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THERAPY IN PRACTICE

# Management of Sleep Disturbances Associated with Smith-Magenis Syndrome

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## Abstract

Smith-Magenis syndrome is a genetic disorder caused by a microdeletion involving the retinoic acid-induced 1 (*RAI1*) gene that maps on the short arm of chromosome 17p11.2 or a pathogenic mutation of *RAI1*. Smith-Magenis syndrome affects patients through numerous congenital anomalies, intellectual disabilities, behavioral challenges, and sleep disturbances. The sleep abnormalities associated with Smith-Magenis syndrome can include frequent nocturnal arousals, early morning awakenings, and sleep attacks during the day. The sleep problems associated with Smith-Magenis syndrome are attributed to haploinsufficiency of the *RAI1* gene. One consequence of reduced function of *RAI1*, and characteristic of Smith-Magenis syndrome, is an inversion of melatonin secretion resulting in a diurnal rather than nocturnal pattern. Treatment of sleep problems in people with Smith-Magenis syndrome generally involves a combination of sleep hygiene techniques, supplemental melatonin, and/or other medications, such as melatonin receptor agonists, $\beta_1$-adrenergic antagonists, and stimulant medications, to improve sleep outcomes. Improvement in sleep has been shown to improve behavioral outcomes, which in turn improves the quality of life for both patients and their caregivers.

**Key Points**

Smith-Magenis syndrome is a genetic disorder characterized by congenital anomalies, intellectual disability, negative behaviors, and sleep disturbances.

The disorder results in an inversion of the typical secretion of melatonin and altered regulation of circadian gene expression, which result in frequent nocturnal arousals, early morning awakenings, and daytime sleep attacks.

Treatment often requires a combination of behavioral modification and sleep aides, such as melatonin agonists, stimulants, $\beta_1$-adrenergic antagonists, and other sleep-promoting agents, to improve sleep-related disturbances.

## 1 Background

Smith-Magenis syndrome (SMS) is a genetic disorder characterized by numerous congenital anomalies and intellectual disabilities; it is clinically recognizable and results from haploinsufficiency of the dosage-sensitive, retinoic acid-induced 1 (*RAI1)* gene, which maps within the short arm of chromosome 17 (OMIM 182290). Chromosome 17p11.2 microdeletions are identified in 90% of patients with SMS, whereas heterozygous pathogenic variants of *RAI1* are identified in the remaining 10% [1]. *RAI1* is a transcriptional regulator that influences downstream gene expression. Haploinsufficiency of *RAI1* causes the cardinal features of SMS; however, other genes within 17p11.2 modify the phenotype in those individuals with the microdeletion [1, 2]. The most sensitive method to confirm the presence of the 17p11.2 microdeletion is through a chromosome microarray. If this analysis returns a normal result in an individual with clinical

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features of SMS, sequencing and deletion/duplication analysis of *RAI1* or broader genomic analysis is indicated [3]. SMS affects at least 1 in 25,000 individuals globally but is likely underdiagnosed and may have a true prevalence closer to 1 in 15,000 individuals [4].

The aim of this article is to provide a review of the treatment options for sleep disturbances in patients with SMS. We utilized the literature, including abstracts, case reports, and published works, from the years 1995–2020. We performed a comprehensive search utilizing the terms SMS, *RAI1*, sleep disturbances in SMS, sleep disturbances in *RAI1*, sleep disruption in SMS, treatment for SMS, treatment for sleep disorders in SMS, and treatment for sleep disturbances in SMS. The recommendations outlined in the article are based on the literature and the authors' clinical knowledge and experience.

SMS is clinically recognizable by distinctive craniofacial features, congenital organ-system anomalies, neurodevelopmental and behavioral abnormalities, and significant sleep disturbances [5]. As is true for many syndromic diagnoses, physical features become more distinctive with age [5]. During infancy, SMS typically presents with hypotonia and global developmental delay, with or without organ-system involvement such as congenital heart defects and/or renal abnormalities. In early childhood, behavioral manifestations prevail and are characterized by self-injury and aggressive behaviors with prolonged tantrums [5]. Medical concerns throughout childhood include recurrent otitis media, emergence of myopia, hearing impairment, and weight gain. With the exception of recurrent otitis media, these problems persist and can be compounded by neuromuscular scoliosis and progressive hearing and vision impairment, as well as obesity in adults with SMS [6]. In addition to global developmental delay and intellectual disability, neurodevelopmental comorbidities such as attention-deficit/hyperactivity disorder, depression, anxiety, and autism frequently are observed [7]. Sleep disturbances are evident in most children and adults with SMS and consist of frequent nocturnal arousals, early morning awakenings, and excessive daytime sleepiness [8]. Sleep problems in patients with SMS typically present in infancy and persist throughout adulthood [9].

## 2 Sleep Abnormalities Associated with Smith-Magenis Syndrome (SMS)

Sleep disturbances in SMS are hypothesized to be due to a combination of disruption of the typical melatonin cycle in addition to disrupted nocturnal sleep, in terms of duration and architecture. An inversion of the typical melatonin secretion is a hallmark of SMS [10, 11]. In typically developing subjects, melatonin levels are low during the day. When environmental light levels begin to fade, melatonin levels rise helping to promote sleep. In patients with SMS, melatonin levels are elevated during the daylight hours and then fall to a lower level during the night [10, 12].

Disrupted nocturnal sleep has been investigated subjectively, utilizing sleep diaries by caregivers, as well as objectively though the utilization of polysomnograms [10, 13–15], multiple sleep latency tests [10], and actigraphy [16, 17]. These studies have revealed the typical sleep disturbances associated with SMS such as decreased nocturnal sleep time, frequent nocturnal awakenings, early morning arousals, and excessive daytime sleepiness. Subjects with SMS have been shown to have a reduced daytime sleep latency during a multiple sleep latency test demonstrating a propensity to daytime sleep [10].

## 3 Typical Progression of Sleep Disturbances in SMS

There are few longitudinal studies examining the sleep disturbances experienced by people with SMS. Despite the lack of such data, it appears that sleep disturbances often begin in infancy with reduced 24-h sleep time being documented in young children [18]. During early childhood, caregivers often begin to notice a variety of sleep concerns including frequent nocturnal awakenings, early morning wake times, enuresis, snoring, and daytime sleepiness [19]. Older children and adolescents with SMS may have difficulty with settling down to sleep, as demonstrated through actigraphy in subjects over the age of 10 years [20]. Adolescents often have shortened nocturnal sleep duration and increased daytime sleep occurring in short but frequent nap periods. These naps are often described as 'sleep attacks' and are difficult to prevent in patients with SMS. Often caregivers report that the nocturnal awakenings become less of a burden in the adolescent and teenage years. This pattern of difficulty with early morning awakenings and sleep attacks will often persist through adulthood in patients with SMS [21].

## 4 Pathophysiology of Sleep Disturbances in SMS

Sleep disturbances are associated with altered *RAI1* gene dosage, observed in both SMS and Potocki-Lupski syndrome, and result in dysregulated expression of several core components that regulate circadian rhythm, including *CLOCK*, *PER1*, *PER2*, *BMAL1*, and others [22, 23]. Disruption of the typical melatonin pattern of secretion is a component of the sleep dysfunction experienced by patients with SMS; however, the pathophysiology

is complex, and other circadian regulators are likely involved. Melatonin is important in transitioning an individual from wake to sleep and contributes to maintenance of somnolence. The melatonin pathway begins as light enters the eye, striking the photosensitive retinal ganglion cell (ipRGC/melanopsin) system in the retina. This system is particularly sensitive to light in the blue wavelength (450–485 nm). This signal is carried to the suprachiasmatic nucleus (SCN) in the hypothalamus, which is the master regulator of the circadian clock [24]. When stimulated by light, the SCN inhibits release of melatonin from the pineal gland [25]. As light levels diminish, the inhibitory signal fades, and melatonin is secreted. As melatonin levels rise, so does the biologic sleep drive. Studies have shown that this pathway is altered in patients with SMS whom experience a diurnal, rather than a nocturnal, secretion of melatonin [10, 11, 26]. Altered melatonin secretion contributes to the sleep difficulties in patients with SMS, resulting in an inability to maintain sleep at night and increased daytime sleepiness [10, 11].

It remains unclear the exact mechanism by which the melatonin pathway is disrupted in patients with SMS. Several mechanisms have been suggested to be responsible for the alteration in the melatonin pathway, such as an alteration in the light signal transduction pathway, a global misalignment of the circadian system, or an impairment of the melatonin secretion pathway between the SCN and the pineal gland [27–29].

## 5 Strategies in Treating Sleep Disturbances in SMS

Management of the sleep disturbances in patients with SMS typically requires a combination of behavioral modifications and medication interventions. With any sleep disturbance, ensuring proper sleep behavior, or sleep hygiene, is essential to improving sleep outcomes. A detailed history to ensure an accurate clinical picture around sleep habits is imperative. Typical bedtime, how long it takes to initiate sleep, frequency of nocturnal awakenings, behaviors occurring around night-time awakenings, and morning wake time should be obtained. Timing and duration of daytime sleeping, including sleep attacks, should be investigated. Dietary history to screen for foods that may influence sleep, such as caffeine, and whether the child seeks food at night should be obtained. Medication use is important to document, as many medications can have side effects that may promote or inhibit sleep.

Pre-bedtime routines should be organized, and remain as consistent as possible, to make preparing for and transitioning into sleep more successful. Typically, a winding-down period without electronic devices is recommended for 1–2 h before bedtime. Removing distractors from the bedroom, such as toys and electronics, is often helpful. Keeping a regular series of activities, occurring in the same order, for approximately the same duration, will help people prepare for transitioning from wake to sleep. Attempting to redirect the child back to bed while minimizing interactions, such as conversation, is recommended to reduce reinforcement of this behavior. If the child is unable to transition back to sleep, then engaging them in an activity that minimizes parental intervention or electronics is preferred. White noise makers, color-changing alarm clocks, and a cool and dark room void of toys or other distractors can all be used to help promote sleep in patients with SMS. Parents have also utilized strategies such as contained beds or locking bedrooms, ensuring a safe environment to help keep children in bed [30]. Physical barriers can help to minimize nocturnal behaviors, which may impair the family sleep dynamic such as waking other family members, food seeking, feces smearing, or other disruptive nocturnal behaviors.

## 6 Medication Therapy for Sleep Disturbances in SMS

### 6.1 Exogenous Melatonin

As patients with SMS typically display a diurnal rather than nocturnal peak in melatonin secretion, exogenous melatonin has been used nocturnally to supplement the typical biological melatonin secretion. By adding an exogenous melatonin dose prior to bedtime, a nocturnal rise in melatonin levels can assist in increasing the biological propensity to sleep. Exogenous melatonin acts on both melatonin type 1 (MT1) and melatonin type 2 (MT2) receptors. The hormone's role as a somnogen exists by activation of these receptors. MT1 inhibits neuronal firing of the SCN, thereby promoting initiation of sleep through release of systemic endogenous melatonin [31]. MT2 also works on the SCN and is responsible for phase shifting, which helps entrain, or synchronize, our circadian rhythm to our environmental light/dark cycles [32]. Studies in typically developing adults have shown that melatonin is effective in reducing sleep onset [32].

In patients with SMS, the use of exogenous melatonin is frequently utilized by families and caregivers; however, the efficacy of exogenous melatonin in SMS is unclear at this time as there have been few studies of this treatment in this specific patient population. It also appears that sex, age, and polypharmacy can influence endogenous melatonin levels [33]. Girls tend to have higher levels of endogenous melatonin levels compared with boys, but boys tend to have a higher response to exogenous melatonin supplementation [33]. Children also have higher endogenous melatonin levels

than adults [33]. The effects of polypharmacy are not clear at this time in regard to exogenous melatonin levels. As such, exogenous melatonin supplementation should be undertaken on an individual basis rather than a broad recommendation covering all patients with SMS [33]. With individual variation in endogenous melatonin secretion combined with many variables affecting the response to exogenous melatonin supplementation, baseline measurements of melatonin can be utilized to better understand the response to exogenous melatonin therapy. Although perhaps ideal, this practice is not commonly utilized in the clinical setting.

Although melatonin is thought to be a safe medication with no serious health sequelae, numerous studies have described side effects associated with its use [34, 35]. The most commonly reported side effects are headache, somnolence, palpitations, and abdominal pain. More rare side effects that have been reported are nasopharyngitis, arthralgia, tachycardia, dizziness, nausea, vomiting, nightmares, difficulty swallowing, difficulty breathing, hypnotic activity, heavy head, heartburn, flatulence, swelling of the arms or legs, sweating or hot flashes, exanthema, sleeping difficulties, depression, and sleep walking [33].

Although melatonin is a commonly utilized sleep aid, it is not regulated by the US Food and Drug Administration (FDA) as a medication. As such, the production of this supplement is not required to adhere to strict quality measures. The content of melatonin has been found to vary in labeled concentrations from − 83% to + 478% [36]. Variability of batches has also been shown to be a common problem, with as much as a 465% difference in the quantity of melatonin in the product. Further, the melatonin is also not always pure and frequently has been found to be contaminated with serotonin, a neurologically active and controlled substance [36]. With such fluctuations in the quality of the medication available, the recommended medication should be of pharmaceutical grade, as it should be able to provide more reliable sleep benefits.

A form of controlled-release melatonin (Circadin®; Neurim Pharmaceuticals, Tel-Aviv Israel, 2 mg) was approved in Israel, Australia, and the European Union for the treatment of insomnia in adults aged over 55 years of age in 2007 [37]. Controlled-release melatonin has also been evaluated, and approved for use in the European Union in 2018, in pediatric populations with autism spectrum disorder, including SMS, and found to be beneficial in reducing sleep onset as well as increase overall sleep time [38]. Pharmaceutical-grade controlled-release melatonin is also available in the USA on the commercial market. The controlled-release form has a higher affinity for the MT1 receptor compared with the MT2 receptor. The benefit of these formulations is to promote a longer half-life in an attempt to promote both sleep initiation and sleep maintenance. Patients with SMS may benefit more from a controlled-release form to help reduce the frequent nocturnal awakenings.

### 6.2 Melatonin Receptor Agonists

Several melatonin agonists exist that may prove to be beneficial in treating sleep problems in patients with SMS. Although these medications have not been specifically created for patients with SMS, they can be used to improve their sleep outcomes.

Ramelteon (Rozerem®; Takeda Pharmaceutical Company Limited, Tokyo, Japan) is a non-selective MT1 and MT2 agonist. It has been approved for use by the FDA since 2005 for the management of insomnia in adults [39]. Ramelteon is the only approved sleep-promoting medication that does not have a direct sedating effect [40]. The half-life is 1–2 h in duration [40]. Common adverse reactions are somnolence (5%), dizziness (5%), and fatigue (4%) [40]. A case report published in 2016 noted improvement in sleep and behavior outcomes of a 7-year-old child with SMS treated with ramelteon and amphetamine-dextroamphetamine [41].

Tasimelteon (Hetlioz; Vanda Pharmaceuticals, Washington D.C., United States) is a selective MT1 and MT2 agonist [42], with greater affinity for the MT2 receptor. It was approved by the FDA in 2014 for the treatment of non-24-h, sleep/wake disorder as a chronobiotic agent to help regulate the sleep/wake cycle in non-sighted individuals. Tasimelteon has a half-life of 2 h [43]. A double-blind, placebo-controlled, randomized cross-over trial in 25 individuals with SMS showed that tasimelteon improved quality of sleep and total sleep time [44]. Side effects include headache, nightmares, upper respiratory infections, and increased urinary tract infections. In animal models, there was concern for fertility and developmental issues, as well as increased risk of developing certain adenomas and carcinomas [44].

Agomelatine is a MT1 and MT2 receptor agonist, as well as a serotonin 5-$HT_{2C}$ agonist. It was approved by the European Union in 2009 for the treatment of depression. It has been shown to improve sleep quality, as well as reducing nocturnal awakenings [45]. The medication is rapidly absorbed but has a short plasma half-life of 1–2 h [46]. Side effects have been reported including nausea, dizziness, migraines, anxiety, fatigue, back pain, hyperhidrosis, and gastrointestinal issues such as diarrhea or constipation [46].

### 6.3 Light Therapy with Melatonin Agonists

Although exogenous melatonin has been used at night in patients with SMS to help regulate sleep, whether altering exposure to light will also improve sleep and behavioral outcomes in these patients remains unclear. A National Institutes of Health study (NCT00506259) investigating whether pediatric patients with SMS benefit from light therapy, either

with or without supplemental melatonin, was completed in 2018. Results of this study are not yet available.

### 6.4 $\beta_1$-Adrenergic Antagonists to Block Diurnal Endogenous Melatonin

In addition to using exogenous melatonin to supplement nocturnal melatonin secretion in patients with SMS, blocking daytime endogenous melatonin has been utilized in treating patients with SMS. $\beta_1$-Adrenergic antagonists have been shown to block the release of melatonin [47]. In a study of nine children [12] with SMS, researchers administered acebutolol, a $\beta_1$-adrenergic antagonist (10 mg/kg dosed in the morning). The results showed an improvement in the sleep disturbances associated with SMS, including onset of sleep (25 min), duration of sleep (40 min longer), and later wake times in the mornings (60 min later). Daytime sleepiness and afternoon sleep attacks were reported to be less frequent after the treatment. Behavioral benefits were also reported: the incidence of tantrums decreased, and parents expressed satisfaction with their children's overall behavior during the day. Children were noted by caregivers and teachers to have increased concentration and less hyperactivity [12]. When morning-dosed β-blockers were used in conjunction with night-time-dosed, controlled-release melatonin, both sleep and behavioral problems improved in children with SMS [11]. With this treatment combination, sleep attacks resolved compared with one to three episodes per day prior to therapy [11]. Children were able to concentrate for longer periods of time, 10 min before therapy to 30–60 min after therapy [11].

Another study of ten pediatric subjects with SMS treated with morning doses of $\beta_1$-adrenergic antagonists with controlled-release melatonin showed improvements in behavioral outcomes, hyperactivity and cognitive performance, and sleep disturbances, a reduction in nocturnal awakenings and increased hours of sleep [48]. Case reports in patients with SMS have shown that the combination of $\beta_1$-adrenergic antagonists in the morning with melatonin in the evening can improve sleep quality as measured by a polysomnogram [49]. Larger studies with long-term outcomes are needed to determine if the use of $\beta_1$-adrenergic antagonists will be beneficial to the SMS population as a whole.

### 6.5 Stimulants to Treat Daytime Sleepiness in SMS

Stimulants are often used to treat symptoms of daytime sleepiness. These medications generally are used for conditions such as idiopathic hypersomnia, narcolepsy, circadian-rhythm disorders, shift-work sleep deprivation, and sleep fragmentation. Amphetamine derivatives, methylphenidate, modafinil, and pemoline psychostimulants are used most frequently to promote daytime wakefulness. These medications have been used successfully to reduce accidents, improve psychological functioning, and improve work performance related to daytime sleepiness [50]. Based on the vigilance-promoting properties, the use of these medications may benefit patients with SMS by reducing daytime sleepiness and incidents of sleep attacks.

A study in 2010 looked at the effects of a variety of psychotropic agents, including stimulants, in patients with SMS [51]. These medications included methylphenidate, amphetamine, pemoline, and modafinil. This study of 62 subjects with SMS did not find a significant improvement in the treatment response with the use of stimulants; however, the authors reported that they also could not show any negative effect of the use of stimulants in children with SMS. The authors concluded that patients with SMS were neither aided nor hurt by the addition of stimulant medications [51]. However, as reported earlier, a published case report documents that a child with SMS and attention-deficit/hyperactivity disorder benefited from treatment with a simulant medication in combination with a melatonin receptor agonist [41].

### 6.6 Other Medications used for Sleep Disturbances in SMS

Numerous other medications have been used to treat sleep disturbances in patients with SMS. Although there is a lack of randomized controlled trials to reinforce the benefits of many of the different medications, many are still used in patients with SMS. A systematic approach to evaluate several of the more commonly used sleep aids will be discussed.

Diphenhydramine is a non-selective $H_1$ receptor antagonist that functions as an anticholinergic drug. It can bind at various receptor sites, accounting for many of its systemic anticholinergic effects. As $H_1$ antagonists can penetrate the blood–brain barrier, they also have sedating effects. Histamine is a wake-promoting agent; hence, antihistamines act as somnogens.

Diphenhydramine has been approved by the FDA as a sleep aid in doses up to 50 mg in adults. Diphenhydramine has been shown to improve subjective sleep efficiency in adults [52]. It also has been reported to decrease nocturnal awakenings in adults [53]. Concerns with the use of diphenhydramine as a sleep aid include residual daytime impairment the following day [54].

Clonidine is a $\alpha_2$-agonist that is approved for use in the treatment of hypertension, migraine headaches, and menopausal flushing. It also has properties that render it an analgesic, sedative, and anxiolytic [55]. It is commonly used to help manage sleep disturbances in children with attention-deficit/hyperactivity disorder [56]. It is also commonly used off-label in pediatrics to treat insomnia. Doses typically range from 0.1 to 0.3 mg given at bedtime. Side effects reported include mouth dryness, depression, fluid retention, and constipation.

Trazodone is a triazolopyridine derivative that was approved by the FDA in 1982 for the treatment of depression. It functions as a serotonin antagonist and reuptake inhibitor. Trazodone has moderate antihistamine activity, as well as suppressing cortisol, both of which lead to its sleep-promoting effects. Trazodone is commonly used in the treatment of insomnia, especially in patients with a comorbidity of depression. Trazodone is now used more commonly in the treatment of insomnia than as an antidepressant [57]. Trazodone has been shown to decrease sleep latency and improve the duration of sleep and daytime functioning [58]. Side effects of trazodone are reported as daytime sleepiness, headache, and orthostatic hypotension [57].

Quetiapine is an atypical antipsychotic medication that was approved by the FDA in 1985 and is used to treat schizophrenia, bipolar disorder, and major depressive disorder. Although an off-label therapy, when quetiapine is used in low doses (< 300 mg), it has been shown to be beneficial in treating anxiety and insomnia. At these doses, quetiapine acts as an antihistamine allowing for sleep-promoting properties. Side effects include metabolic syndrome and weight gain, which is common among atypical antipsychotics [59].

## 7 Conclusions

SMS is a genetic disorder resulting from a microdeletion in the short arm of chromosome 17p11.2 encompassing *RAI1* or by single nucleotide variants in *RAI1*. Haploinsufficiency of this gene results in the major phenotypical features of SMS. SMS affects multiple systems across the lifespan and is characterized further by neurocognitive and neurobehavioral disability. One of the most commonly reported behavioral disorders is sleep disturbance. Frequent nocturnal arousals, early morning wake times, daytime sleepiness, and afternoon sleep attacks all are common sleep-related concerns among caregivers of patients with SMS.

Although the exact mechanism regarding how this loss of genetic material creates the typical sleep problems in patients with SMS remains unknown, it has been shown to alter typical melatonin secretion and disrupt the regulation of the molecular clock by altering circadian gene expression. In an effort to manage the sleep disturbances of patients with SMS, treating the inversion of melatonin secretion has been a focus of therapy. Improvement in the sleep difficulties has been shown to improve behavioral outcomes in patients with SMS. As such, treatment of sleep disturbances can improve the quality of life in both patients and their caregivers.

Treatment strategies for persons with developmental disorders typically hinge on both behavioral strategies and medication therapies [9]. Although sleep hygiene can improve sleep outcomes in SMS, medication therapy is often required to optimize results [9]. There are no controlled clinical trials addressing sleep in SMS; however, reports in the medical literature suggest medical management strategies that may be of benefit for improving sleep in SMS [11, 12, 33, 41, 50]. Replacing nocturnal melatonin through exogenous melatonin supplements or other MT1 and MT2 agonists has been shown to improve sleep in patients with SMS [44]. $\beta_1$-Adrenergic antagonists, stimulants, and other sleep aids may help to optimize sleep outcomes for some patients.

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