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Sleep Complaints, Sleep and Breathing Disorders in Myotonic Dystrophy Type 2

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Abstract

Purpose of Review To update the current knowledge concerning sleep complaints and breathing disorders in myotonic dystrophy type 2 (DM2) and to better understand if sleep and breathing symptoms may add a further clinical definition of DM2.

Recent Findings Although DM2 has been poorly evaluated, the most relevant sleep disorders are sleep-disordered breathing (SDB) (37.5–66.7%) and restless legs syndrome (RLS) (50–60%). Excessive daytime somnolence (EDS) is not consistent with SDB, and a large percentage of patients with sleep complaints (58–69%) report pain. In addition, respiratory dysfunctions are reported in 6 to 15% of DM2 patients, albeit few data are available regarding pulmonary restriction, hypoventilation, and non-invasive ventilation (NIV).

Summary SDB, RLS, and pain may contribute to sleep fragmentation and EDS in DM2. In addition, few studies report hypoventilation and pulmonary restriction, although there are no studies at all on NIV, except for limited clinical experiences. These findings suggest performing a careful pulmonary examination and NIV when required. Furthermore, sleep studies and respiratory evaluation should be recommended if OSA or respiratory muscle dysfunctions are suspected. A large polysomnographic study should be performed to clarify the link between sleep disorders, pain, and sleep disruption in DM2.

Keywords Myotonic dystrophy type 2 · Excessive daytime somnolence · Sleep · Sleep-disordered breathing · Hypoventilation · Fatigue · Pain

Introduction

Myotonic dystrophies are autosomal dominant genetic disorders characterized by progressive and multisystemic involvement disorders including myopathy, myotonia and cardiomyopathy, endocrine abnormalities, and neuropsychological deficits [1]. Myotonic dystrophy types 1 (DM1) and 2 (DM2) represent the two clinical, histopathological, and genetic forms of myotonic dystrophy, although these entities show an overlap in the clinical features [2]. Both dystrophies are caused by genetic repeat expansions; DM1, related to a CTG repeat in the DMPK gene [3] and DM2 to a CCTG repeat expansion in the CNBP gene (also known as ZNF9) [4]. DM2 resembles adult-onset DM1 with similar clinical multi-organ involvement (i.e., muscle atrophy, weakness, myotonia, cardiac arrhythmia, posterior cataract, diabetes, cognitive, and psychiatric disturbances), even if there are significant clinical differences such as proximal muscle involvement, slow and less severe disease progression, later and less prominent respiratory weakness, and better cognitive condition [5•, 6]. Also, DM2 shows sex differences, since women more often have proximal muscle weakness and more severe disease, whereas men more frequently show myalgic and pain symptoms [7••]. Sleep disorders are highly reported in neuromuscular diseases as probable causes of mortality and morbidity [8•]. Persistent and transient sleep hypoxemia due to sleep-disordered breathing (SDB) may induce cardiovascular and pulmonary failure. Furthermore, sleep fragmentation and excessive daytime somnolence (EDS) may impair frailty and may also

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affect psychiatric and cognitive functioning. Although sleep disorders and EDS are highly reported in DM1 [9], DM2 has also been associated with sleep disturbances and respiratory symptoms [10–13]. Firstly, EDS has been mentioned in some anecdotal reports of myotonic dystrophy, and this condition was usually considered secondary to the hypercapnia [14–16]. Obstructive sleep apnea with or without hypoxia and hypercapnia, central EDS, rapid eye movement (REM) sleep dysregulation, and periodic limb movements of sleep (PLMS) were described in DM1 [17–20]. Sleep and breathing disorders are scarcely reported in DM2 patients, according to the recent update on its genetic definition and the low prevalence in some countries [21]. Nevertheless, recent studies show that SDB, EDS [12, 17, 22, 23], restless legs syndrome (RLS) [13, 24], and REM sleep disturbances [12, 18] are also present in DM2, although there are limited polysomnographic data available [12, 25•]. In this narrative review, we aim to highlight the current knowledge regarding sleep and respiratory disorders in DM2, to better characterize the clinical spectrum of this type of myotonic dystrophy.

Clinical Presentation and Differential Diagnosis with DM1

Myotonic dystrophies (DM) are dominantly inherited multisystemic diseases. Steinert and colleagues described the "classic" form of myotonic dystrophy in 1909, and it was called "Steinert's disease" [26]. The primary clinical manifestations of DM1 are facial and distal muscle weakness and wasting, together with grip and percussion myotonia, but a multi-organ involvement is described. In 1992, the gene defect responsible for myotonic dystrophy of Steinert was found to be an abnormal expansion of a CTG repeat in the 3′ untranslated region of myotonic dystrophy protein kinase gene (DMPK; OMIM 605377) on chromosome 19q13.3 [27, 28]. The severity of the disease differs according to the number of CTG repeats and DM1.

Subsequently, it was demonstrated that many of the families with a similar clinical pattern but without that genetic defect had an unstable tetranucleotide CCTG repeat expansion in intron 1 of the nucleic acid-binding protein (CNBP) gene (previously known as zinc finger 9 gene, ZNF9; OMIM 116955) on chromosome 3q21 [4]. Patients with DM2 share similar core features of symptoms with DM1, but also have several different clinical manifestations [26, 29•, 30]. First of all, the onset of DM2 is in adulthood, without reduction of life expectancies and a congenital form has not been reported. Usually, lower-limb weakness is the most common symptoms with the involvement of hip flexors and knee extensors and without the absence of tendon reflexes (that is common in DM1). Moreover, muscle wasting, distal weakness, and clinical myotonia could be absent, and muscle pain is sometimes the dominant symptom. Facial weakness is almost absent. Multi-organ involvement, similar to that described in myotonic dystrophy type 1, also occurs in myotonic dystrophy type 2, which is generally considered less severe and frequent despite the cardiac, respiratory, endocrine, and ocular involvements (see Fig. 1). Since they share the same pathological mechanism of DM1, these alterations could be severe and should not be overlooked. Furthermore, cognitive and behavioral

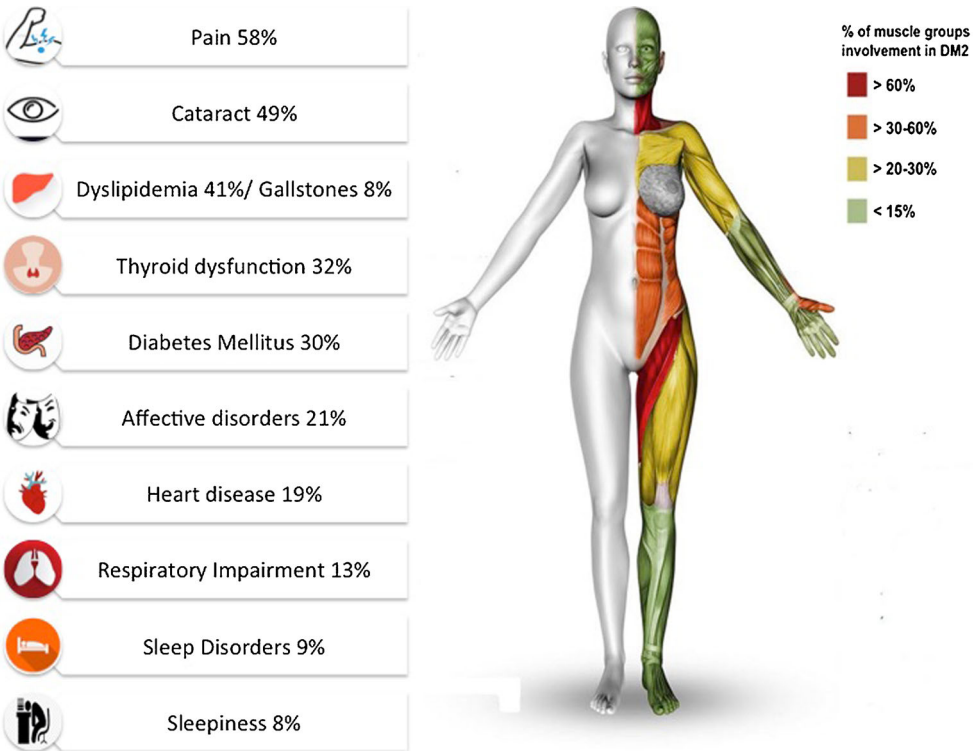

Fig. 1 Summary of the clinical features of myotonic dystrophy type 2 as reported in a large cohort by Montagnese et al. (Modified from Montagnese, F., Mondello, S., Wenninger, S. et al. *Assessing the influence of age and gender on the phenotype of myotonic dystrophy type 2.* J. Neurol. 2017;264:2472–80, with permission from Springer Nature.) [7]

impairment, above mentioned, could lead to the avoidance of medical attention [31]. Thus, diagnosis of DM2 could be challenging, and greater diagnostic delay is not uncommon. The real prevalence of DM2 is quite heterogeneous in different countries; Northern European countries (Czech Republic, Finland, and Germany) manifest a negligible difference between DM1 and DM2 or even higher prevalence than DM1 [32], whereas in Asia and sub-Saharan populations, DM2 is virtually absent. On the other hand, Southern European countries show an estimated prevalence of about 10% that of DM1 (DM1 9.65 per 100,000 and DM2 0.99 per 100,000) [7••, 33••]. Differential diagnosis between DM1 and DM2 is thus possible through genetic testing analysis [26].

Ventilation and Respiratory Muscle Involvement in DM2

In the physiological condition, the respiratory muscle strength exceeds the respiratory load thus normal ventilation is preserved during rest, exercise, and sleep. In neuromuscular diseases, the muscle weakness is associated with an increased respiratory load due to the following: (1) inability to have a useful sigh or to breathe deeply with decreased lung and chest wall compliance; (2) irreversible degeneration of the joint cartilage of the rib cage leading to increased chest wall stiffness; (3) impaired respiratory muscles contractility due to spinal deformities such as thoracic scoliosis. With advancing respiratory muscles weakness, airflow decreases and alveolar hypoventilation occur with an ongoing gradual decline in vital capacity (VC) and disturbed gas exchange escorted by the ventilation-perfusion mismatch [34, 35•]. The respiratory involvement in neuromuscular diseases results in a restrictive defect in which both VC and FEV1 decline before the reduction in total lung capacity [34, 35•]. A fall of VC in the supine position of more than 25% concerning the sitting position indicates a significant diaphragmatic weakness and probably nocturnal hypoxemia. With further progression of diaphragmatic involvement and the continuing decline in VC, patients become more susceptible to sleep-breathing disorders, which appear first during REM sleep [35•, 36••]. In DM1, mortality is mainly due to respiratory problems (failure and pneumonia) in 43% of patients [37] that were unrelated to significant muscle weakness, but to CTG repeat in the DMPK gene [38].

Mutual interaction between skeletal muscle weakness and CNS dysfunction may represent the basis of the respiratory dysfunction [36••,39••]. Irregular breathing patterns, sleep-breathing disorders, and the finding of reduced ventilatory response to CO2 independent of respiratory muscle weakness, all the above symptoms suggest that the central nervous system plays an essential role in pathogenesis. It happens frequently that myotonic patients do not relate their symptoms to respiratory failure as it happens for other symptoms [23, 36••, 39••, 40]. Respiratory parameters are typically monitored upright, while pulmonary function may be better evaluated in supine position, more sensitive at detecting a restrictive ventilatory pattern [6, 38]. Although non-invasive ventilation (NIV) for respiratory weakness may potentially represent a tool to ameliorate survival in myotonic patients, the main limitation is poor adherence and the need for frequent follow-up [35•, 39••]. Few data are available regarding DM2 patients and respiratory disorders. Only a minority of both DM1 and DM2 patients receives a regular evaluation of lung function at the onset, consequently obtains a pulmonary service referral, and is on NIV. Thus, a small number of those patients receive support for secretion management [39••]. Recently, it has been discussed and proposed a respiratory symptoms checklist ("RESPICHECK") for myotonic dystrophies [41]. It includes nine domains: orthopnea, dyspnea, sleep, headaches, apnea, cognitive performance, EDS, fatigue, and chest infection [39••, 41]. Epworth Sleepiness Scale score, correlated with the RESPICHECK questionnaire score, and pCO2 levels show a direct correlation, while both the sitting forced vital capacity and the forced expiratory volume demonstrate an indirect correlation with this questionnaire in DM1 [41]. Few data are available regarding DM2. The magnitude of respiratory involvement is reported in two different studies respectively in 6–15% [39••] and 13% of DM2 patients [7••]. The last of whom fails in finding any sex difference in respiratory impairment in DM2 [7••]. Respiratory function has also been evaluated in a comparative study between DM1 and DM2 [23]. Orthopnea and morning headache were reported in 13% and 19% of patients with DM2, respectively. Respiratory symptoms were not correlated with sleep efficiency and wakefulness during nocturnal sleep. Lack of symptoms of respiratory failure was reported by 25% of DM2 patients versus 16% of DM1. Sitting VC, supine VC, maximal inspiratory pressure, sniff nasal pressure, and phrenic compound motor action potential amplitude are lower in DM2 versus controls but less severely impaired when compared with DM1 patients. Vital capacity dropped more than 30% on the transition from the sitting to the supine position in 3/25 (12%) of DM1 patients, but in none of the DM2 subjects [23]. Lastly, the Serbian registry of DM2 reported that 10% of patients had lung restriction with FVC < 90%, lacking further evaluations of SDB and respiratory impairment [42].

Sleep-Related Breathing Disorders in DM2

SDB may be explained by the weakness and myotonia of respiratory muscles and the altered central control of ventilation. Although this hypothesis is not entirely clarified, earlier studies suggest that reduced respiratory muscle strength itself does not account for the presence of SDB in myotonic dystrophies [17, 18].

The occurrence of sleep-related breathing disorders (SDB) in DM2 has been consistently reported and seems to be the most frequent sleep disorder, but its magnitude has not been evaluated. However, DM2 patients exhibit EDS, poor sleep quality, decreased sleep efficiency, SDB, and diaphragmatic weakness [7••, 9, 14, 20]. Phrenic CMAP amplitudes, an indicator of diaphragm weakness, below normal values have been reported in DM2 and correlated with respiratory functions and sleep quality [20]. Only six studies evaluate the impact of SDB in DM2, including a small population of DM 2 patients, ranging from 5 to 16 [10, 12, 22, 23, 43, 44]. As a whole, 61 patients were studied with different methods: in-lab polysomnography, ambulatory PSG, or at-home cardiorespiratory monitoring (Table 1). The prevalence of SDB, considering an apnea-hypopnea index above 5 [45] varies from 37.5 to 66.7% while the prevalence of moderate-severe SDB (that is, an apnea-hypopnea index above 15), varies from 0 to 50%. The pattern of SDB differs in DM2 as compared with DM1, since respiratory events are mostly obstructive, with a very few observations of central apnea pattern or a mixed (central and obstructive) one.

Moreover, central events do not differ between DM2 patients and controls when evaluated at the population level [23]. Central hypoventilation has not been described in DM2 patients, even if night oxygen desaturation and higher end-tidal C02 have been reported despite less pronounced than in the DM1 population [23]. SDB seems to be one of the leading causes of sleep disruption and EDS in DM2 [12]. The correlation between severity of SDB and EDS is not consistent in the different papers, but this datum could be related to methodological problems since the majority of the studies evaluate subjective sleepiness with Epworth Sleepiness Scale, that is considered as scarcely reliable in this kind of population [19, 25•, 46]. More interestingly, a correlation between SDB and peripheral neuropathy in DM2 patients was described where the amplitude of the ulnar and median sensory nerve action potential (SNAP) was related to nocturnal mean arterial oxygen saturation [44]. The authors propose a two-way mechanism since axonal degeneration may contribute to muscle weakness and cause nocturnal hypoxemia but also vice versa. Moreover, in this population, obstructive and central sleep apneas were correlated with the most of the respiratory parameters [10], even if the involvement of the diaphragm and respiratory DM2 phenotype seems to be milder as compared to DM1.

According to this data, some authors suggest performing PSG evaluation only in patients with altered pulmonary function scores, although it is worth underlining that no clear clinical parameters could predict SDB in patients with neuromuscular diseases.

Non-invasive Ventilation in DM2

Few data are available regarding the approach of respiratory disorders and SDB in DM2. The recent 207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies has attempted to assess the management of respiratory involvement in the EU, The USA, and Canada and has agreed and reported minimum recommendations for screening and treatment of chronic respiratory insufficiency in myotonic dystrophies including indications for NIV [39••]. The Italian experience from NEMO Center reported 8/52 (15%) DM2 patients on NIV. NIV was prescribed by the following criteria: nocturnal desaturation (in 87.5% of patients), HCO3− > 30 mEq/L, paCO2 > 45 mmHg, a difference between supine and sitting FVC > 20%, although the paper did not specify the differences between DM1 and DM2. The most utilized devices were servo-assistant devices, presso-volumetric, and Bilevel devices [39••]. The Canadian registry reported 6% of DM2 patients treated with NIV versus 13% of adult DM1 and 23% of adult congenital DM1. The overall data reported NIV prescription in 15–20% of DM2 compared to 20–60% of adult DM1 and 20–40% of congenital DM1 [39••]. Moreover, no study on ventilation treatment and adherence has been performed. Three DM2 patients presented good clinical response with CPAP [43]. Thus, the compliance and the impact of ventilation in this population need to be evaluated as well as the prevalence in a study with a larger population.

Table 1 Sleep-disordered breathing and DM2

Ref.	Methods	No. of pts	OSA (RDI > 5) *N* (%)	Moderate-severe OSA (RDI > 15) *N* (%)	Central or mixed pattern *N* (%)
[22]	In-lab PSG	5	3 (60%)	0 (0%)	N.A.
[43]	In-lab PSG	6	4 (66.7%)	3 (50%)	1 (16.7%)
[12]	Amb PSG	16	7 (58.3%)	3 (25%)	1 (6.25%)
[10]	CRM	14	6 (42.8%)	2 (14.2%)	2 (14.2%)
[23]	In-lab PSG	16	6 (37.5%)	N.A.	N.A.
[44]	CRM	8	3 (37.5%)	0 (0%)	0

In-lab PSG, In-lab polysomnography; *Amb PSG*, ambulatory polysomnography; *CRM*, home-based cardiorespiratory monitoring; *OSA*, obstructive sleep apnea; *RDI*, respiratory disease index; *N.A.*, not available

Sleep Disorders Other than SDB in DM2

- Several sleep disorders—restless legs syndrome (RLS), EDS, and PLMS—were described both in DM1 and DM2 [17], although few data were specifically reported in DM2 (see Table 2). The first description by Shepard et al. [22] described RLS in a small uncontrolled series of DM2 patients. Two out of eight (25%) DM2 patients were affected by primary RLS since low ferritin levels were found in two out of four DM2 patients with RLS. Considering the high mean age (62 years; range, 43–82 years), RLS *prevalence* may be considered quite higher than the expected prevalence in the general elderly population [47]. Besides, DM2 patients may complain of *RLS mimics* such as myalgias and pain [5, 48] that may overestimate RLS magnitude in DM2. The same research group published a further observational questionnaire-based study [13]. They evaluated 30 DM2 patients (mean age 63 years) and 44 age and sex-matched healthy controls and found a higher significant RLS prevalence in DM2 compared to healthy controls (18/30 DM2 60% vs. 6/43 HC 14%). These authors concluded that RLS was the most relevant sleep disorder in DM2 more than OSAS, which would be represented in DM2 similarly that in healthy controls. However, the lack of polysomnographic data may bias these findings probably underestimating SDB in DM2 [13, 24, 49]. The high prevalence of RLS in DM2 was not confirmed by two polysomnographic controlled studies [12, 23]. REM sleep dysregulation seems to represent a sleep feature of both DM1 [20, 50, 51, 52••] and DM2 [12, 17, 25•, 43, 53]. Small case series [43] and single case reports [53] described REM sleep behavior in OSAS after ventilation by CPAP (1/6 16.6%) and REM sleep without atonia (RSWA, 1/6 16.6%). Our controlled polysomnographic study showed a high prevalence of RSWA in DM2 (6/12 50%; 1/6 RSWA with dream-enacting behavior in severe OSAS, 3/6 RSWA associated with mild to moderate OSAS) [12]. The actual pathogenesis of RSWA in DM2 patients should be clarified. We may hypothesize that RSWA may represent a compensatory mechanism against nocturnal respiratory events [54], and the brainstem and diencephalon involvement (i.e., pedunculopontine and laterodorsal tegmental nuclei) may activate behavioral states during REM sleep [55].

Fatigue, Pain, and Daytime Somnolence in DM2

Diurnal sleepiness is defined as "the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep." The clear distinction between somnolence and fatigue is still difficult especially in neuromuscular diseases such as myotonic dystrophies [25•, 56]. Although DM2 represents a less severe form than DM1, fatigue and EDS are common clinical symptoms of DM2. Recently, the PRISM-2 study reported fatigue in 89.2% and EDS in 77% of DM2 patients [57•]. The study was biased by registry-based design, a female higher prevalence and the lack of information regarding treatments that may influence sleep, fatigue or pain. However, it showed a gender effect, being women more affected by sleep impairment, daytime sleepiness, and fatigue, and a worsening in the quality of life in DM2 patients complaining of EDS and fatigue. A recent study confirmed that EDS and fatigue are present in 27% and 47.8% of DM2 patients respectively [58•]. Finally, a strong

Table 2 Sleep disorders other than SDB in DM2

Ref.	Methods	No. of DM2 pts	Sleep disorders
[11]	P, C, subjective scales	29	EDS 6.9%; poor sleep quality 66%
[22]	R U sleep complaints, PSG	8*	EDS 75%; insomnia 62,5%; RLS 50%
[43]	P U sleep complaints, PSG	6	EDS 100%; insomnia 33.3%; RBD in OSAS after CPAP 16.6%; paradoxical breathing in REM 33.3%; REM sleep without atonia 16.6%; low sleep efficiency—alfa-delta sleep 33.3%
[13]	P C subjective scales	30	RLS 60%; EDS 43%; poor sleep quality (PSQI) 66.7%
[12]	P C, PSG % subjective scales	12	Sleep disturbance pain-related (PSQI) 58%
			EDS (DSS 66.6%; MSLT 33%)
			Low sleep efficiency 100%; PLMS 25%; RBD in severe OSAS 8.3%; RSWA 50%
[10]	P U subjective scales, CRM	14	Poor sleep quality 42.8%; EDS 14.3%

C, controlled; *CPAP*, continuous positive airway pressure; *CRM*, home-based cardiorespiratory monitoring; *DM2*, myotonic dystrophy type 2; *DSS*, daytime sleepiness scale; *EDS*, excessive daytime somnolence; *MSLT*, multiple sleep latency test; *P*, prospective; *PLMS*, periodic limb movements of sleep; *PSG*, polysomnographic study; *PSQI*, Pittsburgh Sleep Quality Index; *R*, retrospective; *RBD*, REM sleep behavior disorder; *RSWA*, REM sleep without atonia; *U*, uncontrolled *5/8 PSG

association with autoimmune and autoantibodies diseases was described in DM2 patients [59], and pro-inflammatory condition may modulate fatigue in neuromuscular disease and sleep disorders [60, 61, 62••]. Patients affected by myotonic dystrophies possibly experienced fatigue, which may be referred to as EDS [11, 25•]. Pain represents a further overlooked clinical feature of DM2 [48]. Pain was reported in about 76% of DM2 patients, is mainly exercise or cold temperature-related, and negatively affects the quality of life [5, 58•, 63, 64••, 65, 66]. The pathophysiology of pain in DM2 is poorly understood. Peripheral and central sensitizations are likely to play a prominent role in chronic musculoskeletal pain [48, 64••, 67]. The correlation between sleep and pain in DM2 patients is still unclear. Tieleman et al. [11] showed that 69% of DM2 patients reported pain as the cause of sleep impairment (compared with 34% of DM1 patients and 17% of controls) but not of EDS, as evaluated by subjective scales, and an important effect of myalgia on nocturnal sleep disruption has been hypothesized. On the other hand, Lam and colleagues [13] found a high prevalence of RLS and EDS in DM2, not related to pain and fatigue in a survey-based study. The first controlled polysomnographic study failed to find significant sleep impairment in pain complaining patients compared with those not complaining, although 58% of subjects reported pain-related sleep disorders through subjective scale (Pittsburgh Sleep Quality Index) [12].

Conclusion

- Although DM2 has been poorly evaluated, further sleep studies should be performed to confirm the high prevalence of SDB in DM2, to detect its role in EDS, fatigue, and sleep fragmentation. Furthermore, RLS and RSWA are frequently reported in DM2 [10, 12, 13, 17, 23, 24, 49]. Few studies report on the frequency of occurrence of hypoventilation and pulmonary restriction in DM2 patients; they evaluate it as 6–15% [7••, 39••, 42]. These findings suggest to perform a careful pulmonary examination including total and predicted FVC from both the sitting and supine positions [39••]. Furthermore, sleep studies and respiratory evaluation should be recommended if OSA or respiratory muscle dysfunctions are suspected. Nevertheless, there are no studies on ventilation treatment and adherence, except for the clinical experience reported in a recent consensus conference [39••]. Nevertheless, a link between pain and sleep disruption in DM2 [11] has been hypothesized; the actual role of pain and fatigue in DM2 patients complaining of EDS, fatigue, and sleep disturbances has not been clarified yet. Thus, a large polysomnographic study should be performed to clarify the clinical phenotype of DM2.

Compliance with Ethical Standards

Conflict of Interest Andrea Romigi reports other from EISAI, personal fees from SANDOZ, personal fees from Fidia Farmaceutici, outside the submitted work. Giuseppe Vitrani received a personal fee from Fidia Farmaceutici outside the submitted work. Enrica Bonanni, Marco Caccamo, Diego Centonze, Michelangelo Maestri, Carmine Nicoletta, Alessandro Sanduzzi, and Gabriele Siciliano each declare no potential conflicts of interest.

Human and Animal Rights The article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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