Sleep Disorders in Prader Willi Syndrome

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Introduction

- PWS is a complex genetic disorder with multiple cognitive, behavioral and endocrine dysfunction
- Sleep alterations and disorders such as sleep disordered breathing and CNS disorders of hypersomnolence's are common
- PWS have a shortened life expectancy and deceased individuals have higher rates of sleep disordered breathing
- Highlight the pathophysiology and clinical features of these common sleep disorders
- Animal models (mice) show dysregulation of hypocretin system in PWS affecting sleep as well as sleep alterations (circadian) and possibly respiratory control

Sleep Disorders: Sleep-disordered breathing

- Frequently reported in PWS
- Prevalence (dependent on age) varies between 40 to 50%
- Spectrum disorders:

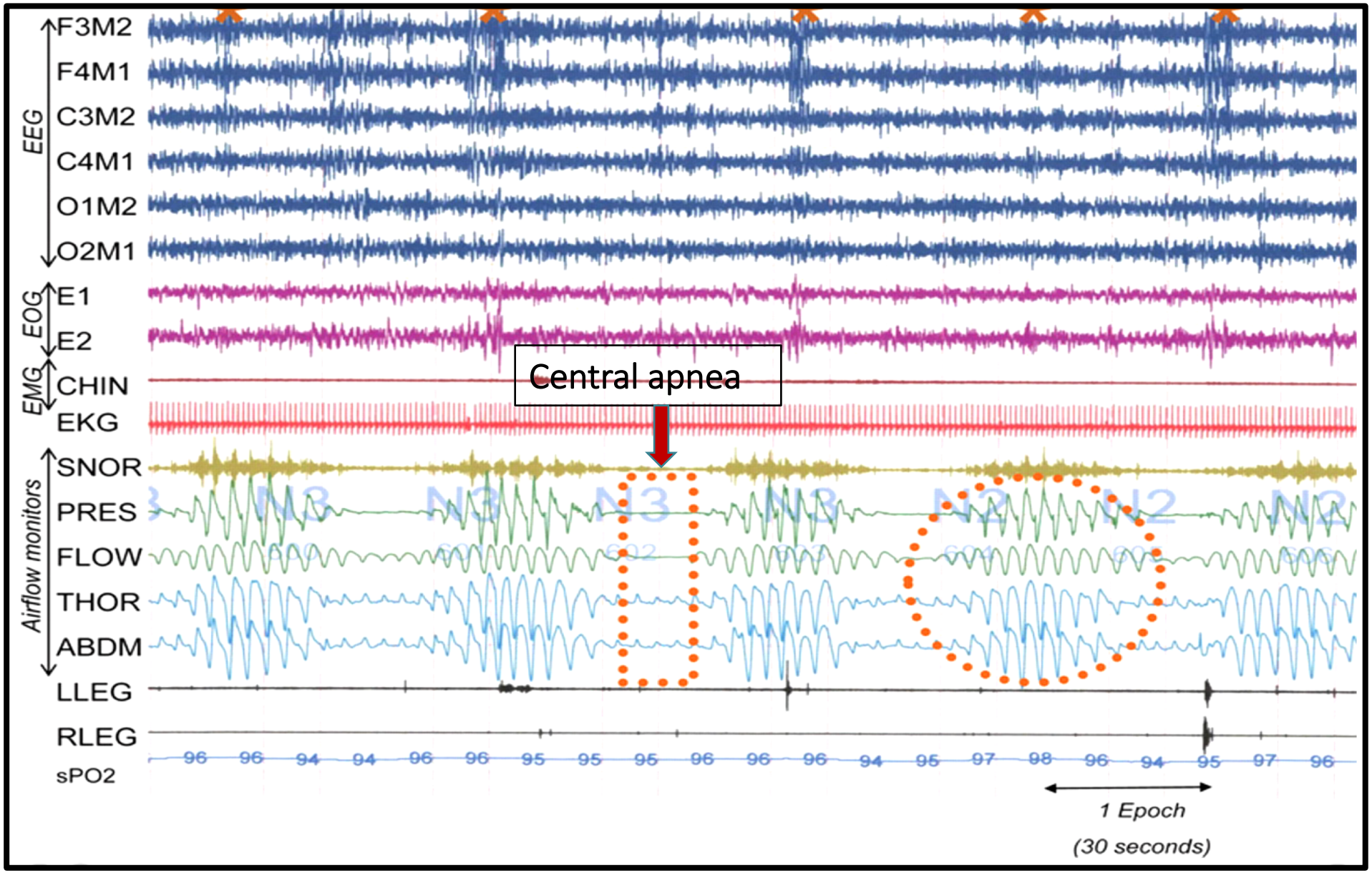
1. *Central sleep apnea (CSA)*
2. *Obstructive sleep apnea (OSA)*
3. *Sleep-related hypoventilation*
4. *Combination of above*

- Aetiology is multifactorial however alteration in ventilatory control (both hypercapnic and hypoxic ventilatory responses) have been implicated

Sleep-disordered breathing: Central Sleep Apnea

- Distinctive feature in infants with PWS (<2 years)
- Usual improves in vast majority (74% within 2 years of baseline PSG)
- Typically periods of apneas with no respiratory effort to breath
- Probably a reflection of brainstem “maturity” and increase in residual functional capacity
- Central events are related to an events leading to a transient increase in ventilatory response with reduction of $PaCO_2$ leading to a central event.

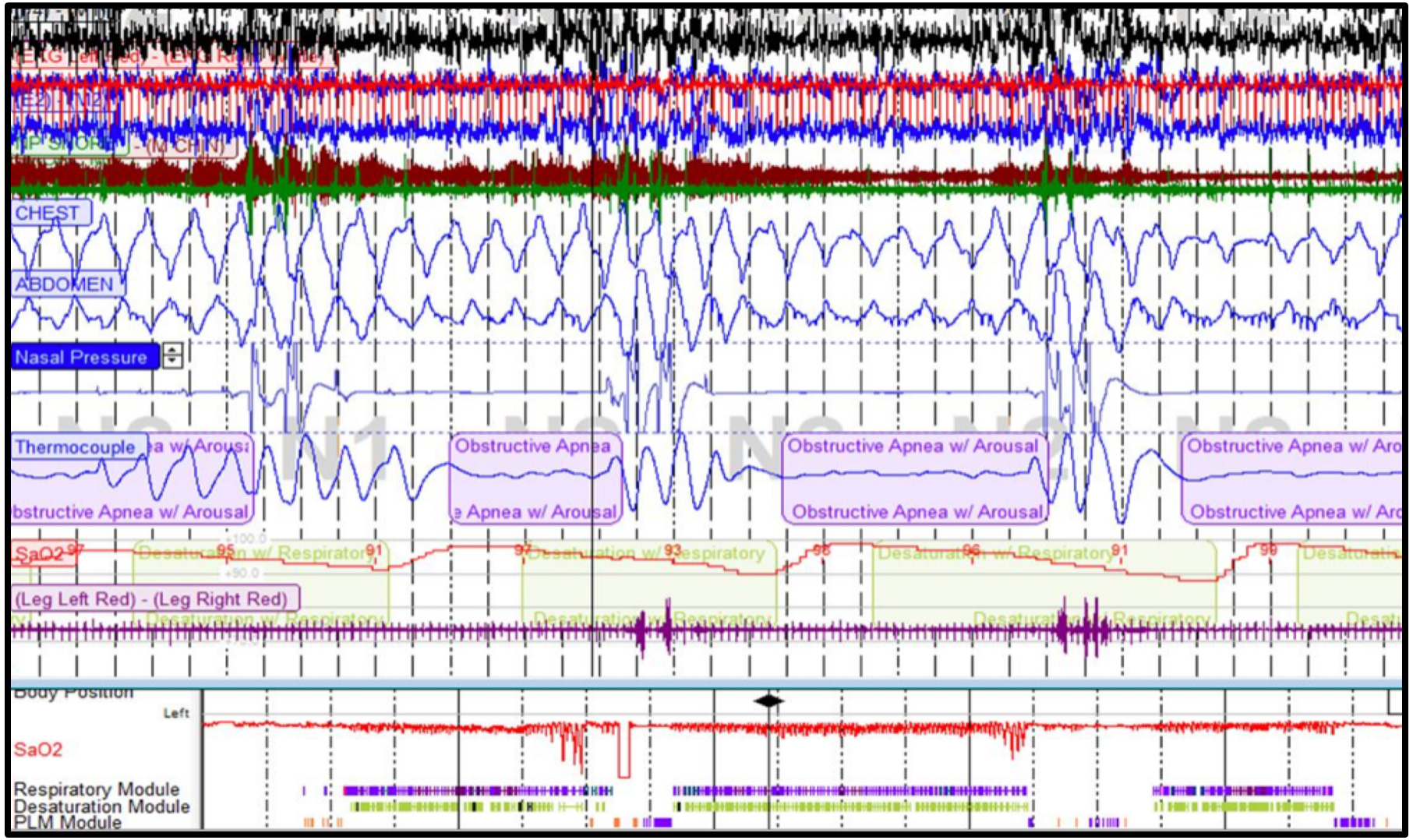
Central sleep apnea



Sleep-disordered breathing: Obstructive Sleep Apnea

- Caused by adenotonsillar hypertrophy, hypotonia, respiratory muscle weakness, facial dysmorphism or pharyngeal narrowing (and obesity)
- Clinically may present with excessive daytime sleepiness (EDS), behaviors (autism like), impulsiveness, failure to thrive and poor cognitive outcomes (and cardiovascular and metabolic complications)
- Diagnosis usually requires polysomnography (level 1-2) however more limited sleep studies (level 3-4) maybe helpful.

Obstructive Sleep Apnea



Sleep-disordered breathing: Nocturnal Hypoventilation

Noctrunal (Sleep-related) hypoventilation

- Maybe common in infants however in adults risk factors include hypotonia/respiratory muscle weakness, obesity and scoliosis
- Hypoventilation usually worse and beginning in REM
- Need to monitor CO2 to confirm nocturnal hypoventilation (rise TcCO2 of 8 mmHg or am ABG)
- Will lead to worse outcomes than simple OSA
- CPAP may not be adequate
- Non-invasive ventilation (bilevel) is more complex device is its can treats hypoventilation (and upper airway obstruction)
- *Settings will include an inspiratory and expiratory pressure (with possible back up rates), inspiratory times etc.*

Central Disorders of Hypersomnolence

- Excessive daytime sleepiness (EDS) is extremely common
- May be associated and independent of SDB (can occur despite treatment of SDB)

60 adult patients with PWS (PSG and MSLT)

1. Almost 50% have isolated CNS hypersomnolence (Narcolepsy (NT 1 or 2), Idiopathic hypersomnolence (IH) or borderline NT/IH)
2. MSLT showing pathological sleepiness and SOREM (sleep onset REM periods)
3. CSF Orexin (hypocretin) are lower (than in normal and IH) however not low as NT
4. Number of hypocretin neurons is not reduced in PWS (compared to NT1) suggestion a disruption of the connecting pathway between hypothalamus, cerebral cortex and brainstem (bidirectional influence of SDB may inhibit/.damage hypocretin neurons)

Ghergan et al. Sleep 2017

Table 1
Clinical and demographic patients' characteristics reported in the included studies. Mean ± standard deviation is reported.

	Study	Clinical data			Genetic data			MSLT		CSF Orexin. Direct Assay, pg/ml
		Study populations	BMI	Cataplexy	15q11-q13 deletion	UPD 15	HLA DQB1*0602 positivity	MSL, min	SOREMPs	
PWS	*Mignot* et al. *2002* [81]	1 (1 M, 16 y)	48.7	0	1		1	3	0	91
	Dauvilliers et al. *2003* [80]	1 (1 M, 21 y)	Unknown	0	1		1	Unknown	Unknown	111
	Nevsimalova et al. *2005* [79]	4 (3 M, 14.3 ± 7.7 y)	Unknown	0	Unknown	Unknown	2	8.6 ± 5.2	0 ± 0.3	175 ± 64.9
	Omokawa et al. *2016* [78]	14 (11 M, 20.3 ± 9.0 y)	31.5 ± 9.1	2	12	2	Unknown	Unknown	Unknown	189.3 ± 55
CTR	*Mignot* et al. *2002* [81]	47 (25 M, 48.5 ± 18.5 y)	24.6 ± 4.1	0	n.a.	n.a.	8	Unknown	Unknown	362.2 ± 111.7
NT1	*Mignot* et al. *2002* [81]	101 (53 M, 39.2 ± 16.1 y)	27.6 ± 6.0	101	n.a.	n.a.	94	Unknown	Unknown	47.5 ± 97.5
	Dauvilliers et al. *2003* [80]	26 (15 M, 35.3 ± 15.1 y)	24.6 ± 4.4	26	n.a.	n.a.	25	4 ± 2.7	3.9 ± 0.9	40.2 ± 60.2
	Omokawa et al. *2016* [78]	37	Unknown	37	n.a.	n.a.	Unknown	Unknown	Unknown	75.5 ± 74.1
IHS	*Mignot* et al. *2002* [81]	29 (11 M, 39.8 ± 11.8 y)	26.6 ± 4.8	0	n.a.	n.a.	15	Unknown	Unknown	308.9 ± 53.3
	Dauvilliers et al. *2003* [80]	7 (5 M, 40.3 ± 11.4)	Unknown	0	n.a.	n.a.	3	5.2 ± 1.2	0.1 ± 0.4	490.4 ± 307.4
	Omokawa et al. *2016* [78]	14	Unknown	0	n.a.	n.a.	Unknown	Unknown	Unknown	308.5 ± 87.2

BMI, Body mass index; CTR, healthy controls; HIS, Idiopathic Hypersomnia; M, males; min, minutes; MSL, mean sleep latency; MSLT, Multiple sleep latency test; NT1, Narcolepsy with cataplexy; PWS, Prader-Willi syndrome; UPD 15, uniparental disomy of chromosome 15; y, years.

Diagnosis of Sleep Disorders

Multidisciplinary approach

- Sleep (respiratory) specialist assessment
- Validated questionnaires not available at this stage however detailed history from patient/carers and family is essential
- In-lab PSG (level 1) +/- multiple sleep latency testing (MSLT) testing in adults (especially with signs and symptoms of a sleep disorder)
- Role of home PSG (level 2) or more simplified sleep studies (level 3-4) maybe more practical although have less information
- Own institute (RPAH): sleep and respiratory physicians, sleep scientists sleep CNC, PAP CNC, respiratory physiotherapists and dieticians

Effect of Growth Hormone (GH) on Respiratory Function and Sleep

- GH treatment is commonly given in PWS to increase adult height, improve neurocognitive function, muscle bulk, exercise capacity and body composition
- GH treatment has not affected sleep macroarchitecture and/or sleep disordered breathing however……
- All children with PWS who died during GH treatment had likely underlying hypoventilation and/or OSA and adenoid hypertrophy
- Hence prior to GH treatment all PWS should been seen by a respiratory/sleep/ENT specialists (possible sleep testing)

Effects of Growth Hormone

Table 2
Available Data on the effects of Growth Hormone on Sleep Abnormalities in Prader Willi Syndrome.

Authors/Year	Design	Population	Results
Zimmermann et al. *2020* [102]	6-month longitudinal observation study	62 children	OSA developed independently of the age of treatment onset
Donze et al. *2019* [96]	2-year randomized double-blind placebo-controlled study	27 young adults	GH did not increase AHI, OAI, CAI
Al-Saleh et al. *2013* [97]	2-year longitudinal observational study	15 children	No change in OAHI and CAI during 2 years of GH treatment
Berini et al. *2013* [98]	48-month longitudinal observational study	50 children	Significant improvement in RDI during GH treatment
Salvatoni et al. *2009* [100]	6-week longitudinal observational study	34 children	GH-treated group did not differ from the control group for the OAHI both before and after 6 weeks of treatment
Miller et al. *2006* [99]	6-week longitudinal observational study	25 patients age range 6 months–39 years	Most of PWS patients had improvement after short-term GH treatment, but 32% of patients with underlying respiratory risk factors had worsening of sleep disturbance
Festen et al. *2006* [101]	6-month longitudinal observational study	53 children	GH treatment didn't aggravate the sleep-related breathing disorders

Abbreviations: AHI = Apnea Hypopnea Index; OAI= Obstructive Apnea Index; OAHI = Apnea Hypopnea Index; CAI= Central Apnea Index; RDI = Respiratory Disturbance Index; OSA = Obstructive Sleep Apnea.

Growth Hormone: Recommendations

- Before starting GH treatment, children with PWS should undergo a multidisciplinary evaluation including PSG, ear, nose and throat (ENT) evaluation, end-tidal or transcutaneous capnography.
- Exclusion criteria for GH treatment include untreated obstructive sleep apnea, severe obesity, uncontrolled diabetes mellitus, active cancer or psychosis.
- Central apneas and scoliosis are not considered a contraindication to GH treatment.
- Therapy should not be started during an acute respiratory infection, but should not be interrupted during subsequent episodes of respiratory infection unless indicated because of the onset of breathing difficulties.
- During GH treatment, changes in breathing (particularly during sleep) should be promptly reported and evaluated by repeat oximetry and/or PSG
- Although no specific guidelines on PSG monitoring are available, we suggest to perform PGS and ENT evaluations within the first 3–6 months of starting therapy (the first months of treatment represent the most vulnerable time for the development of SDB) and to personalize the follow-up based on the patient condition (12–24 months)
- GH dosing should be guided by maintaining IGF-1 within physiological levels (0–2 SD) in order to avoid potential adverse events due to overtreatment (worsening of adentonsillar hypertrophy and obstructive apneas)

GH, growth hormone, ENT, ear, nose and throat; PSG, polysomnography; IGF-1, insulin growth factor-1; SDB, sleep-disordered breathing.

Treatment of Sleep Disorders in PWS

OSA

1. Adenotonsillectomy is first line in pediatric OSA
   - *Meta-analysis showed success rate 71% when using AHI<5 (but only 21% if AHI<1 suggesting complete resolution)*
   - *Need for reevaluation and adjunct treatments (e.g. CPAP)*
2. Continuous Positive Airway Pressure (CPAP)
   - *Very effective in PWS however compliance maybe reduced*
   - *Global PWS Registry suggest less than 50%*
   - *Occasional role of NIV (bi-level) in hypoventilation syndrome*
3. Weight loss (and exercise)
   - *Maybe beneficial but not always consistent*
4. Novel therapies not studied
   - *Mandibular advancement splints (MAS)*
   - *Hypoglossal nerve stimulators (HGNS)*
   - *Positional therapy (PT)*

Treatment of Sleep Disorders in PWS

Excessive Daytime Sleepiness

1. Modafinil (wakefulness promoter) has been used in PWS (observational studies only)
   - *Shown to improve EDS and behavior*
   - *Generally well tolerated (37% transient side effects such as irritation, anxiety, mood and aggression)*
2. Pitolisant (antagonist/agonist histamine receptor)
   - *Shown in small studies in children with minimal side effects*

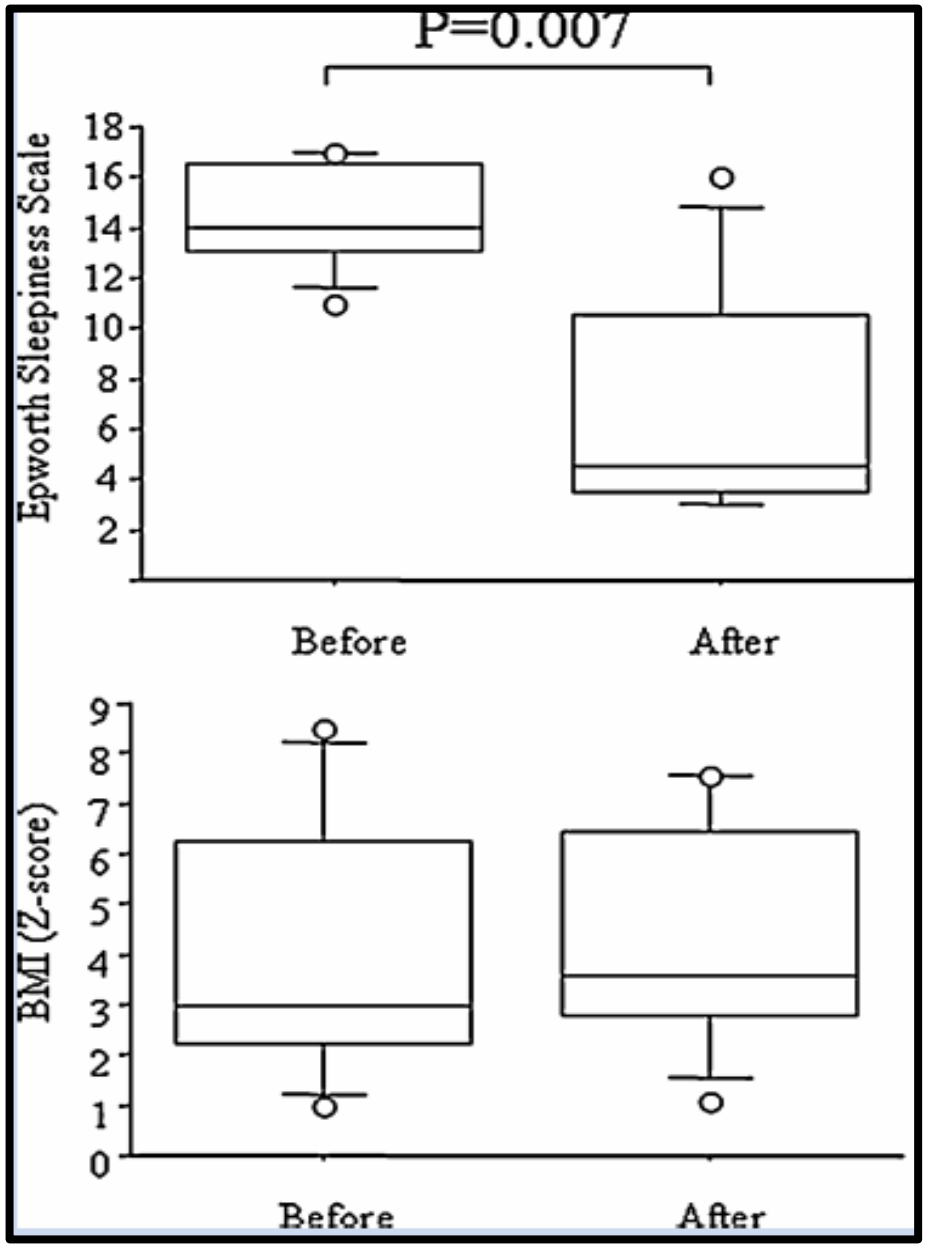
**Both therapies are standard treatment in Narcolepsy guidelines*

Efficacy of Modafinil on Excessive Daytime Sleepiness in Prader–Willi Syndrome

V. Cochen De Cock,[1] G. Diene,[2] C. Molinas,[2] V. Dauriac-Le Masson,[3] I. Kieffer,[2] E. Mimoun,[2] M. Tiberge,[4] and M. Tauber[2]*

Am J Med Genet Part A 155:1552–1557.

Patient	Sex	Age (years)	BMI (kg/m^2)	BMI (Z-score)	Genetic diagnosis	Intelligence quotient	Treatment with GH	ESS (/24)	Modafinil (mg)	modafinil treatment (months)
1	M	17	25.5	+3.0	Deletion	75	Stopped for 2 years	16	200	11
2	F	16	31.3	+5.0	Deletion	75	Stopped for 3 years	13	200	5.5
3	M	15	24.6	+2.6	UPD	69	Under treatment	17	100	5.7
4	M	8	19.8	+2.9	Deletion	64	Under treatment	14	100	12
5	F	17	37.1	+7.5	UPD	—	No	14	200	4.2
6	F	17	39.4	+8.5	Deletion	—	Stopped for 2 years	13	200	14.7
7	M	21	31.6	NA	AMP	—	Under treatment	17	300	1.7
8	F	12	21.1	+1.8	UPD	95	Under treatment	11	200	7.3
9	F	10	17.8	+1.0	Deletion	72	Under treatment	20	100	4.2



Conclusion

- Genetic animal models suggest a “narcoleptic-like” trait of PWS with hypothalamic dysfunction.
- Although GH was not associated with worsening SDB indices, reported deaths suggest predisposing risk factors including hypoventilation, SDB and adenoid hypertrophy.
- CPAP is very effective however compliance is low (probably similar to real world CPAP use).
- Role of wakefulness promoters such as Modafinil should be considered in patients with EDS not explained by SDB.
- Need for multidisciplinary approach is essential.