syndrome registry. J Autism Dev Disord 2025 Aug;55(8):2938–49. https://doi.org/10.1007/s10803-024-06367-6.

[84] O'Sullivan R, Bissell S, Agar G, Spiller J, Surtees A, Heald M, Clarkson E, Khan A, Oliver C, Bagshaw AP, Richards C. Exploring an objective measure of overactivity in children with rare genetic syndromes. J Neurodev Disord 2024 Apr 18;16(1):18. https://doi.org/10.1186/s11689-024-09535-y.

[85] Richdale AL, Schreck KA. Sleep problems in autism spectrum disorders: prevalence, nature, & possible biopsychosocial aetiologies. Sleep Med Rev 2009 Dec;13(6):403–11. https://doi.org/10.1016/j.smrv.2009.02.003.

[86] Oliver C, Petty J, Ruddick L, Bacarese-Hamilton M. The association between repetitive, self-injurious and aggressive behavior in children with severe intellectual disability. J Autism Dev Disord 2012;42(6):910–9. https://doi.org/10.1007/s10803-011-1320-z.

[87] Allen KD. Using behavioral interventions to manage sleep problems in young children. J Pediatr Health Care 1992;6(5 Pt 1):241–5. https://doi.org/10.1016/0891-5245(92)90005-2.
[88] Zhdanova IV, Wurtman RJ, Wagstaff J. Effects of a low dose of melatonin on sleep in children with Angelman syndrome. J Pediatr Endocrinol Metab 1999 Jan-Feb; 12(1):57–67. https://doi.org/10.1515/jpem.1999.12.1.57.
[89] Braam W, Didden R, Smits M, Curfs L. Melatonin for chronic insomnia in Angelman syndrome: a randomized placebo-controlled trial. J Child Neurol 2008; 23(6):649–54. https://doi.org/10.1177/0883073808314153.
[90] Egan M, Farrell K, Hoey E, McGuire BE, Lydon HK. Interventions to improve sleep for individuals with Angelman syndrome: a systematic review. Res Dev Disabil 2020 Feb;97:103554. https://doi.org/10.1016/j.ridd.2019.103554.
[91] Paprocka J, Kijonka M, Wojcieszek P, Pęcka M, Emich-Widera E, Sokół M. Melatonin and angelman syndrome: implications and mathematical model of diurnal secretion. Int J Endocrinol 2017;2017:5853167. https://doi.org/10.1155/2017/5853167.
[92] Takaesu Y, Komada Y, Inoue Y. Melatonin profile and its relation to circadian rhythm sleep disorders in Angelman syndrome patients. Sleep Med 2012;13(9): 1164–70. https://doi.org/10.1016/j.sleep.2012.06.015.
[93] Hanzlik E, Klinger SA, Carson R, Duis J. Mirtazapine for sleep disturbances in Angelman syndrome: a retrospective chart review of 8 pediatric cases. J Clin Sleep Med 2020 Apr 15;16(4):591–5. https://doi.org/10.5664/jcsm.8284.
[94] Golubchik P, Sever J, Weizman A. Low-dose quetiapine for adolescents with autistic spectrum disorder and aggressive behavior: open-label trial. Clin Neuropharmacol 2011 Nov-Dec;34(6):216–9.
[95] Angriman M, Caravale B, Novelli L, Ferri R, Bruni O. Sleep in children with neurodevelopmental disabilities. Neuropediatrics 2015 Jun;46(3):199–210.
[96] Samanta D. Epilepsy in Angelman syndrome: a scoping review. Brain Dev 2021 Jan;43(1):32–44. https://doi.org/10.1016/j.braindev.2020.08.014.
[97] Kuenzle C, Steinlin M, Wohlrab G, Boltshauser E, Schmitt B. Adverse effects of vigabatrin in Angelman syndrome. Epilepsia 1998 Nov;39(11):1213–5. https://doi.org/10.1111/j.1528-1157.1998.tb01314.x. PMID: 9821987.
[98] Pietrafusa N, De Palma L, Armando M, Corsetti T, Vigevano F, Specchio N. Successful use of cannabidiol in nonconvulsive status epilepticus in Angelman syndrome. Epilepsia Open 2024 Oct;9(5):1997–9. https://doi.org/10.1002/epi4.12948.
[99] Wheeler AC, Okoniewski KC, Wylie A, et al. Communication development in adult Angelman syndrome: a 10-year cohort study. Augment Altern Commun 2023;39(1):12–24. https://doi.org/10.1080/07434618.2023.2183712.
[100] Sommese M, Corrado B. A comprehensive approach to rehabilitation interventions in patients with angelman syndrome: a systematic review of the literature. Neurol Int 2021 Jul 28;13(3):359–70. https://doi.org/10.3390/neurolint13030036.
[101] Milazzo C, Mientjes EJ, Wallaard I, Rasmussen SV, Erichsen KD, Kakunuri T, van der Sman ASE, Kremer T, Miller MT, Hoener MC, Elgersma Y. Antisense oligonucleotide treatment rescues UBE3A expression and multiple phenotypes of an Angelman syndrome mouse model. JCI Insight 2021 Aug 9;6(15):e145991. https://doi.org/10.1172/jci.insight.145991.
[102] Vihma H, Li K, Welton-Arndt A, Smith AL, Bettadapur KR, Gilmore RB, Gao E, Cotney JL, Huang HC, Collins JL, Chamberlain SJ, Lee HM, Aubé J, Philpot BD. Ube3a unsilencer for the potential treatment of Angelman syndrome. Nat Commun 2024 Jul 8;15(1):5558. https://doi.org/10.1038/s41467-024-49788-8.
[103] Jagasia R, Bon C, Rasmussen SV, Badillo S, Tehler D, Buchy D, Berrera M, Prasad M, Chamberlain S, Terrigno M, Pandya NJ, Costa V, Wang C, Pedersen L, Miller MT, Erichsen KD, Joenson L, Patsch C, Hipp JF, Bonni A, Müller L, Braendli-Baiocco A, Kremer T, Koller E, Hoener MC. Angelman syndrome patient-derived neuron screen leads to clinical ASO rugonersen targeting UBE3A-ATS with long-lasting effect in monkeys. Nucleic Acids Res 2025 Aug 27;53(16): gkaf851.
[104] Hipp JF, Bacino CA, Bird LM, Bruenig-Traebert I, Chan D, de Wit MC, Fontoura P, Hooper G, Jagasia R, Krishnan ML, Murtagh L, Noci A, Martínez AR, Schwab D, Serrano M, Shen MD, Tillmann J, Tjeertes J, Vincenzi B, Berry-Kravis E, Bonni A, Rugonersen Study Group; all TANGELO investigators. The UBE3A-ATS antisense oligonucleotide rugonersen in children with Angelman syndrome: a phase 1 trial. Nat Med 2025 Sep;31(9):2936–45. https://doi.org/10.1038/s41591-025-03784-7. Epub 2025 Jul 11. PMID: 40646322.