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# Consensus recommendations on sleeping problems in Phelan-McDermid syndrome

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ABSTRACT

Early onset sleep problems and disorders are very common in individuals with Phelan-McDermid Syndrome (PMS) with rates of up to 90%. These sleep problems and disorders cannot be taken lightly. Not only do they have a major impact on the health, behaviour, functioning and learning opportunities of affected individuals, they can also have detrimental effects on the well-being and resilience of parents and caregivers, ultimately affecting the physical health, mental health and well-being of the whole social system.

In this review we aim to understand the types and frequencies of sleeping problems in PMS as the basis for recommendations on their management and treatment and to provide general guidelines for clinicians and practitioners. We conducted an in-depth literature search, summarised findings, and participated in a series of consensus meetings with other consortium members - experts on PMS and stakeholders - to agree on guidelines and recommendations. In parallel, a world-wide survey was created and distributed amongst parents to include their perspective.

Our literature search found only four articles specifically focused on sleeping problems in PMS, although some other articles mentioned prevalence and associated factors. Country-specific prevalence rates ranged between 24% and 46%, whereas our parental survey reported 59%. The main problems reported involved difficulty falling asleep and numerous night awakenings, with being restless in sleep, night-time incontinence, and tooth grinding also commonly reported. Only a small number of individuals had undergone a sleep study monitored by a specialist. Bedtime resistance normally decreases with age, but sleep-onset delay, sleep anxiety, parasomnias, problems falling and remaining asleep remain throughout lifespan, with total sleep time improving during adulthood. However, this improvement was also accompanied by a substantial increase in parasomnias. Ultimately, an increase in sleep disorders in children correlates with increased sleep disorders and daytime sleepiness in parents/caregivers.

No study to date has focused on the underlying causes of sleeping problems in PMS, but comorbid mental health conditions, somatic causes, or (poly)pharmacy have been proposed as triggers for sleeping disturbances. Currently there is no PMS-specific treatment for sleeping problems, and current recommendations are mostly based on individuals with intellectual disability and/or neurodevelopmental conditions.

## 1. Introduction

This study on sleep problems and disorders in Phelan-McDermid syndrome (PMS) is part of a series of studies that together form the European Consensus Guideline for PMS (Schön et al., 2023, this issue). PMS, previously known as 22q13.3 deletion syndrome, is a rare

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neurodevelopmental condition characterised by a heterogeneous array of clinical features that include hypotonia, absent or delayed speech, and in the vast majority of cases, intellectual disability (96%). Additionally, approximately 65% of individuals with PMS are also diagnosed with Autism Spectrum Disorder (ASD; Levy et al., 2022; Phelan, 2008; Schön et al., 2023, this issue). PMS can be caused by a deletion in 22q13.3 containing the *SHANK3* gene or by a pathogenic variant in *SHANK3* (Koza et al., 2023; Vitrac et al., 2022; both this issue). Currently, there is some debate as to whether haploinsufficiency (functional copy number loss) of *SHANK3* is the only genetic cause for the manifestation of this syndrome, but for this review, we consider PMS to be caused by a *SHANK3* haploinsufficiency through either a deletion of the region 22q13.2–33 or a pathogenic variant in *SHANK3* (for further information, see Schön et al., 2023, this issue). Similarly, following recent nomenclatures, we refer to PMS individuals as those with a PMS-*SHANK3* related syndrome (Phelan et al., 2022). The findings of this review may, however, also be in part applicable to *SHANK3*-unrelated PMS.

Sleep problems are very common in individuals with PMS, as they are reported in up to 90% of individuals (Bro et al., 2017), and can be present from early childhood (Ingiosi et al., 2019). A biological connection between *SHANK3* and sleep has been established. Pre-clinical studies showed *SHANK3* playing a role in the regulation of transcription factors for circadian rhythms, unarguably connecting patients with *SHANK3* deletions and sleep problems (Ingiosi et al., 2019). However, sleep is a complex process that can be affected by psychological, physiological, and/or environmental events, leading to disrupted sleep initiation and patterns or to inadequate sleep efficiency. It is important to define whether problems occur at sleep onset, or in the maintenance of sleep, or in both. A sleep problem is considered a sleep disorder when sleep alterations, or poor sleep, occur at least 3 times a week and alter good functioning during the day, provoking fatigue, sleepiness, irritability, and/or reduced concentration and performance. Sleep problems are associated with somatic problems such as back or stomach pain, nausea, or chest pains (Nordin et al., 2021). The International Classification of Sleep Disorders 3rd edition (American Academy of Sleep Medicine, 2014) classified sleep disorders into six main categories: 1) *insomnia* (persistent sleep difficulty despite adequate sleep opportunity, and associated daytime dysfunction), 2) *sleep-related breathing disorders* (abnormal respiration during sleep), 3) *central disorders of hypersomnolence* (excessive sleepiness not caused by poor sleep or circadian rhythm misalignment), 4) *circadian rhythm sleep-wake disorders* (misalignment of the timing of sleep-wake propensity and the external environment), 5) *parasomnias* (physical events during sleep or on the transition to/from sleep), and 6) *sleep-related movement disorders* (movements that prevent or disrupt sleep). In this paper we use the term "sleep problems" to describe conditions that may not fit the full definition of a disorder but do encompass problematic behaviour that may affect the daily functioning of affected individual or others, such as a child insisting on sleeping in the same bed as the parent or following specific rituals to fall asleep. We do use the term "sleep disorders" when referring to literature or studies specifically on sleeping disorders.

The presentation of sleep problems in neurotypical development can vary at different stages of brain development. Young babies, for instance, in whom circadian rhythms have not yet developed, will be expected to spend most of the day sleeping. Around 10–12 weeks of age, when the circadian rhythm starts to function, the child's sleep will naturally become more nocturnal. Until the age of 4, day napping will occur to achieve the needed sleep time. By the age of 5, as day napping decreases, night-time sleeping begins to decrease as well. For further information on how sleep times change during development, see e.g. Galland et al. (2012).

Sleeping problems are common in children and adults with neurological or medical conditions, including epilepsy and vision disorders, but also in people with (genetically-related) intellectual disabilities (ID) and neurodevelopmental disorders (NDDs) such as PMS (Gregory and Sadeh, 2016; Shelton et al., 2020; Spruyt and Curfs, 2015). Depending on the study design and definitions, reported prevalence rates for sleeping problems vary from 24% to 86% in ID and NDDs (Richdale and Baker, 2014), and severe sleep disorders may occur in up to 9.2% of individuals (van de Wouw et al., 2012). In ID, factors associated with sleep problems during adulthood involve challenging behaviours, the use of certain medications (or health factors in general), and comorbid psychiatric conditions (such as bipolar disorder, mania, or depression). However, there is some evidence that behavioural and environmental adjustments can be efficient approaches to improving sleep quality (Maaskant, van de Wouw, van Wijck, Evenhuis and Echteld, 2013; van de Wouw et al., 2012). Bedtime resistance is one of the most common issues described by parents of children with ID (Köse et al., 2017), but problems identifying sleeping problems or not seeking help have also been described (Robinson and Richdale, 2004), making early identification and treatment in this population challenging.

Sleeping problems and disorders cannot be taken lightly because they not only have a major impact on the health, behaviour, functioning, and learning opportunities of affected individuals, they can also have detrimental effects on the well-being and resilience of their parents and caregivers, ultimately affecting the whole family's physical and mental health and well-being. This wider effect has also been reported for individuals with ID or NDDs, including those with PMS (e.g., Bro et al., 2017). A recent study by Ingiosi et al. (2019) in individuals with PMS showed much higher rates of sleep disturbances across a much wider range of ages when compared to typical development, and, as the children grew, greater than that seen in ASD. Furthermore, in a world-wide survey of 587 parents of individuals with PMS, parents reported sleep disturbances in 58% of their offspring, mostly in individuals older than 18 years (73%). When asked about factors contributing to parental stress, 29.8% of parents experienced the sleep deprivation as extremely stressful (Landlust et al., 2023, this issue).

Considering the gravity and impact that sleep problems have on people with PMS and their families, this paper compiles the efforts of a group of experts cooperating in the European Consensus Guidelines for PMS to review the existing literature on sleeping problems and disorders in PMS. The main goal of this review is to better understand the type and frequency of problems and to use them as a basis for creating guidelines and recommendations for treatment.

**Table 1**
Terms used for the searches in Pubmed and Embase.

| |
|---|
| Pubmed: |
| (("telomeric 22q13 monosomy syndrome"[Supplementary Concept]) OR "shank3 protein, human"[Supplementary Concept] OR "chromosome 22 ring"[Supplementary Concept] OR (ring 22[tiab]) OR Phelan-McDermid[tiab] OR (((22q[tiab] AND terminal[tiab]) OR 22q13[tiab] OR SHANK3[tiab]) AND (deletion[tiab] OR monosomy[tiab] OR syndrome[tiab])))) |
| Embase, |
| (('phelan-mcdermid syndrome'/exp OR 'ring chromosome 22':ab,ti OR 'phelan mcdermid':ab,ti OR (('22q terminal':ab,ti OR 22q13:ab,ti OR shank3:ab,ti) AND (deletion:ab,ti OR monosomy:ab,ti OR syndrome:ab,ti))) AND [embase]/lim). |

## 2. Methods

Following the initiative of a group of Dutch experts, who created a Dutch PMS guideline in 2018 (https://nvavg.nl/wp-content/uploads/2018/12/RL-22q13DS-geautoriseerd-oktober-2018.pdf), a consortium of European experts in the field (including paediatricians, psychiatrists, psychologists, neurologists, speech and language therapists, patient representatives, etc.) was formed in late 2020 to develop the European PMS guidelines. These experts were divided into different working groups according to their area of expertise in order to address the bottlenecks (both from existing literature and from a patient representative digital survey) previously identified in the Dutch guideline. All groups conducted an in-depth literature search in Pubmed and Embase

following the same terms used in the Dutch guideline (see Table 1) and then summarised the findings focused on their assigned topic. Consortium members attended a series of regular consensus meetings to comment on the progress of their work and that of the other working groups and, ultimately, to agree on guidelines and recommendations for all chapters. In parallel, to capture the views of family members across the globe, a dedicated working group comprised mainly of experts and patients' representatives created a parental survey that was distributed world-wide via different PMS organisations. The survey consisted of 35 questions divided into four sections (general, diagnosis, clinical features, and support) together with the Genetic Syndrome Stressors Scale on parental stress (Griffith et al., 2011). For further information on the parental survey, see Landlust et al. (2023) in this issue.

For sleep disorders, a subgroup of experts in the field of sleep disorders, as well as a parent representative, met to explore the type of sleep disorders that occur in PMS and their prevalence. The subgroup also explored how sleep problems in PMS can be managed and treated. In February 2021, a general literature search was performed in Pubmed and Embase using the predefined general terms, yielding 936 articles. A second key-term search was then conducted using EndNote® software by entering the term "sleep*" in all fields (e.g., key words, title, abstract), which yielded 37 articles. We then excluded articles on animal models, articles not related specifically to PMS, case studies, non-scientific publications (e.g., letters to the editors, editorials, conference abstracts), and articles not in English. We did include additional studies not captured in the primary search that were identified when reviewing the primary articles if they were relevant to answer the questions in our aims and met the criteria mentioned above. Overall, articles of interest were those that aided a better understanding of the type and frequency of sleeping problems in PMS and could inform recommendations on treatment. To ensure the quality of the work, we used the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers et al., 2010; www.agreetrust.org), an internationally accepted tool that is considered the most useful instrument for guideline development for rare disorders (Pavan et al., 2017). Recommendations were formulated to the extent to which scientific evidence was available, and these recommendations were presented to the full consortium to reach wider consensus in a hybrid meeting (both in-person and online for members who could not be present in person) in June 2022. All recommendations were presented individually, and consortium members then agreed or suggested changes. If changes were proposed, the modified recommendation was presented again for voting. The recommendations we present here thus reflect 100% agreement amongst all members of the consortium.

## 3. Review of the literature

### 3.1. Prevalence and types of sleep problems in PMS

Sleep problems are common in individuals with PMS and also affect other household members (Bro et al., 2017). The consortium guideline survey amongst parents of children with PMS (n = 587) showed a general prevalence of sleep problems of 58% (Landlust et al., 2023, this issue). The ontogenetic reason for these high rates is still not known, with recent studies reporting diverse results. For instance, Nevado et al. (2022) found sleep disorders in 24% of individuals with microdeletions, as compared to 58% of individuals with *SHANK3* variants. Diving further into these results, the authors then performed sub-analyses and reported significant average differences between individuals with deletions greater than 0.25 Mb, those with *SHANK3* variants, and those with additional rearrangements (size 2.99 ± 2.26 Mb), although the authors failed to specify the direction of these differences. By contrast, Moffitt et al. (2022) showed similar rates for individuals with deletions (72%) and those with pathogenic variants (85%).

Overall, early studies of PMS reported very frequent sleep problems (in 6 out of 8 children) that presented as early as 4–5 months of age (Philippe et al., 2008). More recent studies that looked at a wider range of ages report that problems persist into adulthood (Ingiosi et al., 2019; Verhoeven et al., 2020). However, studies focusing specifically on sleep problems in PMS are few, and most either focus on broad questions that lack the rigour to further investigate the specific nature of the disturbances or are based on small samples, thus it is not surprising to find a wide range in reported rates. For instance, reported sleep disturbance rates were 24% in a recent Chinese cohort (Xu et al., 2020), 33% in an adult Dutch cohort (Verhoeven et al., 2020), 39% in a Brazilian cohort (Samogy-Costa et al., 2019), and 41% and 46% in two US cohorts (Soorya et al., 2013 and Sarasua et al., 2014, respectively). However, none of these studies reported the type of sleep difficulties, all used different assessments (e.g., some used parental or clinical judgement, whereas others used standardised tools), and all the samples had fewer than 40 individuals, which limits the generalisability and interpretability of results.

Only four studies to date have presented data for large samples generated using caregiver-reported standardised questionnaires to understand, not only the rates, but the type of presented difficulties (i.e., Bro et al., 2017; Ingiosi et al., 2019; Moffitt et al., 2022, Smith-Hicks et al., 2021). The first, by Bro et al. (2017), used the Children's Sleep Habits Questionnaire (CSHQ; Owens et al., 2000). The authors contacted all the families in the international family registry of the USA Phelan-McDermid Syndrome Foundation (https://pmsf.org/) encouraging them to answer the questionnaire whether or not their child presented with sleep problems. This resulted in a large sample of 193 individuals (median age 8 years, range from <1 to >40 years). In this study, the authors reported that a striking 90% of individuals had a sleep disorder. About half of these individuals (40%) were described as having difficulty falling asleep, often requiring a parent to be present while falling asleep. Furthermore, most (60%) did not fall asleep within 20 minutes of going to bed. Individuals were often reported to be restless in their sleep (70%), incontinent at night (67%), awake for more than 15 minutes in the night (59%) or grinding their teeth (54%). These rates are remarkably high given that the prevalence of difficulties around sleep is 15–30% in typical 2–5 years-olds and 11–15% in typical school age children (Sammer and Sammer, 2020). Despite these high rates, only 22% of individuals in the Bro et al. (2017) sample had undergone a specific sleep study (i.e. overnight monitoring by a sleep specialist), of which 82% were then formally diagnosed with a sleep disorder. Of those with a formal diagnosis, 63% had sleep apnoea, 19% presented with insomnia, 9% reported restless leg syndrome, 6% had a periodic limb movement disorder, and 3% had narcolepsy. In the long term, sleep-onset delay, sleep anxiety, parasomnias, and other difficulties seem to persist over time, although bedtime resistance did decrease with age. Furthermore, an increase in sleep disorders in children correlates with an increase in sleep disorders and daytime sleepiness in parents/caregivers (measured with the Parents' Sleep Habits Questionnaire of Boergers et al., 2007), highlighting how sleep difficulties can extend to other family members. Despite this, of the parents who reported getting 6 hours of sleep or less (40%), only a small proportion received overnight childcare support (8.3%). Altogether, these results may be taken with caution since the questionnaires were sent to all families in the family registry (1035 members), but only 19% (193) returned the questionnaire. This response rate might have resulted in several biases. It is possible that only the parents of those with the most severe problems responded. On the other hand, this could also indicate that parents do not sufficiently recognise sleep problems but do report the difficulties encountered in routines and behaviour related to sleep when using an exhaustive questionnaire.

Sleeping problems reported in individuals with PMS also exceed those reported for their unaffected siblings. A study by Smith-Hicks et al. (2021) using the same standardised questionnaire used by Bro et al. reported a sample of 47 individuals from 1 to 46 years of age with PMS, together with a sample of 61 unaffected siblings (ages 1 to 17) recruited from several clinics in Texas, USA. When comparing both groups, PMS

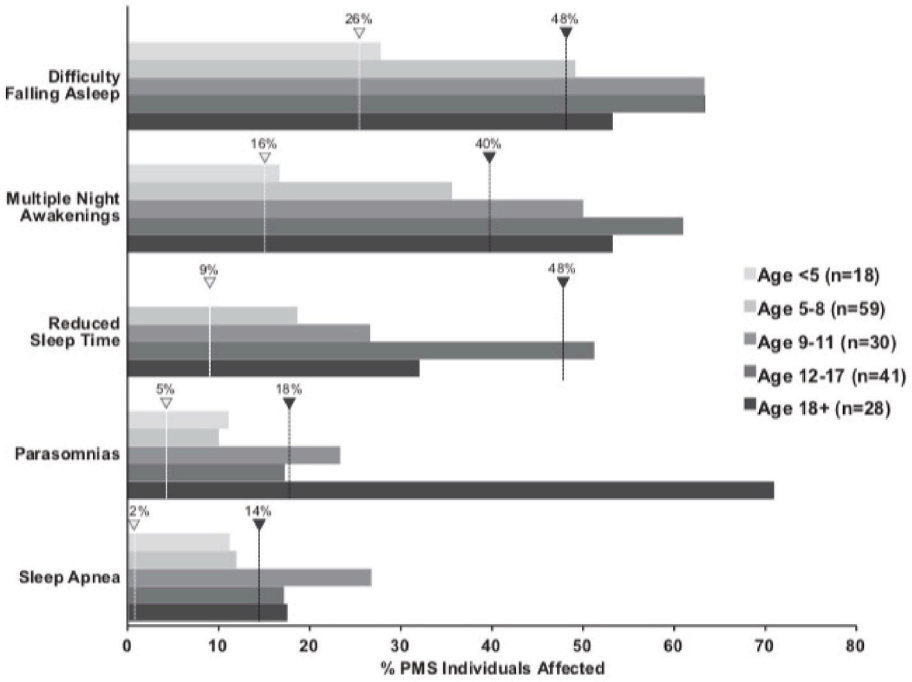


**Fig. 1.** Increased incidence of sleep problems reported in individuals with Phelan-McDermid syndrome (PMS) compared to typically developing (TD) individuals. Dashed lines indicate median incidence observed in TD (white marker) and ASD (black marker) populations computed from reviews of the existing literature. Difficulty falling asleep = more than 1 h to fall asleep. Multiple night awakenings = more than two awakenings. Reduced sleep time = less than 6 h per night. Parasomnias = abnormal movements, behaviours, emotions, perceptions, and dreams that occur while falling asleep or sleeping. Sleep apnoea = clinical diagnosis of sleep apnoea. (From Ingiosi et al., 2019[1]).

individuals scored significantly higher on all subscales except for anxiety around sleep and daytime sleepiness. When the group was divided by age (under 11 and 11 or older), the differences largely remained for the older group. However, for the under-11s, differences were reported only for night awakenings, parasomnias, and disordered breathing.

Ingiosi et al. (2019) used a pool of 176 individuals with a *SHANK3* deletion, also from the Phelan-McDermid Syndrome Foundation international registry (ages 1 to 39, 78 males and 98 females), although on this occasion, the authors used the customised questions from the registry around sleep. Starting at the age of 5, individuals with PMS presented with trouble falling asleep and experienced multiple night awakenings. Difficulties around sleep translated into reduced time asleep, particularly during adolescence. Similar to the results of Bro et al. (2017), problems falling and remaining asleep seemed to continue across lifespan, although total sleep time improved during adulthood. However, this improvement was also accompanied by a substantial increase in parasomnias. Furthermore, and overall, sleeping problems were more common than in typical development across ages, but some problems also more often persisted throughout development in PMS as compared to individuals with ASD alone. The Ingiosi et al. (2019) findings are detailed in Fig. 1. Using the same questionnaire from the PMS Foundation international registry, Moffitt et al. (2022) included all individuals with sleep data regardless of type of mutation, ending with an impressive sample of 384 individuals. The authors divided this sample into toddlers (ages 0–3), children (ages 4–10), adolescents (ages 11–17), and adults (age 18 and above). In the overall sample, difficulty falling asleep, multiple night awakenings, and difficulties falling back asleep were the most common problems, regardless of sex. When the sample was split into age groups, sleep difficulties increased with age, from a rate of 53% in toddlers to 90% in adulthood. It was also common for individuals to present with more than one sleep disturbance. Sleep apnoea was present in 11% of the sample, with no average significant differences for sex, age, or type of mutation.

### 3.2. Sleep problems and other co-occurring conditions

In typical development, sleep problems are often (and mainly) caused by an inadequate sleep hygiene that is maintained long enough to cause long-term disruptions in sleep. However, in many situations, sleep disorders and problems are also caused by other co-occurring, often organic, conditions. For example, a study of comorbidities in rare epilepsies found that out of 795 patients with epilepsy, 29 (3.6%) had PMS. Of those individuals with PMS, 71% (20 patients) had sleep problems, with frequent night-time awakenings being the most prominent (85%, 17 patients; Ho et al., 2018). Another small study of six individuals with PMS (median age 19.5, range 11–20 years) used EEG to study patterns during waking and falling asleep. Three subjects had mild myoclonic or tonic-clonic seizures and paroxysmal EEG abnormalities, especially fronto-temporal anomalies, that increased during sleep (Figura et al., 2014). In our parental survey, carried out by this consortium, we found a significant association between epilepsy and sleeping problems: 73% of individuals with epilepsy had sleeping problems compared to 54% of individuals without epilepsy ($p < .001$; Landlust et al., 2023, this issue).

Specific somatic conditions like reflux, diabetes, asthma, or rheumatic disorders have been associated with sleep problems in the general population (Lazaratou et al., 2012). However, it is also important to screen for mental health problems that can influence or cause disrupted sleep patterns. For instance, sleep problems are often a precursor of manic episodes (Gregory and Sadeh, 2016), and early identification combined with appropriate treatment could prevent a full-blown manic episode. As such, sleep problems have been described in patients with PMS and bipolar disorder, manic episodes, or mood dysregulation (Kohlenberg et al., 2020; Kolevzon et al., 2019), and sleep problems can also be a precursor symptom of such conditions in individuals with developmental delays (e.g., Kleefstra Syndrome; Vermeulen et al., 2017). However, sleeping problems could also be the consequence of another, more prominent, condition. For instance, one study reported insomnia in five of their individuals together with psychosis, catatonia, and depression. In three of these individuals, the sleeping problems were the consequence of a psychiatric episode, while the other two were

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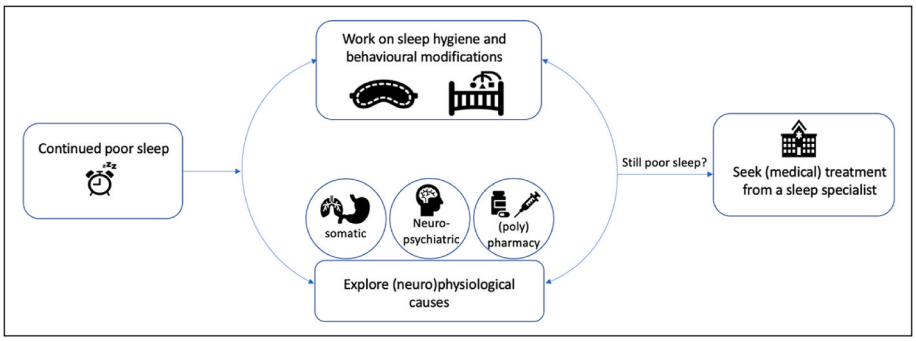


**Fig. 2.** Proposed path to treat sleeping problems in PMS. Note that although working on behavioural modifications and exploring neurophysiological causes are shown in parallel, careful step-by-step examination should be made to investigate possible underlying causes.

reported after significant viral infections that led into developmental regression (Kohlenberg et al., 2020). Similarly, some pharmacological interventions to treat these or other comorbid conditions can also trigger or enhance sleep problems, and close monitoring should be applied in those cases. For more information on how to manage mental health problems that may be related to sleep disorders, see the paper on mental health in PMS in this issue (van Balkom et al., 2023).

### 3.3. *Treatment and guidance for sleep problems in individuals with PMS*

Sleep problems in PMS should always be carefully assessed, with a focus on the possible underlying causes. While increasing activity levels are a common target in treatment of sleep disorders, their effect on the sleep quality of individuals with PMS is not known, therefore changing these levels is not a common recommendation. Sleep problems are mainly/often caused by environmental factors, but mental factors (psychosis, hyperarousal related to stress, a stimulus processing disorder, depression, etc.) and somatic factors (constipation, reflux, pain, respiratory symptoms, etc.) or even the use of certain medications (individual medical treatment or polypharmacy) also need to be explored. Implementing adequate sleep hygiene is normally the first course of action, but co-treatment with pharmacological management is also common. Bro et al. (2017) found that approximately 1/3 of children receive sleep medication, with melatonin (76%) and clonidine (18%) more frequently used, although their efficacy was not reported. To date, no specific behavioural or pharmacological treatments have been defined specifically for PMS, but the experts' consensus of this guideline points to first excluding somatic causes that may underlie sleep disturbances, together with trying to improve the sleep hygiene, and only then moving to the use of pharmacological treatment under the guidance of a sleep specialist. It is common for parents to start working on sleep hygiene and behavioural modifications as a first point of action. However, it is important to also rule out possible somatic causes. When investigating the latter, we recommend briefly pausing behavioural modifications to avoid cross-contamination of results. Fig. 2 shows a proposed flow-chart for dealing with on-going sleeping problems in PMS.

Families should start by keeping a sleep diary for a minimum of 2 weeks to help identify and detail the problems and to ensure more focused professional advice. Additionally, although it has not been validated specifically for PMS, the studies mentioned previously have used the Children's Sleep Habits Questionnaire (Owens et al., 2000), which has been validated for children of up to 11 years of age, or the Sleep Disturbances Scale for Children (Bruni et al., 1996), which has been validated for children 6–15 years of age. If available in the family's language, these tools could help clinicians evaluate the type and severity of the sleep disturbance at young ages. While these instruments are also recommended for children by the WHO, the recommendations for adults who have a verbal ability are based on the use of sleep diaries, or just asking general questions around sleep such as "Are you satisfied with your sleep?", "Do you feel alert most of the day?", or "Do you feel refreshed by your sleep?" (World Health Organization, June 2004). Due to the lack of specific advice for PMS, the following recommendations are mostly based on studies of individuals with NDDs (e.g., Blackmer and Feinstein, 2016; Bruni et al., 2019). Specialised sleep centres in your area may also help in the implementation of some of these recommendations.

## 4. Environmental, sensory, and behavioural modifications

Sometimes, sleep problems may resolve with a few adjustments to the environment. The role of the parents/caregivers is very important here. These are some techniques for clinicians and practitioners to recommend to families. Although some of these techniques have been developed with young infants in mind, they still can be useful for older individuals with ID. These include:

- Creating a consistent bedtime routine appropriate to the developmental age and skills of the person, comprising only a limited number of activities (i.e., avoid creating long routines). A good routine is to have an active, varied day with sufficient daylight, to phase out mental and physical activities in the evening, and to have a recognisable bed routine, with all parts in line with the individual's emotional level of functioning. Bedtimes should always be appropriate for the person's age. Keeping regular bedtimes and meals can also help in establishing routines. Additionally, having a bedtime visual schedule that always uses the same objects, photos, or pictures, so that it can be learnt easily, and rewarding its correct use, may help the individual to settle down for bedtime.
- Use of fixed and appropriate bedtimes (also in relation to age), having a soothing routine before bed, and reducing caffeine or caffeinated drinks and stimulating activities before bedtime. Controlling noise/sounds/smells, ambient light, room temperature, mattress, bed linens, and using a dark, quiet (turn off unnecessary equipment that may create noise), non-stimulating sleeping environment with a dimmed nightlight. If possible, parents are encouraged to help their child use a relaxation technique such as deep breathing or picturing a calm, relaxing scene.
- Light therapy (minimum 3000 lux, minimum 15 minutes) can be used to influence the body's own melatonin production, which can be shifted forward or backward. Circadian alignment can be helped by exposure to natural light. When it is still dark outside, light therapy lamps can help regulate and reinforce this alignment.
- Encouraging behaviours that avoid the child leaving the bed. For example, a *bedtime pass* is a card given to the child at bedtime in exchange for one 'free' trip out of bed or one parent visit after bedtime. After the pass has been used, the parent should take the child back to bed with minimal possible attention. Alternatively, parents or caregivers can use *graduated extinction.* That is, try to ignore negative behaviours for 2 minutes before checking on the child, and increase this time gradually to 4 and then finally 6 minutes

in the same night. The parent can provide reassurance through their presence for a brief time but should keep interaction to a minimum. Additionally, and when possible, the parent should encourage self-soothing skills that allow their child to manage nocturnal awakenings. A similar technique is *gradual distancing* (or gradual withdrawal). For this technique, the parent can sit near the child, even touching the child occasionally if needed. The distance between the parent and the child increases every couple of nights. Occasional soothing sounds can be used, always maintaining the distance.

- If the person has difficulties falling asleep, parents/caregivers may use *bedtime fading*. This technique is based on gradually closing the gap between current bedtime and target bedtime in steps of 15–30 minutes a day. Further information on this technique can be found easily online (e.g., https://parentingscience.com/bedtime-fading/). In some cases, white noise (for example, a whirring fan or radio or television static) may be helpful to induce sleep and can stay on throughout the night. When possible, parents should try to avoid letting their child go to bed earlier to make up for lost sleep.
- When the person suffers from tooth grinding, a dental night guard is recommended to avoid muscular problems and/or headaches during daytime.

## 5. Investigate possible (neuro)physiological reasons

Medication for somatic or psychiatric comorbidities can often cause or enhance sleep problems. Furthermore, combinations of medications can trigger sleep problems that may not be indicated if taken individually. Therefore, interaction of medications should be carefully monitored. Some checks to investigate for possible (neuro)physiological origins involve:

- Ruling out somatic causes, as treating these conditions may ease sleep problems. These somatic causes include pulmonary problems (coughing, obstructive sleep apnoea, asthma, interstitial lung disease, obstructive pulmonary disease, hyperventilation disorders, etc.), cardiovascular diseases (heart failure, coronary artery disease, arrythmias, hypertension, etc.), endocrine diseases (diabetes mellitus, diseases of the thyroid, acromegaly, polycystic ovarian syndrome), cancer, chronic fatigue, pain syndromes, nocturia, (subclinical) epilepsy, spasticity, pain, spasms, hip dislocation, constipation, enuresis, allergies, postural restrictions, reflux, etc.
- Anecdotal evidence shows that some children with PMS suffer from restless legs syndrome. In this case, if there is also sleep disturbance, serum ferritin levels should be checked. Serum ferritin levels that are too low (<50 ng/ml), while not indicative of significant anaemia, should be treated with iron supplementation for at least 3 months (Silber et al., 2004).
- Some epileptiform discharges that may only happen at night may be confused with parasomnias. For these cases, an overnight video-EEG is recommended.
- Investigate whether there is a disruption of the circadian melatonin rhythm (endogenous melatonin production can be measured at various times by means of saliva tests).

## 6. Investigate possible mental health issues

Last, but not least, mental health disturbances should be explored (see also, van Balkom et al., 2023, in this issue).

- Rule out psychiatric causes like manic episodes or hyperactive catatonia that may be preceded by sleep disturbances. If sleep problems are a consequence of these conditions, treating the specific symptoms of each may alleviate sleep difficulties.
- Investigate changes in mood, such as anxieties, depression, etc.
- In case of ASD or other comorbid mental health conditions such as attention deficit hyperativity disorder (ADHD), take care of tension and stress in daily life.

Although some adjustments are easy to achieve without professional help, techniques such as bedtime fading, extinction, and gradual distancing may be applied with professional care (for example, in a sleep centre) with the support of an experienced behavioural expert, who may also use sleep diaries or video recordings. These techniques are proven evidence-based treatments for people with ID (Richdale and Wiggs, 2005). If sleep does not improve, it is important to also consider a centre of expertise in sleep.

### 6.1. Pharmacological treatment

Pharmacological support is only indicated as a temporary support to allow the above interventions to take effect, or if the above steps have been taken and the problem remains and continues to interfere with daily life. In this case, medical treatment should always be assisted by an experienced clinician and should only be recommended if it fits the hypothesis about the nature of what disturbs sleep. Pharmacological options to treat sleep conditions have not yet been systematically tested in PMS, and the side effects are, therefore, unknown in this population. Current pharmacological options in PMS are based on underlying factors and mostly informed by what is known in ID and/or NDDs. Some families provide anecdotal reports of successfully using over-the-counter cannabidiol oil (CBD). However, the scientific evidence is inconclusive, and experts do not specifically recommend it. Indeed, a recent systematic review of clinical and pre-clinical studies concluded that there is insufficient evidence to support the use of CBD for sleep disorders due to lack of published studies and significant bias associated with the studies published to date (Suraev et al., 2020).

Aside from sleep problems related to psychotic disorders, one study of PMS individuals found that melatonin is the most common course of action (Bro et al., 2017). Melatonin is generally the most frequently prescribed sleep medication in this group, although its efficacy has not yet been systematically investigated in PMS specifically. In people with NDDs, the scientific evidence suggests that the use of melatonin is safe (that is, no medication-related serious adverse events have been reported) and that it improved total sleep time and sleep-onset latency compared to placebo in individuals with NDDs (see meta-analysis by Abdelgadir et al., 2018). However, although it has been deemed safe for long-term use in adults, there is still little information about its safety with long-term use in children and adolescents (Andersen et al., 2016). Studies of individuals with ASD show that the amount of endogenous melatonin is inversely correlated to sleep duration (Leu et al., 2011), and some clinical trials generally report improvement in reducing the sleep-onset latency but with no effect on nocturnal or early waking (e.g., Abdelgadir et al., 2018; Halstead et al., 2021). Taking all this into consideration, it remains unclear whether elevating melatonin is always helpful, what is the optimal dose, and whether some types work better than others (e.g., immediate versus delayed release). It also remains unanswered as to whether positive results in studies are a consequence of a zeitgeber (an environmental cue that acts as a trigger for the sleep cycle), a strengthened or corrected circadian rhythm, or a placebo effect. Furthermore, melatonin is a hormone with many other effects in addition to sleep-promotion, and professionals are increasingly becoming more reserved and critical about its use.

Other treatments prescribed by a healthcare professional may consist of clonidine, sedating antidepressants, atypical neuroleptics, or antihistamines. However, these medications also come with secondary effects that need to be taken into consideration by the expert before recommending one. These treatments always need to be considered as a short-term solution, starting at low doses and increasing them slowly only if needed ("Go low, go slow"). Here, we present a summary of the pharmacological recommendations (not following order of priority) of

Bruni et al. (2019) gathered from studies with persons with NDDs.

- Antihistamines are used to relieve symptoms of allergies (e.g., hay fever, hives, conjunctivitis, or reactions to insect bites or stings). They are well tolerated and are the most prescribed and over-the-counter treatment for childhood insomnia. **Diphenhydramine** is the most used antihistaminic due its strong sedative effects, although it has only been approved for patients aged 16 or older, and parents should be informed of off-label use and potential dependency effects. **Hydroxyzine** seems to be effective at 0.5 mg/kg in young people. **Trimeprazine** moderately improves night awakenings in children. **Niaprazine** can help reduce sleep-onset latency and increase sleep duration even when compared to benzodiazepines. However, antihistamines must be used with caution as properly controlled studies have not yet been conducted.
- Clonidine is used to decrease blood pressure but also produces sedation and increases deep sleep. Moderate-to-high doses of clonidine (0.1–0.3 mg) may result in increased deep sleep latency, slow-wave, and stage 2 sleep. Since it has only been approved for patients aged 18 and older, off-label use is indicated for younger ages.
- Guanfacine is used to treat ADHD and high blood pressure. It can be prescribed off-label to treat childhood insomnia. However, it is less sedating than clonidine and may shorten sleeping times.
- Benzodiazepines are efficient for individuals with anxieties and/or catatonia, seizures, and insomnia. Due to the potential risk of dependency, cognitive impairment, and the lack of scientific evidence for efficacy in children, short-term or when-needed administration is usually preferred.
- Gabapentin is approved for the treatment of restless legs syndrome, with positive effects on sleep. It is well tolerated and safe to treat sleep onset and sleep maintenance insomnia in children. In a childhood study where 87% had NDDs, 78% of children showed improvement in their sleep (Robinson and Malow, 2013).
- Orexin antagonists are usually used to treat insomnia as they have few interactions with other drugs often used in children with NDDs. In adults, they can reduce symptoms of insomnia and increase total sleep time.
- Antidepressants are commonly used to treat depression, anxieties, and some chronic pain conditions and to help manage some addictions. Tricyclic (amitriptyline, trimipramine and doxepin) and atypical antidepressants (mirtazapine, nefazodone, and trazodone) are also commonly prescribed in clinical practice to treat insomnia in adults and children. **Amitriptyline and trimipramine** are used in adults due to their sedative effects but are also frequently used in children with NDDs. **Doxepin** is a very powerful antidepressant that can improve overall sleep maintenance and decrease early morning awakenings in adults, at low doses. However, this drug has not yet been approved for children younger than 12, and off-label use must be informed and agreed by parents. Low doses of **mirtazapine** can decrease sleep-onset latency and increment sedation, increase sleep duration, and reduce waking after sleep onset, with little interference in deep sleep. A study in children with ASD and other NDDs also suggests some reduction of insomnia (Posey et al., 2001). **Trazodone**, although it is often prescribed to treat anxiety and mood disorders in children, helps to decrease deep sleep while increasing slow-wave sleep.
- Atypical antipsychotics are usually prescribed to treat schizophrenia or bipolar disorder, although off-label use to treat insomnia in children with psychiatric or developmental disorders is increasing. Atypical antipsychotics come with an increased risk of cardiometabolic complications, or even death in those patients with cardiovascular problems. These risks should always be discussed with parents before starting any treatment. **Risperidone and Olanzapine** are used to treat a comorbid condition (aggressive, self-injurious behaviours in children with ASD) but are often considered to treat sleep difficulties in children when other treatment types have failed. However, a common side effect is weight gain, and they are therefore not recommended when sleep-disordered breathing is present. They should also be used carefully in certain NDDs (Down Syndrome or Prader-Willi syndrome) where hyperglycaemia or hyperprolactinemia may be a problem.
- Supplements are the alternative to prescription medicines and are easy to access (over-the-counter). **Tryptophan/5-hydroxytryptophan (5-HTP)** is a plant-derived product that does not have opioid-like effects and therefore does not impact cognitive performance. However, there is little evidence for its use for insomnia and none on children with NDDs, but it is sometimes used due to its few side effects and users rarely develop tolerance. **Iron**: Low serum ferritin levels are well known to be associated with the restless legs syndrome seen in children with ADHD or ASD, and iron supplements are often used in NDDs, but this is driven more by clinical experience than based on sound scientific support. If prescribed, the doctor should determine whether higher than normal doses are needed. In that case, we recommend that doctors first perform a blood serum test to avoid the risk of constipation due to high iron levels, which could worsen sleeping problems. **Vitamin D**: Low vitamin D may impact sleep via increased pain, myopathy, immune dysregulation, and cardiovascular disease and may be associated with short sleep duration and poor sleep quality in adults (Kordas et al., 2009).

**Table 2**
Conclusions from the literature review.

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| Sleep problems occur in a substantial percentage of individuals with PMS. Most commonly reported sleep problems involve difficulties falling asleep and multiple night awakenings, which occur from childhood throughout lifespan. There is some evidence that parasomnias increase drastically with age, and have been reported in up to 63% of individuals. Overall, sleep problems in PMS persist and increase in adulthood, and multiple sleep problems can occur simultaneously. |
| On occasions, sleep problems are secondary or preliminary to other mental health conditions, or other possible physiological causes, and these also need to be explored. |
| The most crucial elements of counselling/treatment are: exploring other possible somatic problems, good sleep hygiene, treating behavioural problems (possibly with the help of a sleep centre), and, if necessary, pharmacological intervention under the guidance of an expert. |
| If sleep pathology or persistent sleep problems are suspected, further exploration in a specialised sleep centre is recommended. |
| Overall, there are currently no specific pharmacological treatments for sleep problems in PMS, and most evidence is based on treatment in individuals with intellectual disability and/or neurodevelopmental conditions. Melatonin and clonidine are currently the most prescribed treatments in PMS, but there is a lack of scientific evidence about their efficacy. |

Conclusions from the literature reviewed here are presented in Table 2.

## 7. Discussion

Sleep problems have a major impact on the health, behaviour, and functioning of individuals with PMS and their families. Sleep problems can have devastating effects both for the person with PMS and for parents and caregivers, ultimately affecting overall quality of life for all. Sleep problems occur in a very high percentage of individuals with PMS, more so than in other NDDs, and these problems remain or worsen as the child grows (Ingiosi et al., 2019). Accurate diagnosis and treatment of sleep problems and disorders are of foremost importance and should be the foremost focus of attention. Possible somatic causes (including epilepsy) and pharmacological causes should be examined and treated. Interacting mental health issues (e.g., depression, anxiety, psychosis) should also be examined and treated. Sleep hygiene and behavioural interventions are important and effective in the treatment of sleep problems. Melatonin is widely used in the treatment of sleep problems and is proven to generally be a safe medication. However, it should

**Table 3**
Recommendations agreed upon by the European Phelan-McDermid syndrome consortium.

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| Every individual with PMS and sleep problems should be evaluated for somatic and/or environmental and/or neuropsychiatric causes. |
| Mental health conditions co-occurring with sleep problems in individuals with PMS need to be investigated and treated. |
| In individuals with PMS with sleep problems, sleep hygiene should be evaluated, and caregivers should be supported in establishing a structured approach (behavioural interventions). |
| If sleep problems persist despite appropriate interventions, the individual with PMS should be referred to a specialist experienced in sleep problems or a specialist sleep centre.[a] |

[a] To find specific information about help in your country, visit the European Sleep Research Society https://esrs.eu/about/associate-national-sleep-societies/affiliated-national-sleep-societies-map/or your Affiliated National Sleep Society http://esrs.eu/national-sleep-society/.

always be used with caution due to the lack of general understanding of its mechanistic pathways. If used, it is preferable to have it prescribed by doctors with experience in treating sleep problems (paediatricians specialising in heritable and congenital disorders, intellectual disability physicians, psychiatrists, etc.) and with careful clinical monitoring (multidisciplinary, if needed). Other pharmacological treatments have shown positive results in children with ID and/or NDD conditions, but their long-term effect is yet to be understood.

Literature review and the experts' opinions from a series of meetings carried out by the members of the consortium resulted in the recommendations on sleep problems and disorders in PMS in Table 3.

For information on the use of melatonin, see https://www.nccih.nih.gov/health/melatonin-what-you-need-to-know or https://www.sleepfoundation.org/melatonin. For an alternative guide on handling sleep problems in PMS, please see the ECHO project (USA) at https://pmsf.org/wp-content/uploads/2021/04/PMS-NCG-Combined-Recommendations-1.pdf.

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## CRediT authorship contribution statement

**A. San José Cáceres:** Investigation, Data curation, Conceptualization, Writing – original draft, Writing – review & editing. **A.M. Landlust:** Conceptualization, Writing – review & editing. **J.M. Carbin:** Conceptualization, Writing – review & editing. **E. Loth:** Conceptualization, Writing – review & editing, the European Phelan-McDermid Syndrome: Conceptualization, Methodology, Validation, Supervision, Project administration, Funding acquisition.

## Data availability

No data was used for the research described in the article.

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## References

Abdelgadir, I.S., Gordon, M.A., Akobeng, A.K., 2018. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. Arch. Dis. Child. 103 (12), 1155–1162. https://doi.org/10.1136/archdischild-2017-314181.

American Academy of Sleep Medicine, 2014. *The International Classification Of Sleep Disorders:(ICSD-3)*: American Academy of Sleep Medicine.

Andersen, L.P.H., Gögenur, I., Rosenberg, J., Reiter, R.J., 2016. The safety of melatonin in humans. Clin. Drug Invest. 36 (3), 169–175. https://doi.org/10.1007/s40261-015-0368-5.

Blackmer, A.B., Feinstein, J.A., 2016. Management of sleep disorders in children with neurodevelopmental disorders: a review. Pharmacotherapy 36 (1), 84–98. https://doi.org/10.1002/phar.1686.

Boergers, J., Hart, C., Owens, J.A., Streisand, R., Spirito, A., 2007. Child sleep disorders: associations with parental sleep duration and daytime sleepiness. J. Fam. Psychol. 21 (1), 88. https://doi.org/10.1037/0893-3200.21.1.88.

Bro, D., O'Hara, R., Primeau, M., Hanson-Kahn, A., Hallmayer, J., Bernstein, J.A., 2017. Sleep disturbances in individuals with phelan-McDermid syndrome: correlation with caregivers' sleep quality and daytime functioning. Sleep 40 (2). https://doi.org/10.1093/sleep/zsw062.

Brouwers, M.C., Kho, M.E., Browman, G.P., Burgers, J.S., Cluzeau, F., Feder, G., Hanna, S.E., 2010. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ (Can. Med. Assoc. J.) 182 (18), E839–E842. https://doi.org/10.1016/j.ypmed.2010.08.005.

Bruni, O., Angriman, M., Melegari, M.G., Ferri, R., 2019. Pharmacotherapeutic management of sleep disorders in children with neurodevelopmental disorders. Expet Opin. Pharmacother. 20 (18), 2257–2271. https://doi.org/10.1080/14656566.2019.1674283.

Bruni, O., Ottaviano, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., Giannotti, F., 1996. The Sleep Disturbance Scale for Children (SDSC) Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J. Sleep Res. 5 (4), 251–261.

Figura, M.G., Coppola, A., Bottitta, M., Calabrese, G., Grillo, L., Luciano, D., Elia, M., 2014. Seizures and EEG pattern in the 22q13.3 deletion syndrome: clinical report of six Italian cases. Seizure 23 (9), 774–779. https://doi.org/10.1016/j.seizure.2014.06.008.

Galland, B.C., Taylor, B.J., Elder, D.E., Herbison, P., 2012. Normal sleep patterns in infants and children: a systematic review of observational studies. Sleep Med. Rev. 16 (3), 213–222. https://doi.org/10.1016/j.smrv.2011.06.001.

Gregory, A.M., Sadeh, A., 2016. Annual research review: sleep problems in childhood psychiatric disorders–a review of the latest science. JCPP (J. Child Psychol. Psychiatry) 57 (3), 296–317. https://doi.org/10.1111/jcpp.12469.

Griffith, G., Hastings, R., Oliver, C., Howlin, P., Moss, J., Petty, J., Tunnicliffe, P., 2011. Psychological well-being in parents of children with Angelman, Cornelia de Lange and Cri du Chat syndromes. J. Intellect. Disabil. Res. 55 (4), 397–410.

Halstead, E.J., Joyce, A., Sullivan, E., Tywyn, C., Davies, K., Jones, A., Dimitriou, D., 2021. Sleep disturbances and patterns in children with neurodevelopmental conditions. Frontier. Pediatrics. 9, 637770 https://doi.org/10.3389/fped.2021.637770.

Ho, N.T., Kroner, B., Grinspan, Z., Fureman, B., Farrell, K., Zhang, J., Nye, K., 2018. Comorbidities of rare epilepsies: results from the rare epilepsy Network. J. Pediatr. 203, 249–258.e245. https://doi.org/10.1016/j.jpeds.2018.07.055.

Ingiosi, A.M., Schoch, H., Wintler, T., Singletary, K.G., Righelli, D., Roser, L.G., Peixoto, L., 2019. Shank3 modulates sleep and expression of circadian transcription factors. Elife 8, e42819. https://doi.org/10.7554/eLife.42819.

Kohlenberg, T.M., Trelles, M.P., McLarney, B., Betancur, C., Thurm, A., Kolevzon, A., 2020. Psychiatric illness and regression in individuals with Phelan-McDermid syndrome. J. Neurodev. Disord. 12 (1), 7. https://doi.org/10.1186/s11689-020-9309-6.

Kolevzon, A., Delaby, E., Berry-Kravis, E., Buxbaum, J.D., Betancur, C., 2019. Neuropsychiatric decompensation in adolescents and adults with Phelan-McDermid syndrome: a systematic review of the literature. Mol. Autism. 10, 50. https://doi.org/10.1186/s13229-019-0291-3.

Kordas, K., Siegel, E.H., Olney, D.K., Katz, J., Tielsch, J.M., Kariger, P.K., Stoltzfus, R.J., 2009. The effects of iron and/or zinc supplementation on maternal reports of sleep in

infants from Nepal and Zanzibar. J. Dev. Behav. Pediatr.: JDBP (J. Dev. Behav. Pediatr.) 30 (2), 131.
Köse, S., Yılmaz, H., Ocakoğlu, F.T., Özbaran, N.B., 2017. Sleep problems in children with autism spectrum disorder and intellectual disability without autism spectrum disorder. Sleep Med. 40, 69–77. https://doi.org/10.1016/j.sleep.2017.09.021.
Koza, S., Tabet, A.C., Bonaglia, M.C., Andres, S., Stiefsohn, D., Anderlid, B.M., Kant, S., 2023. Consensus Recommendations on Counselling in Phelan-McDermid Syndrome *European Journal Of Medical Genetics (this issue*.
Landlust, A., Koza, S., Roberts, S., Vyshka, K., consortium, T.E. P.-M.s., Van Ravenswaaij-Arts, C.M., 2023. Parental Perspectives on Phelan-McDermid Syndrome; Results of a World-wide Survey. European Journal of Medical Genetics *(this issue*.
Lazaratou, H., Soldatou, A., Dikeos, D., 2012. Medical comorbidity of sleep disorders in children and adolescents. Curr. Opin. Psychiatr. 25 (5), 391–397. https://doi.org/10.1097/YCO.0b013e3283556c7a.
Leu, R.M., Beyderman, L., Botzolakis, E.J., Surdyka, K., Wang, L., Malow, B.A., 2011. Relation of melatonin to sleep architecture in children with autism. J. Autism Dev. Disord. 41 (4), 427–433. https://doi.org/10.1007/s10803-010-1072-1.
Levy, T., Foss-Feig, J.H., Betancur, C., Siper, P.M., Trelles-Thorne, M.d.P., Halpern, D., Britvan, B., 2022. Strong evidence for genotype–phenotype correlations in Phelan-McDermid syndrome: results from the developmental synaptopathies consortium. Hum. Mol. Genet. 31 (4), 625–637. https://doi.org/10.1093/hmg/ddab280.
Maaskant, M., van de Wouw, E., van Wijck, R., Evenhuis, H.M., Echteld, M.A., 2013. Circadian sleep–wake rhythm of older adults with intellectual disabilities. Res. Dev. Disabil. 34 (4), 1144–1151. https://doi.org/10.1016/j.ridd.2012.12.009.
Moffitt, B.A., Sarasua, S.M., Ward, L., Ivankovic, D., Valentine, K., Rogers, C., Boccuto, L., 2022. Sleep and phelan–McDermid syndrome: lessons from the international registry and the scientific literature. Mol. Gene. Genom. Med. 10 (10), e2035 https://doi.org/10.1002/mgg3.2035.
Nevado, J., García-Miñaúr, S., Palomares-Bralo, M., Vallespín, E., Guillén-Navarro, E., Rosell, J., Del Campo, M., 2022. Variability in phelan-McDermid syndrome in a cohort of 210 individuals. Front. Genet. 13 https://doi.org/10.3389/fgene.2022.652454.
Nordin, G., Sundqvist, R., Nordin, S., Gruber, M., 2021. Somatic symptoms in sleep disturbance. Psychol. Health Med. 1–11. https://doi.org/10.1080/13548506.2021.1985149.
Owens, J.A., Spirito, A., McGuinn, M., 2000. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep-New York- 23 (8), 1043–1052. https://doi.org/10.1093/sleep/23.8.1d.
Pavan, S., Rommel, K., Mateo Marquina, M.E., Höhn, S., Lanneau, V., Rath, A., 2017. Clinical practice guidelines for rare diseases: the orphanet database. PLoS One 12 (1), e0170365. https://doi.org/10.1371/journal.pone.0170365.
Phelan, K., Boccuto, L., Powell, C.M., Boeckers, T.M., Van Ravenswaaij-Arts, C.M., Rogers, R.C., Bennett, W.E., 2022. Phelan-McDermid syndrome: a classification system after 30 years of experience. Orphanet J. Rare Dis. 17 (1), 1–4. https://doi.org/10.1186/s13023-022-02180-5.
Phelan, M.C., 2008. Deletion 22q13.3 syndrome. Orphanet J. Rare Dis. 3, 14. https://doi.org/10.1186/1750-1172-3-14.
Philippe, A., Boddaert, N., Vaivre-Douret, L., Robel, L., Danon-Boileau, L., Malan, V., Munnich, A., 2008. Neurobehavioral profile and brain imaging study of the 22q13.3 deletion syndrome in childhood. Pediatrics 122 (2), e376–e382. https://doi.org/10.1542/peds.2007-2584.
Posey, D.J., Guenin, K.D., Kohn, A.E., Swiezy, N.B., McDougle, C.J., 2001. A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. J. Child Adolesc. Psychopharmacol. 11 (3), 267–277.
Richdale, A.L., Baker, E.K., 2014. Sleep in individuals with an intellectual or developmental disability: recent research reports. Curr. Dev. Disorder. Rep. 1 (2), 74–85. https://doi.org/10.1007/s40474-014-0010-x.
Richdale, A.L., Wiggs, L., 2005. Behavioral 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) 1 (3), 165. https://doi.org/10.1037/h0100743.
Robinson, Malow, B.A., 2013. Gabapentin shows promise in treating refractory insomnia in children. J. Child Neurol. 28 (12), 1618–1621.
Robinson, A., Richdale, A., 2004. Sleep problems in children with an intellectual disability: parental perceptions of sleep problems, and views of treatment effectiveness. Child Care Health Dev. 30 (2), 139–150. https://doi.org/10.1111/j.1365-2214.2004.00395.x.
Sammer, A., Sammer, F., 2020. Sleeping disorders in children. Manuel. Med. 58 (3), 154–159. https://doi.org/10.1007/s00337-020-00670-w.
Samogy-Costa, C.I., Varella-Branco, E., Monfardini, F., Ferraz, H., Fock, R.A., Barbosa, R. H.A., Passos-Bueno, M.R., 2019. A Brazilian cohort of individuals with Phelan-McDermid syndrome: genotype-phenotype correlation and identification of an atypical case. J. Neurodev. Disord. 11 (1), 13. https://doi.org/10.1186/s11689-019-9273-1.
Sarasua, S.M., Boccuto, L., Sharp, J.L., Dwivedi, A., Chen, C.F., Rollins, J.D., DuPont, B. R., 2014. Clinical and genomic evaluation of 201 patients with Phelan-McDermid syndrome. Hum. Genet. 133 (7), 847–859. https://doi.org/10.1007/s00439-014-1423-7.
Schön, M., Lapunzina, P.D., Nevado, J., Matina, T., Gunnarson, C., Hadzsiev, K., Hennekam, R., 2023. Definition and Clinical Variability of SHANK3-Related Phelan-McDermid Syndrome. Europen Journal of Medical Genetics *(this issue*.
Shelton, A.R., Duis, J., Malow, B., 2020. Neurodevelopmental disorders. In: Chopra, A., Das, P., Doghramji, K., Chopra, A., Das, P., Doghramji, K. (Eds.), Management of Sleep Disorders in Psychiatry. Oxford University Press, 0.
Silber, M.H., Ehrenberg, B.L., Allen, R.P., Buchfuhrer, M.J., Earley, C.J., Hening, W.A., Rye, D.B., 2004. An algorithm for the management of restless legs syndrome. Mayo Clin. Proc. 79 (7), 916–922. https://doi.org/10.4065/79.7.916.
Smith-Hicks, C., Wright, D., Kenny, A., Stowe, R.C., McCormack, M., Stanfield, A.C., Holder, J.L., 2021. Sleep abnormalities in the synaptopathies—SYNGAP1-related intellectual disability and phelan–McDermid syndrome. Brain Sci. 11 (9), 1229. Retrieved from. https://www.mdpi.com/2076-3425/11/9/1229.
Soorya, L., Kolevzon, A., Zweifach, J., Lim, T., Dobry, Y., Schwartz, L., Buxbaum, J.D., 2013. Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency. Mol. Autism. 4 (1), 18. https://doi.org/10.1186/2040-2392-4-18.
Spruyt, K., Curfs, L.M., 2015. Non-pharmacological management of problematic sleeping in children with developmental disabilities. Dev. Med. Child Neurol. 57 (2), 120–136. https://doi.org/10.1111/dmcn.12623.
Suraev, A.S., Marshall, N.S., Vandrey, R., McCartney, D., Benson, M.J., McGregor, I.S., Hoyos, C.M., 2020. Cannabinoid therapies in the management of sleep disorders: a systematic review of preclinical and clinical studies. Sleep Med. Rev. 53, 101339 https://doi.org/10.1016/j.smrv.2020.101339.
van Balkom, I., Burdeus-Olavarrieta, M., Cooke, J., de Cuba, A.G., Turner, A., consortium, T.E. P.-M.s., Maurani, A., 2023. Consensus Recommendations on Mental Health Issues in Phelan-McDermid Syndrome. European Journal of Medical Genetics *(this issue*.
van de Wouw, E., Evenhuis, H., Echteld, M., 2012. Prevalence, associated factors and treatment of sleep problems in adults with intellectual disability: a systematic review. Res. Dev. Disabil. 33 (4), 1310–1332. https://doi.org/10.1016/j.ridd.2012.03.003.
Verhoeven, W.M.A., Egger, J.I.M., de Leeuw, N., 2020. A longitudinal perspective on the pharmacotherapy of 24 adult patients with Phelan McDermid syndrome. Eur. J. Med. Genet. 63 (3), 103751 https://doi.org/10.1016/j.ejmg.2019.103751.
Vermeulen, K., Staal, W.G., Janzing, J.G., van Bokhoven, H., Egger, J.I., Kleefstra, T., 2017. Sleep disturbance as a precursor of severe regression in Kleefstra syndrome suggests a need for firm and rapid pharmacological treatment. Clin. Neuropharmacol. 40 (4), 185–188. https://doi.org/10.1097/WNF.0000000000000226.
Vitrac, A., Leblond, C.S., Rolland, T., Cliquet, F., Mathieu, A., Maurani, A., Bourgeron, T., 2022. Dissecting the 22q13 Region to Explore the Genetic and Phenotypic Diversity in Patients with Phelan McDermid Syndrome. Europan Journal of Medical Genetics *(this issue*.
World Health Organization, 2004. WHO technical meeting on sleep and health. Retrieved from Bonn, Germany. https://www.euro.who.int/_data/assets/pdf_file/0008/114101/E84683.pdf.
Xu, N., Lv, H., Yang, T., Du, X., Sun, Y., Xiao, B., Yu, Y., 2020. A 29 Mainland Chinese cohort of patients with Phelan-McDermid syndrome: genotype-phenotype correlations and the role of SHANK3 haploinsufficiency in the important phenotypes. Orphanet J. Rare Dis. 15 (1), 335. https://doi.org/10.1186/s13023-020-01592-5.