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Sleep in patients with dystonia: a systematic review on the state of research and perspectives

Elisabeth Hertenstein[1], Nicole K. Y. Tang[2], Celia Bernstein[3], Christoph Nissen[1], Martin Underwood[3], and Harbinder Sandhu[3]

[1] Department of Psychiatry and Psychotherapy, University of Freiburg Medical Center, Germany

[2] Department of Psychology, University of Warwick, Coventry, UK

[3] Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK

Address for correspondence:

Elisabeth Hertenstein

University of Freiburg Medical Center

Department of Psychiatry and Psychotherapy

Hauptstraße 5, 79104 Freiburg, Germany

phone: +49 761 270 69810

Email: elisabeth.hertenstein@uniklinik-freiburg.de

1 **Summary**

2 Patients with primary dystonia, the third most prevalent movement disorder, suffer from a

3 markedly reduced quality of life. This might, at least in part, be mediated by non-motor

4 symptoms, including sleep disturbances. Characterising and treating sleep disturbances might

5 provide new inroads to improve relevant patient-centred outcomes. This review evaluates the

6 state of research on sleep in patients with dystonia and outlines an agenda for future research.

7 A literature search was performed in July 2014 using PubMed, Medline via Ovid, PsycInfo,

8 PsycArticles via Proquest and Embase via Ovid. Search results were screened for eligibility

9 by two independent raters. Peer-reviewed publications reporting on sleep in patients with

10 primary dystonia were included. Of 1,445 studies identified through the search strategy, 18

11 met the inclusion criteria. In total, the included studies reported on 708 patients diagnosed

12 with focal dystonia (cervical dystonia or blepharospasm), torsion dystonia, and dopa-

13 responsive dystonia. The results indicate that at least half of the patients with focal cranial

14 dystonia suffer from sleep disturbances, but excessive daytime sleepiness is uncommon.

15 Sleep disturbance is associated with depressive symptoms. The frequency and duration of

16 dystonic movements is markedly reduced during sleep. Reduced sleep quality appears to

17 persist after treatment with botulinum toxin that successfully reduces motor symptoms. The

18 findings are limited by a high clinical and methodological heterogeneity. Future research is

19 needed to i) further characterize subjective and PSG sleep in patients with different types of

20 dystonia, ii) determine the aetiology of sleep disturbances (e.g., abnormal brain function

21 associated with dystonia, side effects of medication, psychological reasons), and iii) test

22 whether targeted sleep interventions improve sleep and quality of life in patients with primary

23 dystonia.

24

1 **Glossary**

2 <u>blepharospasm:</u> form of focal cranial dystonia, involuntary muscle contractions of the eyelid

3 <u>cervical dystonia:</u> also called spasmodic torticollis, form of focal cranial dystonia involving
4 the neck, causing an often painful involuntary turning of the head

5 <u>cranial dystonia:</u> different forms of focal dystonia localized in the head area

6 <u>dopa-responsive dystonia:</u> also known as hereditary progressive dystonia with marked diurnal
7 fluctuation or Segawa syndrome, very rare form of generalized dystonia beginning in
8 childhood or adolescence

9 <u>dystonia:</u> neurological movement disorder characterized by involuntary muscle contractions
10 causing twisting and repetitive movements or abnormal postures

11 <u>focal dystonia:</u> dystonia symptoms are limited to one body are such as the neck in cervical
12 dystonia

13 <u>generalized dystonia:</u> dystonia symptoms mostly begin in one limb and gradually spread to
14 other limbs and the trunk

15 <u>Meige's syndrome:</u> includes symptoms of dystonia in several different facial muscles such as
16 the eyes, jaw, tongue and mouth

17 <u>torsion dystonia:</u> very rare and severe form of dystonia typically beginning in childhood or
18 adolescence

19

20 **Abbreviations**

21 BDI, Beck Depression Inventory; BSP, blepharospasm; CD, cervical dystonia; CDIP-58,
22 Cervical Dystonia Impact Profile; EEG, electroencephalogram; EMG, electromyogram; ESS,
23 Epworth Sleepiness Sclae; FMDRS, Burke–Fahn–Marsden rating scale of dystonia severity;
24 L-dopa, JRS, Jankovic Rating Scale for severity of blepharospasm; HAM-A, Hamilton
25 Rating Scale for Anxiety; levodopa; NMSQuest, nonmotor symptom questionnaire; n.a., not
26 applicable; NOA, number of awakenings; n.r., not reported; PSG, polysomnography; PSQI,
27 Pittsburgh Sleep Quality Index; REM sleep, rapid eye movement sleep; RLS, restless legs
28 syndrome; SE, sleep efficiency; SOL, sleep onset latency; SSS, Stanford Sleepiness Scale;
29 TST, total sleep time; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale;
30 UDRS, Unified Dystonia Rating Scale; WASO, wake time after sleep onset; WHOQOL,
31 World Health Organization Quality of Life Questionnaire; ↑ indicates significant increase; ↓
32 indicates significant decrease.

33

34

1 **Introduction**

2 Primary dystonia is a neurological movement disorder characterised by involuntary muscle

3 contractions causing twisting and repetitive movements or abnormal postures.[1] In contrast to

4 secondary dystonia that has a known causation, such as head injury or a side effect of

5 medication (tardive dystonia), the pathophysiological mechanisms of most forms of primary

6 dystonia are unknown and the diagnosis is based on clinical observations.[2] Primary dystonia

7 is considered the third most prevalent movement disorder after essential tremor and

8 Parkinson's disease. Its exact prevalence is unclear due to a high variability in prevalence

9 estimates between different studies. A recent review found that the prevalence estimates for

10 patients with primary dystonia seeking medical attention were between 24 and 50 per million

11 for early onset dystonia and between 136 to 430 per million for late onset dystonia.[3] Focal

12 forms of primary dystonia are limited to a specific part of the body, such as the eyelids in

13 blepharospasm or the neck in cervical dystonia (spasmodic torticollis), and typically begin in

14 adulthood. Generalised forms of dystonia, in contrast, are often early-onset and involve

15 several limbs and the trunk.

16

17 Various domains of quality of life, such as physical and social functioning and vitality, are

18 impaired in patients with dystonia,[4,5] which is, at least in part, attributable to the often

19 disabling, disfiguring and stigmatising nature of this disorder. Botulinum toxin injection into

20 the affected muscles is considered the first line treatment for cervical dystonia.[6] This

21 treatment is well tolerated and of longstanding efficacy for the improvement of abnormal

22 movement.[6,7] A limitation is that immune resistance may occur in some patients as a side

23 effect of repeated injections.[8] Pallidal deep brain stimulation is a newer treatment option for

24 patients with medically refractive dystonia.[9,10] Benefits of deep brain stimulation include

25 substantial improvements of dystonia symptoms, disability and quality of life in previously

1 treatment resistant patients [11]. A recent study found that treatment effects were maintained

2 three and five years after surgery [12]. On the other hand, deep brain stimulation bears a risk of

3 serious side effects. In a clinical trial of 40 patients with primary generalised or segmental

4 dystonia,[12] 49 new adverse events occurred between six months and five years after the brain

5 stimulation treatment, 21 of which were rated serious and were almost exclusively device

6 related. One participant attempted suicide shortly after the six-month visit during a depressive

7 episode. As for non-serious adverse events, the most commonly reported side effect were

8 dysarthria and transient worsening of dystonia.

9

10 Current treatment of dystonia tends to focus on the improvement of motor symptoms. The

11 importance of non-motor symptoms including abnormal sensory phenomena, psychiatric

12 symptoms, cognitive deficits, pain, and sleep disturbances is increasingly recognised;

13 although their aetiology and treatment options are insufficiently characterised.[13,14] Non-motor

14 symptoms have a large impact on the quality of life[15,16] and seem not to remit after botulinum

15 toxin treatment and deep brain stimulation.[14] This underlines that targeted clinical

16 assessment is necessary and treatments of non-motor syndromes need to be developed.

17 Importantly, patients with dystonia consider sleep to be a prime determinant of their quality

18 of life. There is a stronger link of quality of life with sleep than motor symptom severity in

19 patients living with dystonia.[5] These findings fit within the broader context that sleep

20 disorders are increasingly recognised as a frequent comorbidity of neurological disorders,[17]

21 with potential implications for early diagnosis, pathomechanistic insights, and treatment.

22

23 The aim of this review is to summarise the state of research, critically evaluate the

24 methodological quality of existing studies, and highlight areas requiring future investigation.

25 More specifically, we sought to identify research reporting on polysomnographically

1 determined sleep, self-reported sleep and variables associated with sleep such as side effects

2 of medication and depressive symptoms in patients living with primary dystonia.

3

Methods

Search strategy

A literature search was performed in July 2014 using PubMed, Medline via Ovid, PsycInfo,

PsycArticles via Proquest and Embase via Ovid. No restriction of publication date was

applied. To capture all relevant studies on aspects of sleep in different forms of dystonia, the

following comprehensive set of terms was used for a search in all fields:

'insom*' OR 'sleep*' OR 'wake*' OR 'nap*' OR 'polysomnogr*' OR 'actigr*' OR

'fatigue*' OR 'nightmare*' OR 'hypersom*' OR 'apnea*' OR 'circadian*' OR '(restless

leg*)' OR 'shiftwork*' OR 'bruxism*' OR 'drowsiness*' OR 'parasom**, linked to

'dystonia*' OR 'torticollis*' OR '(spasmodic dysphonia*)' OR '(musician* cramp)' OR

'(writer* cramp)' OR 'blepharospasm*' OR '(Meige* syndrome)'.

The reference lists of identified papers were screened for further relevant studies.

Selection Criteria

We first screened titles and abstracts for eligibility, which was confirmed by reading the full

paper. This was done by two raters (EH and CB) who worked independently. Discrepancies

between the two raters were resolved by discussion with a third author (NT). Studies were

included if they reported on patients with primary dystonia and included a quantitative or

qualitative psychological or physiological outcome measure of sleep. Studies were excluded

if they were not published original articles (i.e. secondary analyses, reviews, guidelines,

statements, meeting summaries, comments or unpublished abstracts), were investigating

animals, were reporting on tardive dystonia or dystonia in patients with another primary

1   disorder, or were published in languages other than English, German, French, Spanish, Italian

2   or Chinese. When potentially relevant unpublished abstracts were identified, the authors were

3   contacted and asked about a published article on the respective study.

4

5   *Data extraction*

6   Data extracted from the included studies were socio-demographical and clinical description

7   of the sample, diagnosis, study design, measures, statistical methods as well as results

8   concerning apparative measures of sleep (e.g., polysomnography), subjective measures of

9   sleep (e.g., questionnaires) and variables associated with sleep (e.g., symptom severity,

10   depressive symptoms). Data extraction for 20% of the included studies (n=4) was performed

11   by two authors working independently. Data extraction for the other studies was performed

12   by the first author. We present overall characteristics of the included studies and report

13   findings grouped by dystonia subtype.

14

15   *Assessment of risk of bias*

16   For each included study, the risk of bias originating from six different aspects of

17   methodology was assessed. The six aspects were the diagnostic process, sample size, nature

18   of control group, sleep measures, medication and statistics. The criteria for the ratings of low,

19   moderate, high or unclear risk of bias are pictured in table 1. The rating scheme has been

20   modified from the methodology checklist by the Agency for Healthcare Research and

21   Quality,[18] which has been recommended for cross-sectional studies in a recent systematic

22   review.[19] Following the recommendation of the Cochrane Collaboration,[20] which advises

23   against the use of summary scores, we use a descriptive approach. Risk of bias was assessed

24   by two independent raters. Conflicts were resolved by discussion.

25

1   - Please insert table 1 here -

2

3   **Results**

4   *Search Results*

5   The process of study selection is illustrated in Figure 1. After the automatic removal of

6   duplicates, we identified 1,445 records. After screening of titles and abstracts, 63 articles

7   were retained for fulltext assessment. Following examination of fulltexts, 18 articles were

8   included into the review. Included studies were published between 1976 and 2014. In total,

9   the included studies reported on 708 participants.

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11
12   - Please insert Figure 1 here -
13
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16

17   *Socio-demographic and clinical characteristics of the samples*

18   The main findings of the 18 studies, grouped by subtype of dystonia, are summarised in

19   Tables 2–5. Samples of patients with focal dystonia were older than those with generalised

20   dystonia. All but one study reported an equal gender distribution or included more females.

21   Age at onset of generalised dystonia was typically in childhood or adolescence, whereby the

22   onset of focal dystonia was in adulthood. Three studies (Silvestri et al. 1990,[34] Sforza et al.

23   1991,[21] Lobbezoo et al. 1996[22]) reported on drug-free participants. Two reports referred to

24   published criteria for the diagnosis of dystonia: Fish et al.[23] made diagnoses based on Fahn's

25   recommendations.[24] Avanzino et al.[25] used Albanese's diagnostic criteria.[26] None used the

26   ICD-10 criteria. Eight studies did not report on the diagnostic process at all. The other studies

1 stated that diagnoses were made by experienced movement specialists or neurologists, but did

2 not define any diagnostic criteria.

3

4 *Sleep measures*

5 Twelve studies included polysomnography (PSG) and seven included self-report measures of

6 sleep. Only Brüggemann et al., 2014[27] reported both PSG and self-reports. All authors using

7 PSG reported that scoring was performed visually according to the recommendations by

8 Rechtschaffen and Kales.[28] Only Fish et al., 1990[23] reported on the use of an automated EEG

9 analysis. Brüggemann et al.[22] and Gadoth et al.[31] performed one night of PSG. In all other

10 PSG studies, the duration was two or three nights including one adaptation night. Of the

11 seven studies reporting on self-ratings of sleep quality, five used validated sleep

12 questionnaires such as the Pittsburgh sleep quality index (PSQI)[29] and the Epworth sleepiness

13 scale (ESS).[30] The other two were the study by Klingelhoefer et al., [31] who used the

14 NMSQuest (non-motor symptom questionnaire), a non-motor symptom scale validated for

15 Parkinson's disease[32], and Miller et al.,[33] who used the sleep items of the Beck depression

16 inventory.[34]

17

18 *Study designs*

19 Fifteen papers reported cross-sectional case descriptions and cross-sectional group

20 comparisons. Two studies investigated the effects of L-dopa on PSG determined sleep.[35,36]

21 One study evaluated self-reported sleep quality before and after botulinum toxin injections.[37]

22 Fifteen studies included some form of control group, thirteen included healthy controls.

23 However, matching for age or age and sex was performed in only eight studies. Three of the

24 included studies by the same research group reported on the same sample of patients with

25 torsion dystonia.

1

2   To obtain a statistical power of 80% and a probability level of 5% for a t-test, a sample size

3   of approximately 20 participants per group is needed to detect a large group difference

4   (Cohen's d = 0.8); approximately 50 participants per group are needed to detect a moderate

5   difference (Cohen's d = 0.5), and approximately 310 participants per group are needed to

6   detect a small difference (Cohen's d = 0.2). Five studies, all on focal dystonia, were

7   sufficiently powered to detect a moderate effect,[25,31,37–39] none was sufficiently powered to

8   detect a small effect. Nine of the controlled studies included less than 20 participants per

9   group, thus were clearly underpowered.

10

11   *Risk of bias assessment*

12   The results of the risk of bias assessment are pictured in Figure 2. Together, the main issues

13   limiting the validity and generalisability of the results are the failure to use validated

14   diagnostic criteria, small heterogeneous samples, a lack of matching for age and sex, a

15   paucity of studies measuring both self-reported and PSG determined sleep, a lack of studies

16   on unmedicated patients, and insufficient reporting of the statistical approach.

17

18   - Please insert Figure 2 here -

19

20

21   *Main results*

22   We present the main results by dystonia subtype, beginning with the most prevalent (focal

23   cranial dystonia, Table 2), followed by generalised torsion dystonia (Table 3), dopa-

24   responsive dystonia (Table 4) and mixed dystonias (Table 5).

25

26
27

1

2   *Focal cranial dystonia, cervical dystonia and blepharospasm*

3   Cranial dystonia refers to different forms of focal dystonia localised in the head area.

4   Cervical dystonia (also called spasmodic torticollis) is a focal dystonia involving the neck,

5   causing an often painful involuntary turning of the head. Patients with blepharospasm,

6   another form of focal dystonia, suffer from involuntary muscle contractions of the eyelid.

7   Meige's syndrome includes symptoms of dystonia in several different facial muscles such as

8   the eyes, jaw, tongue and mouth. In contrast to dopa responsive dystonia and generalised

9   torsion dystonia, cranial dystonia mostly begins in adulthood and is associated with a lesser

10   degree of disability.

11

12   We found eight studies of patients with focal cranial dystonia (see Table 2): Silvestri et al.

13   (N=8), Sforza et al. (N=10), Lobbezoo et al. (N=9 with dystonia, N=9 controls), Trotti et al.

14   (N=43 with dystonia, N=49 healthy controls, N= 19 controls with other focal movement

15   disorders), Avanzino et al. (N=52 with blepharospasm, N=46 with cervical dystonia, N=56

16   healthy controls), Paus et al. (N=110 with blepharospasm, N=111 with cervical dystonia, N=

17   93 healthy controls), Eichenseer et al. (N=54 with dystonia N=55 healthy controls), and

18   Klingelhoefer et al. (N=102).

19   Only three small studies (Silvestri, Sforza, and Lobbezoo) used PSG in focal cranial dystonia.

20   Their results are inconclusive concerning PSG determined sleep continuity and architecture.

21   Sforza et al.[21] found a disturbed sleep continuity and abnormal sleep architecture in patients

22   with blepharospasm and oromandibular dystonia. Lobbezoo et al.[22] found no group

23   differences between patients with cervical dystonia and healthy controls. These differences

24   may be attributable to different subtypes of focal cranial dystonia. All three studies using

25   PSG in focal cranial dystonia found a marked decrease of frequency and duration, but not a

1 total disappearance of dystonic movement during sleep, most prominently in deeper NREM

2 sleep stages and REM sleep [21,22,40]. Silvestri et al. reported only on movement during sleep,

3 not on sleep continuity and architecture.

4 The remaining five larger studies investigated self-reported sleep [25,31,37–39]. Three studies

5 found reduced mean scores on the PSQI and an increased number of subjects with PSQI

6 scores in the clinical range compared to healthy controls [25,37,39]. The percentage of patients

7 with impaired sleep quality according to the PSQI varied between over 40% in the study by

8 Paus et al.[39] and over 70% in the study by Avanzino et al.[25] It is difficult to tell where this

9 considerable discrepancy stems from as both studies investigated outpatients with cervical

10 dystonia or blepharospasm and used the same criterion for impaired sleep quality (PSQI score

11 > 5). The BDI scores were only marginally higher in Avanzino's sample.[25] A normal daytime

12 sleepiness according to the ESS was found in four studies [25,37–39]. Patients in all questionnaire

13 studies were medicated, so that it cannot be ruled out that the impaired sleep quality occurred

14 as a side effect of medication. Two studies suggest that sleep quality impairment is associated

15 with depressive symptoms, but not with the severity of dystonia [25,39]. Interestingly, Paus et al.

16 found that impaired sleep quality was associated with symptoms of restless legs syndrome

17 (RLS) [39]. The percentage of patients with RLS was elevated in patients with dystonia

18 compared to healthy controls (20% of patients with blepharospasm, 18% of patients with

19 cervical dystonia, 2% of controls). Importantly, Eichenseer et al.[37] found that sleep quality

20 was not improved after botulinum toxin treatment despite a significant improvement of motor

21 functioning.

22 In summary, prevalence estimates for sleep disturbances are between 40 and 70% in patients

23 with focal cranial dystonia. The level of daytime sleepiness seems comparable to healthy

24 controls. Interestingly, impaired sleep quality was more prominently associated with

25 depressive symptoms than with the severity of motor symptoms. During PSG-measured

1 sleep, a marked decrease of the frequency and duration of dystonic movements was found.

2 Sleep quality was not improved after botulinum toxin treatment despite a significant

3 improvement of motor functioning.

4 - Please insert Table 2 here -

5 *Generalised torsion dystonia*

6 Generalised torsion dystonia is a rare and severe form of dystonia with a presumed significant

7 genetic component,[41] typically beginning in childhood or adolescence. In contrast to dopa

8 responsive dystonia, however, patients with torsion dystonia do not markedly respond to L-

9 dopa.

10

11 We found six studies on generalised torsion dystonia (Table 3): Wein and Golubev (N=12

12 with generalised dystonia, N=15 with focal torsion dystonia, N= 10 healthy controls), Jankel

13 et al. 1984 (N=9 with dystonia, N=9 healthy controls), Jankel et al. 1984a (N=1), Fish et al.

14 1990 (N=14 with dystonia, N=10 healthy controls, N=39 controls with other neurological

15 disorders), Fish et al. 1991 (N=12 with dystonia, N=12 controls), and Fish et al. 1991a (N=14

16 with dystonia, N=10 healthy controls). The three studies by Fish all included the same group

17 of participants with generalised torsion dystonia.

18

19 Disturbed PSG determined sleep continuity in patients with torsion dystonia was found by

20 both Wein & Golubev[42] and Jankel et al.[43] They found an increased sleep onset latency and

21 number of awakenings and a reduced total sleep time and sleep efficiency. However, due to

22 the methodology used in these studies, it cannot be concluded that the disturbed sleep

23 continuity was directly caused by dystonia. Wein & Golubev[42] did not report the medication

24 status of the patients and matching for age and sex with the control subjects was not

25 performed. Jankel et al.[43] investigated a small sample of medicated patients. Thus, it is

1   possible that the observed group differences were due to age and sex differences and sleep

2   continuity might have been disturbed by medication.

3

4   Abnormal sleep spindle activity was found by Wein & Golubev[42], Jankel et al. (1984)[43] and

5   Jankel et al. (1984a)[44], but was not replicated by Fish et al. 1990.[23] The former found an

6   increased number of unusually large sleep spindles (amplitudes larger than 80 respectively

7   150 microvolts) in their patients with severe generalised torsion dystonia. Jankel et al.[43]

8   report that three of their four patients presenting with this abnormality were on diazepam;

9   Wein & Golubev[42] did not report on the medication of their sample. It is plausible that the

10   sleep spindles with abnormally large amplitude were an effect of medication, most likely

11   benzodiazepines, which are known to produce a typical 'benzodiazepine signature' with

12   excessive sleep spindles.[45]

13   A reduced duration of REM sleep compared to healthy controls was found by Wein and

14   Golubev[42] and Jankel et al.[43] Since Wein and Golubev did not report the medication of their

15   patients, the mechanisms underpinning REM suppression remain speculative. In the study by

16   Jankel et al. (1984), REM suppression might be attributable to medication, e.g. diazepam

17   which was taken by half of the patients in their sample.

18

19   Concerning sleep-related movement, there are no definite, replicated findings. One study by

20   Fish et al. 1991[46] found that abnormal movements were rare during sleep and that abnormal

21   movements associated with awakening or lightening of sleep almost always occurred after the

22   stage change. This suggests that sleep continuity disturbance is not caused by dystonic

23   movement. Patients with Parkinson's disease often present with REM sleep behavior

24   disorder[47], which has been identified as a risk factor for the de novo onset of

25   synucleinopathies[48]. Fish et al. 1991[49] found that REM atonia was well maintained in patients

1   with torsion dystonia. There was no study on self-reported sleep in patients with generalised

2   torsion dystonia.

3

4   In summary, the present findings support the hypothesis that patients with torsion dystonia

5   suffer from a disturbed sleep continuity which occurs despite a marked decrease of abnormal

6   movement during sleep. This hypothesis needs to be tested in future research.

7

8   -   Please insert Table 3 here -

9

10   *Dopa responsive dystonia*

11   Dopa Responsive Dystonia, also known as hereditary progressive dystonia with marked

12   diurnal fluctuation or Segawa syndrome, is a rare form of generalised dystonia beginning in

13   childhood or adolescence.[50] Dystonia symptoms mostly begin in one foot and gradually

14   spread to other limbs. Patients without treatment are often severely impaired. The syndrome

15   is characterised by a marked worsening of symptoms over the course of the day, an

16   improvement after sleep and a considerable, sustained response to low doses of L-dopa. Dopa

17   responsive dystonia is frequently, but not always caused by mutations of the guanosine

18   triphosphate cyclohydrolase 1 gene (GCH1) leading to a reduction of dopamine synthesis.[51]

19   We found three studies on dopa responsive dystonia (Table 4): Segawa et al. (N=4), Gadoth

20   et al. (N=3 patients, N=11 phenotypically healthy immediate relatives) and Brüggemann et al.

21   (N=23 with dystonia, N=26 healthy controls). The results suggest that PSG determined and

22   subjective sleep continuity are by and large normal in patients with dopa responsive dystonia.

23   Brüggemann et al.[27] found an increased REM sleep latency. Segawa et al.[35] found that gross

24   body movements involving the trunk and twitches were 'few', but occurred in all sleep stages

25   including REM sleep, suggesting abnormal behavior during REM sleep. However, as the

1 study did not include healthy controls, it is difficult to judge to which extent the amount of

2 movement was abnormal. Gadoth et al.[36] observed increased movement during REM sleep

3 compared to phenotypically normal immediate relatives. Segawa[35] reported an increase of

4 abnormal movement during sleep after L-dopa, which was not replicated by Gadoth et al.[36]

5 Brüggemann et al.[27] investigated self-reported daytime sleepiness in a sample of 23 patients

6 with dystonia and did not find any significant differences compared to healthy controls.

7

8 In summary, the results suggest that PSG determined and self-reported sleep continuity are

9 normal in dopa responsive dystonia. Preliminary evidence of abnormal movement during

10 REM sleep has been found. However, the results must be classified as inconclusive because

11 PSG was only performed in very small samples of medicated patients.

12

13 - please insert Table 4 here -

14

15 *Mixed dystonias*

16 We found one study investigating mixed forms of dystonia (Table 5): Miller et al. (N=83

17 with primary dystonia, N=354 with Parkinsons's disease, N=53 with essential tremor). Using

18 the sleep-related items of the BDI as a measure of sleep disturbance, this study found that

19 55% of the patients with dystonia reported insomnia and 76% reported fatigue. These results

20 were comparable to patients with Parkinsons disease and essential tremor.

21

22

23

24 **Summary**

1   This review found that in patients with focal cranial dystonia, the most prevalent form of

2   primary dystonia, self-reported sleep quality is reduced compared to healthy controls.

3   Prevalence estimates for disturbed sleep were between 40 and 70%, although the level of

4   daytime sleepiness seems comparable to healthy subjects. Of particular note, impaired sleep

5   quality was more prominently associated with depressive symptoms than with the severity of

6   motor symptoms. A marked decrease of the frequency and duration, but not a total

7   disappearance of abnormal movement during sleep was observed in these patients. Sleep

8   quality was not improved after botulinum toxin treatment despite a significant improvement

9   of motor functioning. In generalised torsion dystonia, the results imply that patients present

10 with disturbed PSG determined sleep continuity. REM sleep atonia was well maintained in

11 generalised torsion dystonia, but the results suggest that abnormal movement during REM

12 sleep may be present in dopa responsive dystonia. Together, the literature provides

13 preliminary support for the notion that disturbed sleep is highly prevalent in patients with

14 primary dystonia. The pattern of reduced subjective sleep quality in the absence of daytime

15 sleepiness resembles insomnia.[52] Our results are in line with the broader notion that insomnia

16 symptoms are highly prevalent but underinvestigated and undertreated in patients with

17 neurological disorders.[17] According to the current guidelines by the European Federation of

18 Neurological Societies, botulinum toxin is the first line treatment for primary cranial and

19 cervical dystonia and pallidal deep brain stimulation can be considered if pharmacological

20 treatment fails [53]. Future research is necessary to evaluate more thoroughly whether these

21 treatments are sufficiently effective to improve sleep. If not, the development and evaluation

22 of specialized sleep treatments for dystonia is warranted.

23

24

25

1 **Potential mediators of sleep disturbance in dystonia**

2 While the results consistently indicate that patients with focal cranial dystonia suffer from

3 reduced sleep quality as measured by validated self-report questionnaires, the mediators of

4 sleep disturbance remain poorly understood. The reported disturbances of sleep continuity are

5 unspecific and can be found in many other neurological disorders.[17]

6 A first hypothesis is that sleep disturbances stem from the same brain dysfunction that causes

7 dystonia. Whereas the pathophysiology of dystonia is not yet fully understood, it can be

8 speculated that the disorder stems from a malfunction of brain areas associated with

9 movement, such as the basal ganglia. The dramatic response to L-dopa in dopa responsive

10 dystonia points to an involvement of the dopaminergic system at least in some forms of

11 dystonia. Further support for the hypothesis of an involvement of the dopaminergic system

12 stems from tardive dystonia, which occurs as a side effect of antidopaminergic medication

13 and clinically mimics primary dystonia.[54] Research also supports a potential role of dopamine

14 in the maintenance of wakefulness,[55] suggesting that dystonia and sleep disturbance may be

15 due to the same pathological mechanisms. This, however, remains a speculative hypothesis

16 which is to be tested in future research.

17

18 A second hypothesis is that sleep disturbances occur as a side effect of medication. Patients

19 with cervical dystonia in the presented studies were mostly treated with botulinum toxin,

20 which is the first line treatment for focal cervical dystonia.[6] Botulinum toxin is not known to

21 disturb sleep. A considerable percentage of patients, however, were treated with other

22 medications. Eichenseer et al.[37] provide a detailed report of the medication in addition to

23 botulinum toxin for their sample of 54 patients with cervical dystonia: 35% took

24 benzodiazepines, 20% took antidepressants, 7% took baclofen and 4% took anticholinergics.

25 Benzodiazepines and benzodiazepine receptor agonists are an established treatment for short-

1 term insomnia.[56] However, they are also known to supress slow wave sleep[57] and have the

2 potential to produce morning sleepiness, sedation and rebound insomnia after

3 discontinuation,[58] and may therefore be responsible for a reduced sleep quality in some

4 patients. Most antidepressants, including selective serotonin reuptake inhibitors (SSRIs), are

5 known to supress REM sleep.[59] SSRIs can disturb sleep continuity in some patients with

6 dystonia.[60] Thus, it cannot be excluded that reduced sleep quality occurs as a side effect of

7 medication in patients with dystonia.

8

9 A third hypothesis is that sleep disturbance is caused by dystonic movement and associated

10 pain. However, several findings speak against the assumption that impaired sleep quality is

11 predominantly caused by abnormal movement. First, dystonia severity was not correlated

12 with self-reported sleep in three studies.[25,38,39] Second, Eichenseer et al.[37] found that sleep

13 quality was not improved after botulinum toxin treatment despite a significant improvement

14 of motor symptoms. Third, several studies demonstrated that the frequency and duration of

15 abnormal movement considerably decreases during sleep.[21,22,40,46] The latter is an interesting

16 but so far poorly understood phenomenon which could potentially be informative about the

17 pathophysiology and the development of new treatments. It could possibly be indicative of a

18 normal functioning of descending motor inhibition during sleep – or a positive effect of sleep

19 on the brain regions that produce abnormal movement. However, Lobbezoo et al.[22] found that

20 abnormal movements were already markedly decreased after patients had adopted a supine

21 position without the intention to fall sleep. This suggests that the decrease in abnormal

22 movement may be associated with the supine position rather than sleep itself. As one study

23 found that RLS was more prevalent in patients with dystonia than in controls, and that RLS

24 was associated with disturbed sleep [39], it is also possible that sleep disturbance is at least in

25 part mediated by RLS. This needs to be further elucidated in future research.

A fourth hypothesis is that psychological distress is a mediator of sleep disturbance. A recent study measuring health related quality of life in 70 patients with cervical dystonia found that 47% reported feeling depressed, annoyed or bitter, 33% felt lonely or isolated, and 73% reported feeling uneasy in public, probably due to visible symptoms of dystonia.[61] Two studies found that PSQI scores were positively correlated with BDI scores in patients with focal dystonia [25,39].

In summary, while some evidence suggests that depressive symptoms are associated with sleep disturbance in patients with cervical dystonia, the exact pathophysiological pathways remain to be further elucidated.

Implications for treatment

Our review puts the idea forward that sleep disturbances might, at least in part, mediate a decrease in quality of life in patients with primary dystonia. However, since quality of life has not been directly measured in the studies included in this review, the association between sleep disturbance and quality of life needs to be further elucidated in future research. Still, focussing on non-motor symptoms, such as sleep disturbances, might provide new inroads into treatment. In the first place, clarification of the nature of the sleep disturbances or sleep disorders associated with different subtypes of dystonia is needed. Future research is then needed to evaluate the efficacy of state-of-the-art treatment for the improvement of sleep disturbance and related symptoms. Targeted sleep interventions need to be developed for patients with dystonia if existing treatments are ineffective concerning sleep disturbance.

1 **Limitations**

2 Our review has several limitations. Unpublished literature was not considered, which may

3 have led to a publication bias, i.e. an overrepresentation of studies which found differences

4 between dystonia patients and controls. The rationale for restricting the review to published

5 literature was to include only research of adequate quality which had passed through a peer

6 review process. The limitations of the included studies also limit the validity of the review.

7 Few of the studies on sleep in patients with dystonia are of sufficient methodological quality

8 (see Fig. 2). First, as different kinds of sleep disturbance represent a potential side effect of

9 many medications, it is a significant limitation that only three studies reported on drug-free

10 samples. Second, considering that the prevalence of insomnia is increased in older subjects

11 and in women,[62,63] it is also an apparent failure that less than half of the studies included a

12 group of healthy controls matched for age and sex. Third, only two studies defined dystonia

13 based on published diagnostic criteria, complicating the comparability between different

14 studies. Fourth, the small sample sizes especially in the PSG studies are a further limitation –

15 they are, however, understandable in studies on dopa responsive dystonia and generalised

16 torsion dystonia, as the prevalence of these disorders is low. Future studies should fulfil the

17 following methodological standards: use a prospective controlled study design, include

18 measures of subjective sleep, objective sleep and potential processes associated with sleep

19 disturbance, investigate unmedicated patients, match patients and controls for age and sex,

20 diagnose dystonia according to a published set of diagnostic criteria and describe the

21 diagnostic process in sufficient detail, and use sufficiently large samples or increase the

22 duration of the study to create greater testing power by generating more data points.

23

24 **Future Research Priorities**

1   This review demonstrates that there is a need for more high quality research on sleep in

2   patients with dystonia. First, characteristics of self-reported and PSG determined sleep and

3   sleep disturbance need to be assessed more rigorously in larger drug-free samples compared

4   to age- and sex-matched healthy subjects. For example, it needs to be further investigated

5   whether self-reported sleep disturbances in patients with focal cranial dystonia are reflected

6   in PSG determined sleep continuity, architecture or microstructure. The preliminary findings

7   indicating a marked decrease of abnormal movement during sleep in focal dystonia, abnormal

8   movement during REM sleep in dopa responsive dystonia and well maintained REM atonia

9   in generalised torsion dystonia need replication. Studies on self-reported sleep in generalised

10   dystonia and sleep studies in patients with other forms of dystonia, such as writer's cramp,

11   musician's cramp or spasmodic dysphonia need to be conducted.

12   Second, the hypotheses concerning the aetiology of sleep disturbances outlined in this review

13   need to be tested. The role of abnormal brain functioning, abnormal movement, pain, and

14   psychological distress as mediators of sleep disturbance needs further investigation. Daily

15   process studies[64] would be suitable to tease apart the temporal associations between these

16   constructs.

17   Third, sleep needs to be targeted in therapy. Preliminary evidence suggests that sleep is not

18   sufficiently improved after botulinum toxin treatment, thus sleep quality should be included

19   as an outcome in treatment studies. If the finding that sleep is not improved after state of the

20   art treatment is replicated, standard sleep treatments such as cognitive behavioural therapy for

21   insomnia need to be evaluated and, if necessary, adapted for patients with dystonia. It has

22   been shown that cognitive behavioural therapy is effective in patients with insomnia and

23   comorbid medical disorders,[65,66] thus it can be speculated that this treatment may also

24   improve sleep in patients with dystonia. A first step, however, is to evaluate the efficacy of

25   existing state of the art treatments such as botulinum toxin treatment for improving sleep.

Newer forms of behaviour therapy such as acceptance and commitment therapy are currently evaluated for the improvement of quality of life in patients with chronic sleep disturbance.[67] As this therapy is disorder unspecific and has a special focus on the improvement of quality of life, it may be tested as another psychological approach for the improvement of non-motor syndromes in patients with dystonia.

Practice Points

- Research suggests a prevalence of impaired sleep quality between 40 and 70% in patients with focal cranial dystonia. Impaired quality of life in patients with dystonia might, at least in part, be mediated by non-motor symptoms, including sleep disturbances. Current research indicates that patients with focal cranial dystonia do not suffer from excessive daytime sleepiness.
- Patients with dystonia should routinely be assessed for disturbed sleep.
- Brief, validated sleep questionnaires such as the Pittsburgh Sleep Quality Index can be used to screen for sleep disturbances.
- The occurrence of sleep disturbances as a side effect of medication should be carefully monitored.
- Preliminary research results suggest that botulinum toxin treatment is not effective to improve sleep in cervical dystonia.
- Short term treatment with benzodiazepines and cognitive behavioural therapy for insomnia are effective treatments for patients with insomnia comorbid with medical disorders, but have not yet been investigated in patients with dystonia. However, since patients with dystonia may already be on sedating medications for their dystonia, caution is neccessary before adding hypnotic medication for insomnia.

Research Agenda

- Characteristics of sleep as measured with PSG and validated self-report instruments need to be assessed more rigorously in larger drug-free samples of patients with primary dystonia compared to age- and sex-matched healthy controls.
- Sleep in patients with previously uninvestigated forms of dystonia, such as focal hand dystonia and spasmodic dysphonia, should also be investigated.

1 ▪ Research into the aetiology of sleep disturbances in patients with dystonia is needed.
2 More specifically, the role of abnormal brain functioning, abnormal movement, pain, and
3 psychological distress as mediators of sleep disturbance needs further investigation.

4 ▪ Psychological processes potentially linked to insomnia in dystonia such as dysfunctional
5 beliefs and attitudes about sleep, anxiety and preoccupation, sleep effort, and sleep
6 hygiene practice need to be assessed.

7 ▪ Sleep quality should be included as an outcome in treatment studies.

8 ▪ Preliminary results suggest that botulinum toxin is ineffective for the improvement of
9 sleep in cervical dystonia despite a significant improvement of dystonia symptoms, thus
10 targeted sleep interventions should be developed and evaluated.

11

1 **References (* indicates 10 most important key references)**

2 1. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VSC *et al.*
3   Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013; **28**:
4   863–873.

5 2. LeDoux MS. Dystonia: phenomenology. *Parkinsonism Relat Disord* 2012; **18 Suppl 1**:
6   S162–164.

7 3. Defazio G. The epidemiology of primary dystonia: current evidence and perspectives.
8   *Eur J Neurol* 2010; **17 Suppl 1**: 9–14.

9 4. Zetterberg L, Aquilonius S-M, Lindmark B. Impact of dystonia on quality of life and
10   health in a Swedish population. *Acta Neurol Scand* 2009; **119**: 376–382.

11 5. *Soeder A, Kluger BM, Okun MS, Garvan CW, Soeder T, Jacobson CE *et al.* Mood and
12   energy determinants of quality of life in dystonia. *J Neurol* 2009; **256**: 996–1001.

13 6. Marsh WA, Monroe DM, Brin MF, Gallagher CJ. Systematic review and meta-analysis of
14   the duration of clinical effect of onabotulinumtoxinA in cervical dystonia. *BMC Neurol*
15   2014; **14**: 91.

16 7. Ramirez-Castaneda J, Jankovic J. Long-term efficacy, safety, and side effect profile of
17   botulinum toxin in dystonia: A 20-year follow-up. *Toxicon* 2014; **90**: 344–348.

18 8. Chen S. Clinical uses of botulinum neurotoxins: current indications, limitations and future
19   developments. *Toxins* 2012; **4**: 913–939.

20 9. Hu W, Stead M. Deep brain stimulation for dystonia. *Transl Neurodegener* 2014; **3**: 2.

21 10. Bjerknes S, Skogseid IM, Sæhle T, Dietrichs E, Toft M. Surgical site infections after deep
22   brain stimulation surgery: frequency, characteristics and management in a 10-year period.
23   *PLoS ONE* 2014; **9**: e105288.

24 11. Kupsch A, Benecke R, Müller J, Trottenberg T, Schneider G-H, Poewe W, et al. Pallidal
25   deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med*
26   2006;**355**: 1978–90.

27 12. Volkmann J, Wolters A, Kupsch A, Müller J, Kühn AA, Schneider G-H et al. Pallidal
28   deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year
29   follow-up of a randomised trial. *Lancet Neurol* 2012; **11**: 1029–1038.

30 13. *Kuyper DJ, Parra V, Aerts S, Okun MS, Kluger BM. Nonmotor manifestations of
31   dystonia: a systematic review. *Mov Disord* 2011; **26**: 1206–1217.

32 14. *Stamelou M, Edwards MJ, Hallett M, Bhatia KP. The non-motor syndrome of primary
33   dystonia: clinical and pathophysiological implications. *Brain* 2012; **135**: 1668–1681.

34 15. Ben-Shlomo Y, Camfield L, Warner T, ESDE collaborative group. What are the
35   determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg*
36   *Psychiatr* 2002; **72**: 608–614.

16. Page D, Butler A, Jahanshahi M. Quality of life in focal, segmental, and generalized dystonia. *Mov Disord* 2007; **22**: 341–347.

17. Mayer G, Jennum P, Riemann D, Dauvilliers Y. Insomnia in central neurologic diseases – Occurrence and management. *Sleep Med Rev* 2011; **15**: 369–378.

18. Manchikanti L, Singh V, Smith HS, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: part 4: observational studies. *Pain Physician* 2009;**12**:73–108.

19. Zeng X, Zhang Y, Kwong JSW, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for pre-clinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med* 2015; **8**:2-10.

20. Higgins JPT, Green S (eds): Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

21. Sforza E, Montagna P, Defazio G, Lugaresi E. Sleep and cranial dystonia. *Electroencephalogr Clin Neurophysiol* 1991; **79**: 166–169.

22. *Lobbezoo F, Thu TM, Rémillard G, Montplaisir JY, Lavigne GJ. Relationship between sleep, neck muscle activity, and pain in cervical dystonia. *Can J Neurol Sci* 1996; **23**: 285–290.

23. *Fish DR, Allen PJ, Sawyers D, Marsden CD. Sleep spindles in torsion dystonia. *Arch Neurol* 1990; **47**: 216–218.

24. Fahn S, Marsden CD, Calne DB, others. Classification and investigation of dystonia. *Mov Disord* 1987; **2**: 332–358.

25. *Avanzino L, Martino D, Marchese R, Aniello MS, Minafra B, Superbo M *et al.* Quality of sleep in primary focal dystonia: a case-control study. *Eur J Neurol* 2010; **17**: 576–581.

26. Albanese A, Barnes MP, Bhatia KP, Fernandez-Alvarez E, Filippini G, Gasser T *et al.* A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force. *Eur J Neurol* 2006; **13**: 433–444.

27. Brüggemann N, Stiller S, Tadic V, Kasten M, Münchau A, Graf J *et al.* Non-motor phenotype of dopa-responsive dystonia and quality of life assessment. *Parkinsonism Relat Disord* 2014; **20**: 428–431.

28. Rechtschaffen A, Kales A. *A manual of standardized terminology, scoring system for sleep stages of human subjects*. Washington, DC: U.S. Dept. of Health, Education and Welfare; 1968.

29. Buysse DJ, Reynolds CF, Monk TH, Berman SR. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* 1989; **28**: 193–213.

30. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14**: 540–545.

31. Klingelhoefer L, Martino D, Martinez-Martin P, Sauerbier A, Rizos A, Jost W *et al.* Nonmotor symptoms and focal cervical dystonia: Observations from 102 patients. *Basal Ganglia* 2014; **4**: 117–120.

32. Rios Romenets S, Wolfson C, Galatas C, Pelletier A, Altman R, Wadup L *et al.* Validation of the non-motor symptoms questionnaire (NMS-Quest). *Parkinsonism Relat Disord* 2012; **18**: 54–58.

33. Miller KM, Okun MS, Fernandez HF, Jacobson CE, Rodriguez RL, Bowers D. Depression symptoms in movement disorders: comparing Parkinson's disease, dystonia, and essential tremor. *Mov Disord* 2007; **22**: 666–672.

34. Beck AT, Steer R, Brown G. *Beck Depression Inventory, 2nd edn. Manual*. San Antonio: The Psychological Corporation; 1996.

35. Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. *Adv Neurol* 1976; **14**.

36. Gadoth N, Costeff H, Harel S, Lavie P. Motor abnormalities during sleep in patients with childhood hereditary progressive dystonia, and their unaffected family members. *Sleep* 1989; **12**: 233–238.

37. *Eichenseer SR, Stebbins GT, Comella CL. Beyond a motor disorder: a prospective evaluation of sleep quality in cervical dystonia. *Parkinsonism Relat Disord* 2014; **20**: 405–408.

38. *Trotti LM, Esper CD, Feustel PJ, Bliwise DL, Factor SA. Excessive daytime sleepiness in cervical dystonia. *Parkinsonism Relat Disord* 2009; **15**: 784–786.

39. *Paus S, Gross J, Moll-Müller M, Hentschel F, Spottke A, Wabbels B *et al.* Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study. *J Neurol* 2011; **258**: 1835–1840.

40. Silvestri R, De Domenico P, Di Rosa AE, Bramanti P, Serra S, Di Perri R. The effect of nocturnal physiological sleep on various movement disorders. *Mov Disord* 1990; **5**: 8–14.

41. Brüggemann N, Stiller S, Tadic V, Kasten M, Münchau A, Graf J *et al.* Non-motor phenotype of dopa-responsive dystonia and quality of life assessment. *Parkinsonism Relat Disord* 2014; **20**: 428–431.

42. Wein A, Golubev V. Polygraphic analysis of sleep in dystonia musculorum deformans. *Waking Sleeping* 1979; **3**: 41–50.

43. Jankel WR, Niedermeyer E, Graf M, Kalsher M. Polysomnography of torsion dystonia. *Arch Neurol* 1984; **41**: 1081–1083.

44. Jankel WR, Niedermeyer E, Graf M, Kalsher MJ. Case report: polysomnographic effects of thalamotomy for torsion dystonia. *Neurosurgery* 1984; **14**:495–8.

45. Feige B, Voderholzer U, Riemann D, Hohagen F, Berger M. Independent sleep EEG slow-wave and spindle band dynamics associated with 4 weeks of continuous application of short-half-life hypnotics in healthy subjects. *Clin Neurophysiol* 1999; **110**: 1965–1974.

46. *Fish DR, Sawyers D, Allen PJ, Blackie JD, Lees AJ, Marsden CD. The effect of sleep on the dyskinetic movements of Parkinson's disease, Gilles de la Tourette syndrome, Huntington's disease, and torsion dystonia. *Arch Neurol* 1991; **48**: 210–214.

47. Chahine LM, Kauta SR, Daley JT, Cantor CR, Dahodwala N. Surface EMG activity during REM sleep in Parkinson's disease correlates with disease severity. *Parkinsonism Relat Disord* 2014; **20**: 766–771.

48. Iranzo A, Stockner H, Serradell M, Seppi K, Valldeoriola F, Frauscher B *et al.* Five-year follow-up of substantia nigra echogenicity in idiopathic REM sleep behavior disorder. *Mov Disord* 2014; **29**: 1774–1780.

49. Fish DR, Sawyers D, Smith SJ, Allen PJ, Murray NM, Marsden CD. Motor inhibition from the brainstem is normal in torsion dystonia during REM sleep. *J Neurol Neurosurg Psychiatr* 1991; **54**: 140–144.

50. Segawa M. Dopa-responsive dystonia. *Handb Clin Neurol* 2011; **100**: 539–557.

51. Cai C, Shi W, Zeng Z, Zhang M, Ling C, Chen L *et al.* GTP cyclohydrolase I and tyrosine hydroxylase gene mutations in familial and sporadic dopa-responsive dystonia patients. *PLoS ONE* 2013; **8**: e65215.

52. Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M *et al.* The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 2010; **14**: 19–31.

53. Albanese A, Asmus F, Bhatia KP, Elia AE, Elibol B, Filippini G, *et al.* EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol* 2011;**18**: 5–18.

54. Mehta SH, Morgan JC, Sethi KD. Drug-induced Movement Disorders. *Neurol Clin* 2015; **33**: 153–174.

55. Dauvilliers Y, Tafti M, Landolt HP. Catechol-O-methyltransferase, dopamine, and sleep-wake regulation. *Sleep Med Rev* 2014. doi:10.1016/j.smrv.2014.10.006.

56. Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M *et al.* The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med* 2007; **22**: 1335–1350.

57. Aeschbach D, Dijk DJ, Trachsel L, Brunner DP, Borbély AA. Dynamics of slow-wave activity and spindle frequency activity in the human sleep EEG: effect of midazolam and zopiclone. *Neuropsychopharmacology* 1994; **11**: 237–244.

58. Kales A, Kales JD. Sleep laboratory studies of hypnotic drugs: efficacy and withdrawal effects. *J Clin Psychopharmacol* 1983; **3**: 140–150.

59. Bridoux A, Laloux C, Derambure P, Bordet R, Monaca Charley C. The acute inhibition of rapid eye movement sleep by citalopram may impair spatial learning and passive avoidance in mice. *J Neural Transm* 2013; **120**: 383–389.

60. Wilson SJ, Nutt DJ. SSRIs and Sleep in Man. In: *Sleep and Sleep Disorders*. New York City: Springer US; 2006. pp 269–273.

61. Werle RW, Takeda SYM, Zonta MB, Guimarães ATB, Teive HAG. The physical, social and emotional aspects are the most affected in the quality of life of the patients with cervical dystonia. *Arq Neuropsiquiatr* 2014; **72**: 405–410.

62. Sivertsen B, Krokstad S, Øverland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. *J Psychosom Res* 2009; **67**: 109–116.

63. Zhang B, Wing Y-K. Sex differences in insomnia: A meta-analysis. *Sleep* 2006; **29**: 85–93.

64. Tang NKY, Goodchild CE, Sanborn AN, Howard J, Salkovskis PM. Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. *Sleep* 2012; **35**: 675–687A.

65. Vitiello MV, McCurry SM, Shortreed SM, Balderson BH, Baker LD, Keefe FJ *et al.* Cognitive-behavioral treatment for comorbid insomnia and osteoarthritis pain in primary care: the lifestyles randomized controlled trial. *J Am Geriatr Soc* 2013; **61**: 947–956.

66. Rybarczyk B, Stepanski E, Fogg L, Lopez M, Barry P, Davis A. A placebo-controlled test of cognitive-behavioral therapy for comorbid insomnia in older adults. *J Consult Clin Psych* 2005; **73**: 1164.

67. Hertenstein E, Thiel N, Lueking M, Kuelz AK, Schramm E, Spiegelhalder K *et al.* Quality of Life Improvements after Acceptance and Commitment Therapy (ACT) in Nonresponders to Cognitive Behavioral Therapy for Primary Insomnia (CBT-I). *Psychother Psychosom* 2014; **83**: 371-373.

Figure Legends

Figure 1. Process of study selection

Figure 2. Rating of risk of bias originating from six different aspects of methodology (see ordinate). The abscissa shows the total number of studies with low, moderate, high and unclear risk of bias. Ratings were made according to Table 1.

Table 1. Scheme for the rating of risk of bias in included primary studies

	Risk of bias rating			
	low	moderate	high	unclear
Diagnostic process	diagnosis according to established, published criteria	diagnostic process is described in sufficient detail, but no published criteria were used	authors mention who performed the diagnosis (e.g., experienced movement specialists) but do not describe the diagnostic process itself	diagnostic process not described
Sample size	≥ 100 per group (sufficient to detect an effect of Cohen's d=0.35)	21-99 per group	< 20 per group (not sufficient to detect a sample size of Cohen's d = 0.8)	sample size not mentioned
Control group	healthy controls matched for age and sex	unmatched healthy controls, matched only for age or only for sex, historical control group, controls with another disorder but no healthy controls	no control group	not mentioned whether control group was included
Sleep measure	valid sleep measures of subjective *and* objective sleep, e.g. PSG performed according to published recommendations and one validated questionnaire	one adequate sleep measure, e.g. PSG *or* validated questionnaire(s)	PSG not performed according to published recommendations (e.g., only one night of PSG), questionnaire insensitive or otherwise inappropriate or unvalidated	measures not sufficiently described
Medication	unmedicated sample	medicated sample, medication reported in detail	medicated sample, medication insufficiently described	medication not described
Statistics	analysis/statistical approach is adequate for design and sample size, conditions for use of statistical approach tested and described in sufficient detail	minor shortcomings leading to imprecision, but not invalidation of the results, e.g. conditions for use of statistical approach not tested or not described	major shortcomings, e.g. no significance testing, inappropriate statistical procedure	statistical approach not sufficiently described

Table 2. Sleep in focal cranial dystonia (cervical dystonia and blepharospasm)					
Citation	**Sample** (mean age) (% female) (ON, onset resp. DU, duration of dystonia) medication	**Measures**	**Sleep Results**		
			PSG-determined	**self-reported**	**variables associated with sleep disturbance**
Silvestri et al. 1990 [40]	N=8 (64y) (63%f) (ON n.r.) Meige's syndrome (N=6), BSP (N=1), tonic foot syndrome (N=1), drug-free	at least 2 nights of PSG	**abnormal movement** considerable decrease of frequency and duration, but not disappearance of abnormal movements in all sleep stages compared to wakefulness	n.r.	
Sforza et al. 1991 [21]	N=10 (52±13.7y) (50%f) (ON n.r.) blepharospasm and oromandibular dystonia, drug-free comparison to published norm values matched for age and sex	three nights of PSG	**disturbed continuity** SE↓ WASO↑ NOA↑ **disturbed architecture** % REM↓ % stage N1 ↑ **abnormal movement** spasms significantly decreased with deeper sleep, without disappearance of abnormal movement, gradual re-occurrence later in the night	n.r.	sleep disturbance more marked in patients with more severe dystonia
Lobbezoo et al. 1996 [22]	N=9 (42±7.6y) (44%f) (DU 4.8±3.4y) cervical dystonia, drug-free N=9 healthy controls matched for age and sex	two nights of PSG, additional EMG of sternocleidomastoid and upper trapezius muscle	**normal continuity** no group difference for SOL, WASO, SE, NOA **normal architecture** no group difference for REM latency, % of sleep stages, number of stage shifts **abnormal movement** significant decrease of abnormal muscle contractions until first stage N2	n.r.	

			Normal activity levels throughout night from first stage N2.		
Trotti et al. 2009 [38]	N=43 (57.4y) (63%f) (ON n.r.) cervical dystonia, medicated with botox N=19 with other focal movement disorders N=49 healthy controls matched for age and sex	ESS, TWSTRS	n.r.	**normal mean daytime sleepiness** ESS 7.23± 3.98, n.s. compared to both controls; % with excessive daytime sleepiness↑ (21%)	**anticholinergic medication** accounted for some but not all increase in excessive daytime sleepiness age, sex, race, dystonia severity, other medication not associated with excessive daytime sleepiness
Avanzino et al. 2010 [25]	N=52 with BSP (67y) (75%f) (DU 6y) medicated with botox N=46 with CD (60y) (67%f) (DU 10.5y) medicated N=56 healthy controls matched for age and sex	PSQI, ESS, BDI, FMDRS	n.r.	**reduced sleep quality** % with reduced sleep quality↑ (75% in BSP, 72% in CD) mean PSQI score↑ (7.5 in BSP, 7 in CD) **normal daytime sleepiness** normal % with excessive daytime sleepiness (7.7% in BSP, 8.7 in CD) normal mean ESS score	dystonia severity and duration uncorrelated with PSQI in BSP. In CD, no correlation with PSQI when adjusted for BDI. **BDI** score accounted for poorer sleep quality only in CD
Paus et al. 2011 [39]	N=110 with BSP (66.2±11.2y) (68%f) (DU 10.7±8.9y) part of the sample medicated, mostly with botox N=111 with CD (59.8±11.5y) (68%f) (DU 15.4±10.2y) medicated N=93 healthy controls, no matching	PSQI, ESS, BDI, TWSTRS, JRS	n.r.	**reduced sleep quality** % with disturbed sleep quality↑ (BSP 46%, CD 44%) mean PSQI score↑ (BSP: 6.0±4.2, CD: 6.3±3.7) **normal daytime sleepiness** normal % with excessive daytime sleepiness (BSP 7%, CD 5%) % with RLS↑ (BSP 20%, CD 18%)	correlated with PSQI in BSP: **sex (higher in women), dystonia duration, RLS, BDI** correlated with PSQI in CD: **RLS, bruxism, BDI.** uncorrelated with PSQI in both groups: symptom severity, pain
Eichenseer et al. 2014 [37]	N=54 with CD (62±10.1y) (80%f)	PSQI, ESS, BDI,	n.r.	**reduced sleep quality** % with disturbed sleep	no improvement in PSQI or ESS after treatment with botox despite

				quality↑ (65%) mean PSQI score↑ (baseline 7.5±4.2) **normal daytime sleepiness** normal % with excessive daytime sleepiness normal mean ESS score (baseline 5.04±4.0)	improvement in dystonia severity
	(DU 18.7±14.7y) medicated N=55 healthy controls matched for age and sex	HAM-A, TWSTRS, CDIP-58			
Klingelhoefer et al., 2014 [31]	N=102 with CD (59.19±1.21y) (68%f) (DU 10.99±7.10y) medicated with botox	clinical consultation, aided by supplementary use of questions from the NMSQuest, validated for use in Parkinson's disease UDRS	n.r.	percentage of "yes" answers: 60% difficulties falling or staying asleep; 51% fatigue which limits daytime activities; 40% feeling not refreshed after sleep	weak but significant correlation between number of non-motor syptoms and motor severity assessed with UDRS (r=0.23)

"normal" and "abnormal" refer to comparisons with the respective control groups.

Table 3. Sleep in generalised torsion dystonia						
Citation	**Sample n (mean age) (% female) (ON onset resp. DU duration of dystonia) medication**	**Measures**	**Sleep Results**			**Comment**
			PSG-determined	**self-reported**	**correlates of sleep disturbance**	
Wein & Golubev 1979 [42]	N=27 (31y) (% f n.r) (DU 6.5y), N=12 with generalized and N=15 with focal torsion dystonia, medication n.r. N=10 healthy controls (matching n.r.)	three nights of PSG	**disturbed continuity** SOL↑ TST↓ **disturbed architecture** REM latency↑ REM duration↓ **disturbed microstructure** spindle amplitude↑, spindles with amplitudes 40-60, 60-80 and over 80 microvolts more frequent in generalized torsion dystonia than controls and focal dystonia **abnormal movement** number of rapid eye movements and minor body movements↓	n.r.	sleep abnormality more pronounced in patients with generalized than focal torsion dystonia; sleep spindle abnormality only in generalized dystonia	statistical significance of group differences not clearly reported Medication n.r. sleep spindle abnormality likely influenced by medication (benzodiazepine signature)
Jankel et al. 1984 [43]	N=9 (38y) (50%f) (DU 20y) medicated N=9 healthy controls matched for age and sex	three nights of PSG	**disturbed continuity** SOL↑ NOA↑ SE↓ **disturbed architecture** REM duration↓ **disturbed microstructure** spindle amplitude↑, spindles with amplitudes > 150 microvolts were only observed in severely affected patients	n.r.	disturbed sleep continuity correlated with severity of dystonia; sleep spindle abnormality only in severely affected patients	sleep spindle abnormality in N=4, of which N=3 treated with diazepam
Jankel et al. 1984a [44]	N=1 (32y) (100%f, ON 29y) medicated, unilateral stereotactic thalamotomy of left	three nights of PSG	**disturbed continuity** baseline: TST↓ SE↓ SOL↑ **disturbed architecture**	n.r.	**improvement with surgery**: improved sleep continuity and architecture, marked decrease in sleep spindles	baseline medication status not clearly reported, sleep spindle abnormality may be due

	ventral lateral nucleus N=1 healthy control matched for age and sex		% stage N2↑ **disturbed microstructure** spindle amplitude↑, spindles with amplitudes > 100 microvolts were observed in the patient			to benzodiazepine intake
Fish et al. 1990 [23]	N=14 (28.5y) (57%f) (ON 19y) medicated N=10 healthy controls, no matching N=39 patients with other neurological disorders	two nights of PSG (one adaptation night, one study night)	**normal microstructure** normal spindle number in all but 3 patients normal spindle amplitude in all but 1 patient (proportions of spindles above 50 and 100 microvolts were measured)	n.r.	All 3 patients with abnormal sleep spindles had severe dystonia and were on diazepam	no evidence of disease-specific spindle abnormality in torsion dystonia in this study
Fish et al. 1991 [46]	N=12 (see Fish et al. 1990), medicated N=8 healthy controls, no matching	two nights of PSG, amendments to describe sleep stage transitions applied	**abnormal movement** dyskinesias most frequent during awakening, followed by lightening and stage N1. Very rare dyskinesias during SWS and REM sleep. 97% of dyskinesias associated with awakening/lightening occured after stage change, not before.	n.r.		same sample as Fish et al. 1990
Fish et al. 1991a [49]	N=14 (see Fish et al. 1990) , medicated N=10 healthy controls, no matching	two nights of PSG, submental EMG, video recordings, scalp magnetic stimulation of abductor digiti minimi	**normal REM atonia** well maintained atonia during REM sleep	n.r.		same sample as Fish et al. 1990

"normal" and "abnormal" refer to comparisons with the respective control groups.

Table 4. Dopa responsive dystonia (Hereditary Progressive Dystonia with marked diurnal fluctuation, Segawa syndrome)						
Citation	Sample n (mean age) (% female) (ON onset resp. DU duration of dystonia) medication	Measures	Sleep Results			Comment
			PSG-determined	self-reported	correlates of sleep disturbance	
Segawa et al. 1976 [35]	N=4 (7.5y) (50%f) (ON 4.8), on L-dopa, PSG performed before and after L-dopa in two patients, under selective sleep deprivation in the other two	two nights of PSG	**abnormal movement** gross body movements and twitches were "few" but occurred during all sleep stages including REM. Number of twitches per hour REM increased in later sleep cycles.	n.r.	after L-dopa, an increased number of gross body movements, twitches, and rapid eye movements was observed.	No control group, thus difficult to judge whether amount of movement was abnormal
Gadoth et al. 1989 [36]	N=3 (15y) (100%f) (ON 5.3), two investigated before and after L-dopa, the third only under L-dopa N= 11 phenotypically normal immediate relatives	one night of PSG in two patients, one night of PSG in one patient and in controls	**abnormal movement** number of gross body movements involving trunk during REM sleep↑ **normal continuity and architecture** SE ≥ 83%; SOL ≤ 15 min; normal stage distribution, no periodic leg movements	n.r.	no significant change in intensity or frequency of movements after L-dopa	results indicate abnormal movement during REM sleep in dopa responsive dystonia, which was not found in generalized torsion dystonia (table 2)
Brüggemann et al. 2014 [27]	N=23 (39.2±20.1y) (70%f) (DU 30±19.4y) PSG in N=6!, dopaminergic medication (lisuride and seligilin in one patient, l-dopa in the others) N=26 healthy controls matched for age	one night of PSG, comparison with norm values (no PSG in controls) PSQI, ESS, SSS, WHOQOL	**normal continuity** mean SOL and SE normal **disturbed architecture** REM latency↑, sleep fragmentation caused by spontaneous arousals in 3/6 patients	**normal sleep quality** normal mean PSQI (10.0±6.2) **normal daytime sleepiness** normal mean ESS (6.6±4.5), normal mean SSS (21.1±13.4)	sleep impairment associated with lower Quality of Life	PSQI score classified as normal because of n.s. compared to controls – however, clearly in excess of the common cutoff for disturbed sleep (>5)

"normal" and "abnormal" refer to comparisons with the respective control groups.

Table 5. Mixed Dystonias				
Citation	**Sample**	**Measures**	**Sleep Results**	
			PSG-determined	**self-reported**
Miller et al. 2007 [33]	N=83 (62.8±12.0y) (64%f) (DU 12.7±11.2y) different primary dystonias medicated N=354 with Parkinson's disease N=53 with essential tremor	endorsement (=non zero) of BDI sleep items	n.r.	55.4% insomnia, 75.9% fatigability, n.s. compared to essential tremor and Parkinson's diseasae