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

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Summary

Patients with primary dystonia, the third most prevalent movement disorder, suffer from a markedly reduced quality of life. This might, at least in part, be mediated by non-motor symptoms, including sleep disturbances. Characterising and treating sleep disturbances might provide new inroads to improve relevant patient-centred outcomes. This review evaluates the state of research on sleep in patients with dystonia and outlines an agenda for future research. A literature search was performed in July 2014 using PubMed, Medline via Ovid, PsycInfo, PsycArticles via Proquest and Embase via Ovid. Search results were screened for eligibility by two independent raters. Peer-reviewed publications reporting on sleep in patients with primary dystonia were included. Of 1,445 studies identified through the search strategy, 18 met the inclusion criteria. In total, the included studies reported on 708 patients diagnosed with focal dystonia (cervical dystonia or blepharospasm), torsion dystonia, and dopa-responsive dystonia. The results indicate that at least half of the patients with focal cranial dystonia suffer from sleep disturbances, but excessive daytime sleepiness is uncommon. Sleep disturbance is associated with depressive symptoms. The frequency and duration of dystonic movements is markedly reduced during sleep. Reduced sleep quality appears to persist after treatment with botulinum toxin that successfully reduces motor symptoms. The findings are limited by a high clinical and methodological heterogeneity. Future research is needed to i) further characterize subjective and PSG sleep in patients with different types of dystonia, ii) determine the aetiology of sleep disturbances (e.g., abnormal brain function associated with dystonia, side effects of medication, psychological reasons), and iii) test whether targeted sleep interventions improve sleep and quality of life in patients with primary dystonia.

Glossary

blepharospasm: form of focal cranial dystonia, involuntary muscle contractions of the eyelid

cervical dystonia: also called spasmodic torticollis, form of focal cranial dystonia involving the neck, causing an often painful involuntary turning of the head

cranial dystonia: different forms of focal dystonia localized in the head area

dopa-responsive dystonia: also known as hereditary progressive dystonia with marked diurnal fluctuation or Segawa syndrome, very rare form of generalized dystonia beginning in childhood or adolescence

dystonia: neurological movement disorder characterized by involuntary muscle contractions causing twisting and repetitive movements or abnormal postures

focal dystonia: dystonia symptoms are limited to one body are such as the neck in cervical dystonia

generalized dystonia: dystonia symptoms mostly begin in one limb and gradually spread to other limbs and the trunk

Meige's syndrome: includes symptoms of dystonia in several different facial muscles such as the eyes, jaw, tongue and mouth

torsion dystonia: very rare and severe form of dystonia typically beginning in childhood or adolescence

Abbreviations

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

Introduction

Primary dystonia is a neurological movement disorder characterised by involuntary muscle contractions causing twisting and repetitive movements or abnormal postures.[1] In contrast to secondary dystonia that has a known causation, such as head injury or a side effect of medication (tardive dystonia), the pathophysiological mechanisms of most forms of primary dystonia are unknown and the diagnosis is based on clinical observations.[2] Primary dystonia is considered the third most prevalent movement disorder after essential tremor and Parkinson's disease. Its exact prevalence is unclear due to a high variability in prevalence estimates between different studies. A recent review found that the prevalence estimates for patients with primary dystonia seeking medical attention were between 24 and 50 per million for early onset dystonia and between 136 to 430 per million for late onset dystonia.[3] Focal forms of primary dystonia are limited to a specific part of the body, such as the eyelids in blepharospasm or the neck in cervical dystonia (spasmodic torticollis), and typically begin in adulthood. Generalised forms of dystonia, in contrast, are often early-onset and involve several limbs and the trunk.

Various domains of quality of life, such as physical and social functioning and vitality, are impaired in patients with dystonia,[4,5] which is, at least in part, attributable to the often disabling, disfiguring and stigmatising nature of this disorder. Botulinum toxin injection into the affected muscles is considered the first line treatment for cervical dystonia.[6] This treatment is well tolerated and of longstanding efficacy for the improvement of abnormal movement.[6,7] A limitation is that immune resistance may occur in some patients as a side effect of repeated injections.[8] Pallidal deep brain stimulation is a newer treatment option for patients with medically refractive dystonia.[9,10] Benefits of deep brain stimulation include substantial improvements of dystonia symptoms, disability and quality of life in previously treatment resistant patients [11]. A recent study found that treatment effects were maintained three and five years after surgery [12]. On the other hand, deep brain stimulation bears a risk of serious side effects. In a clinical trial of 40 patients with primary generalised or segmental dystonia,[12] 49 new adverse events occurred between six months and five years after the brain stimulation treatment, 21 of which were rated serious and were almost exclusively device related. One participant attempted suicide shortly after the six-month visit during a depressive episode. As for non-serious adverse events, the most commonly reported side effect were dysarthria and transient worsening of dystonia.

Current treatment of dystonia tends to focus on the improvement of motor symptoms. The importance of non-motor symptoms including abnormal sensory phenomena, psychiatric symptoms, cognitive deficits, pain, and sleep disturbances is increasingly recognised; although their aetiology and treatment options are insufficiently characterised.[13,14] Non-motor symptoms have a large impact on the quality of life[15,16] and seem not to remit after botulinum toxin treatment and deep brain stimulation.[14] This underlines that targeted clinical assessment is necessary and treatments of non-motor syndromes need to be developed. Importantly, patients with dystonia consider sleep to be a prime determinant of their quality of life. There is a stronger link of quality of life with sleep than motor symptom severity in patients living with dystonia.[5] These findings fit within the broader context that sleep disorders are increasingly recognised as a frequent comorbidity of neurological disorders,[17] with potential implications for early diagnosis, pathomechanistic insights, and treatment.

The aim of this review is to summarise the state of research, critically evaluate the methodological quality of existing studies, and highlight areas requiring future investigation. More specifically, we sought to identify research reporting on polysomnographically determined sleep, self-reported sleep and variables associated with sleep such as side effects of medication and depressive symptoms in patients living with primary dystonia.

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 disorder, or were published in languages other than English, German, French, Spanish, Italian or Chinese. When potentially relevant unpublished abstracts were identified, the authors were contacted and asked about a published article on the respective study.

Data extraction

Data extracted from the included studies were socio-demographical and clinical description of the sample, diagnosis, study design, measures, statistical methods as well as results concerning apparative measures of sleep (e.g., polysomnography), subjective measures of sleep (e.g., questionnaires) and variables associated with sleep (e.g., symptom severity, depressive symptoms). Data extraction for 20% of the included studies (n=4) was performed by two authors working independently. Data extraction for the other studies was performed by the first author. We present overall characteristics of the included studies and report findings grouped by dystonia subtype.

Assessment of risk of bias

For each included study, the risk of bias originating from six different aspects of methodology was assessed. The six aspects were the diagnostic process, sample size, nature of control group, sleep measures, medication and statistics. The criteria for the ratings of low, moderate, high or unclear risk of bias are pictured in table 1. The rating scheme has been modified from the methodology checklist by the Agency for Healthcare Research and Quality,[18] which has been recommended for cross-sectional studies in a recent systematic review.[19] Following the recommendation of the Cochrane Collaboration,[20] which advises against the use of summary scores, we use a descriptive approach. Risk of bias was assessed by two independent raters. Conflicts were resolved by discussion.

- Please insert table 1 here -

Results

Search Results

The process of study selection is illustrated in Figure 1. After the automatic removal of duplicates, we identified 1,445 records. After screening of titles and abstracts, 63 articles were retained for fulltext assessment. Following examination of fulltexts, 18 articles were included into the review. Included studies were published between 1976 and 2014. In total, the included studies reported on 708 participants.

- Please insert Figure 1 here -

Socio-demographic and clinical characteristics of the samples

The main findings of the 18 studies, grouped by subtype of dystonia, are summarised in Tables 2–5. Samples of patients with focal dystonia were older than those with generalised dystonia. All but one study reported an equal gender distribution or included more females. Age at onset of generalised dystonia was typically in childhood or adolescence, whereby the onset of focal dystonia was in adulthood. Three studies (Silvestri et al. 1990,[34] Sforza et al. 1991,[21] Lobbezoo et al. 1996[22]) reported on drug-free participants. Two reports referred to published criteria for the diagnosis of dystonia: Fish et al.[23] made diagnoses based on Fahn's recommendations.[24] Avanzino et al.[25] used Albanese's diagnostic criteria.[26] None used the ICD-10 criteria. Eight studies did not report on the diagnostic process at all. The other studies stated that diagnoses were made by experienced movement specialists or neurologists, but did not define any diagnostic criteria.

Sleep measures

Twelve studies included polysomnography (PSG) and seven included self-report measures of sleep. Only Brüggemann et al., 2014[27] reported both PSG and self-reports. All authors using PSG reported that scoring was performed visually according to the recommendations by Rechtschaffen and Kales.[28] Only Fish et al., 1990[23] reported on the use of an automated EEG analysis. Brüggemann et al.[22] and Gadoth et al.[31] performed one night of PSG. In all other PSG studies, the duration was two or three nights including one adaptation night. Of the seven studies reporting on self-ratings of sleep quality, five used validated sleep questionnaires such as the Pittsburgh sleep quality index (PSQI)[29] and the Epworth sleepiness scale (ESS).[30] The other two were the study by Klingelhoefer et al., [31] who used the NMSQuest (non-motor symptom questionnaire), a non-motor symptom scale validated for Parkinson's disease[32], and Miller et al.,[33] who used the sleep items of the Beck depression inventory.[34]

Study designs

Fifteen papers reported cross-sectional case descriptions and cross-sectional group comparisons. Two studies investigated the effects of L-dopa on PSG determined sleep.[35,36] One study evaluated self-reported sleep quality before and after botulinum toxin injections.[37] Fifteen studies included some form of control group, thirteen included healthy controls. However, matching for age or age and sex was performed in only eight studies. Three of the included studies by the same research group reported on the same sample of patients with torsion dystonia.

To obtain a statistical power of 80% and a probability level of 5% for a t-test, a sample size of approximately 20 participants per group is needed to detect a large group difference (Cohen's d = 0.8); approximately 50 participants per group are needed to detect a moderate difference (Cohen's d = 0.5), and approximately 310 participants per group are needed to detect a small difference (Cohen's d = 0.2). Five studies, all on focal dystonia, were sufficiently powered to detect a moderate effect,[25,31,37–39] none was sufficiently powered to detect a small effect. Nine of the controlled studies included less than 20 participants per group, thus were clearly underpowered.

Risk of bias assessment

The results of the risk of bias assessment are pictured in Figure 2. Together, the main issues limiting the validity and generalisability of the results are the failure to use validated diagnostic criteria, small heterogeneous samples, a lack of matching for age and sex, a paucity of studies measuring both self-reported and PSG determined sleep, a lack of studies on unmedicated patients, and insufficient reporting of the statistical approach.

- Please insert Figure 2 here -

Main results

We present the main results by dystonia subtype, beginning with the most prevalent (focal cranial dystonia, Table 2), followed by generalised torsion dystonia (Table 3), dopa-responsive dystonia (Table 4) and mixed dystonias (Table 5).

Focal cranial dystonia, cervical dystonia and blepharospasm

Cranial dystonia refers to different forms of focal dystonia localised in the head area. Cervical dystonia (also called spasmodic torticollis) is a focal dystonia involving the neck, causing an often painful involuntary turning of the head. Patients with blepharospasm, another form of focal dystonia, suffer from involuntary muscle contractions of the eyelid. Meige's syndrome includes symptoms of dystonia in several different facial muscles such as the eyes, jaw, tongue and mouth. In contrast to dopa responsive dystonia and generalised torsion dystonia, cranial dystonia mostly begins in adulthood and is associated with a lesser degree of disability.

We found eight studies of patients with focal cranial dystonia (see Table 2): Silvestri et al. (N=8), Sforza et al. (N=10), Lobbezoo et al. (N=9 with dystonia, N=9 controls), Trotti et al. (N=43 with dystonia, N=49 healthy controls, N= 19 controls with other focal movement disorders), Avanzino et al. (N=52 with blepharospasm, N=46 with cervical dystonia, N=56 healthy controls), Paus et al. (N=110 with blepharospasm, N=111 with cervical dystonia, N= 93 healthy controls), Eichenseer et al. (N=54 with dystonia N=55 healthy controls), and Klingelhoefer et al. (N=102).

Only three small studies (Silvestri, Sforza, and Lobbezoo) used PSG in focal cranial dystonia. Their results are inconclusive concerning PSG determined sleep continuity and architecture. Sforza et al.[21] found a disturbed sleep continuity and abnormal sleep architecture in patients with blepharospasm and oromandibular dystonia. Lobbezoo et al.[22] found no group differences between patients with cervical dystonia and healthy controls. These differences may be attributable to different subtypes of focal cranial dystonia. All three studies using PSG in focal cranial dystonia found a marked decrease of frequency and duration, but not a total disappearance of dystonic movement during sleep, most prominently in deeper NREM sleep stages and REM sleep [21,22,40]. Silvestri et al. reported only on movement during sleep, not on sleep continuity and architecture.

The remaining five larger studies investigated self-reported sleep [25,31,37–39]. Three studies found reduced mean scores on the PSQI and an increased number of subjects with PSQI scores in the clinical range compared to healthy controls [25,37,39]. The percentage of patients with impaired sleep quality according to the PSQI varied between over 40% in the study by Paus et al.[39] and over 70% in the study by Avanzino et al.[25] It is difficult to tell where this considerable discrepancy stems from as both studies investigated outpatients with cervical dystonia or blepharospasm and used the same criterion for impaired sleep quality (PSQI score > 5). The BDI scores were only marginally higher in Avanzino's sample.[25] A normal daytime sleepiness according to the ESS was found in four studies [25,37–39]. Patients in all questionnaire studies were medicated, so that it cannot be ruled out that the impaired sleep quality occurred as a side effect of medication. Two studies suggest that sleep quality impairment is associated with depressive symptoms, but not with the severity of dystonia [25,39]. Interestingly, Paus et al. found that impaired sleep quality was associated with symptoms of restless legs syndrome (RLS) [39]. The percentage of patients with RLS was elevated in patients with dystonia compared to healthy controls (20% of patients with blepharospasm, 18% of patients with cervical dystonia, 2% of controls). Importantly, Eichenseer et al.[37] found that sleep quality was not improved after botulinum toxin treatment despite a significant improvement of motor functioning.

In summary, prevalence estimates for sleep disturbances are between 40 and 70% in patients with focal cranial dystonia. The level of daytime sleepiness seems comparable to healthy controls. Interestingly, impaired sleep quality was more prominently associated with depressive symptoms than with the severity of motor symptoms. During PSG-measured sleep, a marked decrease of the frequency and duration of dystonic movements was found. Sleep quality was not improved after botulinum toxin treatment despite a significant improvement of motor functioning.

- Please insert Table 2 here -

Generalised torsion dystonia

Generalised torsion dystonia is a rare and severe form of dystonia with a presumed significant genetic component,[41] typically beginning in childhood or adolescence. In contrast to dopa responsive dystonia, however, patients with torsion dystonia do not markedly respond to L-dopa.

We found six studies on generalised torsion dystonia (Table 3): Wein and Golubev (N=12 with generalised dystonia, N=15 with focal torsion dystonia, N= 10 healthy controls), Jankel et al. 1984 (N=9 with dystonia, N=9 healthy controls), Jankel et al. 1984a (N=1), Fish et al. 1990 (N=14 with dystonia, N=10 healthy controls, N=39 controls with other neurological disorders), Fish et al. 1991 (N=12 with dystonia, N=12 controls), and Fish et al. 1991a (N=14 with dystonia, N=10 healthy controls). The three studies by Fish all included the same group of participants with generalised torsion dystonia.

Disturbed PSG determined sleep continuity in patients with torsion dystonia was found by both Wein & Golubev[42] and Jankel et al.[43] They found an increased sleep onset latency and number of awakenings and a reduced total sleep time and sleep efficiency. However, due to the methodology used in these studies, it cannot be concluded that the disturbed sleep continuity was directly caused by dystonia. Wein & Golubev[42] did not report the medication status of the patients and matching for age and sex with the control subjects was not performed. Jankel et al.[43] investigated a small sample of medicated patients. Thus, it is possible that the observed group differences were due to age and sex differences and sleep continuity might have been disturbed by medication.

Abnormal sleep spindle activity was found by Wein & Golubev[42], Jankel et al. (1984)[43] and Jankel et al. (1984a)[44], but was not replicated by Fish et al. 1990.[23] The former found an increased number of unusually large sleep spindles (amplitudes larger than 80 respectively 150 microvolts) in their patients with severe generalised torsion dystonia. Jankel et al.[43] report that three of their four patients presenting with this abnormality were on diazepam; Wein & Golubev[42] did not report on the medication of their sample. It is plausible that the sleep spindles with abnormally large amplitude were an effect of medication, most likely benzodiazepines, which are known to produce a typical 'benzodiazepine signature' with excessive sleep spindles.[45]

A reduced duration of REM sleep compared to healthy controls was found by Wein and Golubev[42] and Jankel et al.[43] Since Wein and Golubev did not report the medication of their patients, the mechanisms underpinning REM suppression remain speculative. In the study by Jankel et al. (1984), REM suppression might be attributable to medication, e.g. diazepam which was taken by half of the patients in their sample.

Concerning sleep-related movement, there are no definite, replicated findings. One study by Fish et al. 1991[46] found that abnormal movements were rare during sleep and that abnormal movements associated with awakening or lightening of sleep almost always occurred after the stage change. This suggests that sleep continuity disturbance is not caused by dystonic movement. Patients with Parkinson's disease often present with REM sleep behavior disorder[47], which has been identified as a risk factor for the de novo onset of synucleinopathies[48]. Fish et al. 1991[49] found that REM atonia was well maintained in patients with torsion dystonia. There was no study on self-reported sleep in patients with generalised torsion dystonia.

In summary, the present findings support the hypothesis that patients with torsion dystonia suffer from a disturbed sleep continuity which occurs despite a marked decrease of abnormal movement during sleep. This hypothesis needs to be tested in future research.

- Please insert Table 3 here -

Dopa responsive dystonia

Dopa Responsive Dystonia, also known as hereditary progressive dystonia with marked diurnal fluctuation or Segawa syndrome, is a rare form of generalised dystonia beginning in childhood or adolescence.[50] Dystonia symptoms mostly begin in one foot and gradually spread to other limbs. Patients without treatment are often severely impaired. The syndrome is characterised by a marked worsening of symptoms over the course of the day, an improvement after sleep and a considerable, sustained response to low doses of L-dopa. Dopa responsive dystonia is frequently, but not always caused by mutations of the guanosine triphosphate cyclohydrolase 1 gene (GCH1) leading to a reduction of dopamine synthesis.[51]
We found three studies on dopa responsive dystonia (Table 4): Segawa et al. (N=4), Gadoth et al. (N=3 patients, N=11 phenotypically healthy immediate relatives) and Brüggemann et al. (N=23 with dystonia, N=26 healthy controls). The results suggest that PSG determined and subjective sleep continuity are by and large normal in patients with dopa responsive dystonia. Brüggemann et al.[27] found an increased REM sleep latency. Segawa et al.[35] found that gross body movements involving the trunk and twitches were 'few', but occurred in all sleep stages including REM sleep, suggesting abnormal behavior during REM sleep. However, as the

study did not include healthy controls, it is difficult to judge to which extent the amount of movement was abnormal. Gadoth et al.[36] observed increased movement during REM sleep compared to phenotypically normal immediate relatives. Segawa[35] reported an increase of abnormal movement during sleep after L-dopa, which was not replicated by Gadoth et al.[36] Brüggemann et al.[27] investigated self-reported daytime sleepiness in a sample of 23 patients with dystonia and did not find any significant differences compared to healthy controls.

In summary, the results suggest that PSG determined and self-reported sleep continuity are normal in dopa responsive dystonia. Preliminary evidence of abnormal movement during REM sleep has been found. However, the results must be classified as inconclusive because PSG was only performed in very small samples of medicated patients.

- please insert Table 4 here -

Mixed dystonias

We found one study investigating mixed forms of dystonia (Table 5): Miller et al. (N=83 with primary dystonia, N=354 with Parkinsons's disease, N=53 with essential tremor). Using the sleep-related items of the BDI as a measure of sleep disturbance, this study found that 55% of the patients with dystonia reported insomnia and 76% reported fatigue. These results were comparable to patients with Parkinsons disease and essential tremor.

Summary

This review found that in patients with focal cranial dystonia, the most prevalent form of primary dystonia, self-reported sleep quality is reduced compared to healthy controls. Prevalence estimates for disturbed sleep were between 40 and 70%, although the level of daytime sleepiness seems comparable to healthy subjects. Of particular note, impaired sleep quality was more prominently associated with depressive symptoms than with the severity of motor symptoms. A marked decrease of the frequency and duration, but not a total disappearance of abnormal movement during sleep was observed in these patients. Sleep quality was not improved after botulinum toxin treatment despite a significant improvement of motor functioning. In generalised torsion dystonia, the results imply that patients present with disturbed PSG determined sleep continuity. REM sleep atonia was well maintained in generalised torsion dystonia, but the results suggest that abnormal movement during REM sleep may be present in dopa responsive dystonia. Together, the literature provides preliminary support for the notion that disturbed sleep is highly prevalent in patients with primary dystonia. The pattern of reduced subjective sleep quality in the absence of daytime sleepiness resembles insomnia.[52] Our results are in line with the broader notion that insomnia symptoms are highly prevalent but underinvestigated and undertreated in patients with neurological disorders.[17] According to the current guidelines by the European Federation of Neurological Societies, botulinum toxin is the first line treatment for primary cranial and cervical dystonia and pallidal deep brain stimulation can be considered if pharmacological treatment fails [53]. Future research is necessary to evaluate more thoroughly whether these treatments are sufficiently effective to improve sleep. If not, the development and evaluation of specialized sleep treatments for dystonia is warranted.

Potential mediators of sleep disturbance in dystonia

While the results consistently indicate that patients with focal cranial dystonia suffer from reduced sleep quality as measured by validated self-report questionnaires, the mediators of sleep disturbance remain poorly understood. The reported disturbances of sleep continuity are unspecific and can be found in many other neurological disorders.[17]

A first hypothesis is that sleep disturbances stem from the same brain dysfunction that causes dystonia. Whereas the pathophysiology of dystonia is not yet fully understood, it can be speculated that the disorder stems from a malfunction of brain areas associated with movement, such as the basal ganglia. The dramatic response to L-dopa in dopa responsive dystonia points to an involvement of the dopaminergic system at least in some forms of dystonia. Further support for the hypothesis of an involvement of the dopaminergic system stems from tardive dystonia, which occurs as a side effect of antidopaminergic medication and clinically mimics primary dystonia.[54] Research also supports a potential role of dopamine in the maintenance of wakefulness,[55] suggesting that dystonia and sleep disturbance may be due to the same pathological mechanisms. This, however, remains a speculative hypothesis which is to be tested in future research.

A second hypothesis is that sleep disturbances occur as a side effect of medication. Patients with cervical dystonia in the presented studies were mostly treated with botulinum toxin, which is the first line treatment for focal cervical dystonia.[6] Botulinum toxin is not known to disturb sleep. A considerable percentage of patients, however, were treated with other medications. Eichenseer et al.[37] provide a detailed report of the medication in addition to botulinum toxin for their sample of 54 patients with cervical dystonia: 35% took benzodiazepines, 20% took antidepressants, 7% took baclofen and 4% took anticholinergics. Benzodiazepines and benzodiazepine receptor agonists are an established treatment for short-term insomnia.[56] However, they are also known to supress slow wave sleep[57] and have the potential to produce morning sleepiness, sedation and rebound insomnia after discontinuation,[58] and may therefore be responsible for a reduced sleep quality in some patients. Most antidepressants, including selective serotonin reuptake inhibitors (SSRIs), are known to supress REM sleep.[59] SSRIs can disturb sleep continuity in some patients with dystonia.[60] Thus, it cannot be excluded that reduced sleep quality occurs as a side effect of medication in patients with dystonia.

A third hypothesis is that sleep disturbance is caused by dystonic movement and associated pain. However, several findings speak against the assumption that impaired sleep quality is predominantly caused by abnormal movement. First, dystonia severity was not correlated with self-reported sleep in three studies.[25,38,39] Second, Eichenseer et al.[37] found that sleep quality was not improved after botulinum toxin treatment despite a significant improvement of motor symptoms. Third, several studies demonstrated that the frequency and duration of abnormal movement considerably decreases during sleep.[21,22,40,46] The latter is an interesting but so far poorly understood phenomenon which could potentially be informative about the pathophysiology and the development of new treatments. It could possibly be indicative of a normal functioning of descending motor inhibition during sleep – or a positive effect of sleep on the brain regions that produce abnormal movement. However, Lobbezoo et al.[22] found that abnormal movements were already markedly decreased after patients had adopted a supine position without the intention to fall sleep. This suggests that the decrease in abnormal movement may be associated with the supine position rather than sleep itself. As one study found that RLS was more prevalent in patients with dystonia than in controls, and that RLS was associated with disturbed sleep [39], it is also possible that sleep disturbance is at least in 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.

Limitations

Our review has several limitations. Unpublished literature was not considered, which may have led to a publication bias, i.e. an overrepresentation of studies which found differences between dystonia patients and controls. The rationale for restricting the review to published literature was to include only research of adequate quality which had passed through a peer review process. The limitations of the included studies also limit the validity of the review. Few of the studies on sleep in patients with dystonia are of sufficient methodological quality (see Fig. 2). First, as different kinds of sleep disturbance represent a potential side effect of many medications, it is a significant limitation that only three studies reported on drug-free samples. Second, considering that the prevalence of insomnia is increased in older subjects and in women,[62,63] it is also an apparent failure that less than half of the studies included a group of healthy controls matched for age and sex. Third, only two studies defined dystonia based on published diagnostic criteria, complicating the comparability between different studies. Fourth, the small sample sizes especially in the PSG studies are a further limitation – they are, however, understandable in studies on dopa responsive dystonia and generalised torsion dystonia, as the prevalence of these disorders is low. Future studies should fulfil the following methodological standards: use a prospective controlled study design, include measures of subjective sleep, objective sleep and potential processes associated with sleep disturbance, investigate unmedicated patients, match patients and controls for age and sex, diagnose dystonia according to a published set of diagnostic criteria and describe the diagnostic process in sufficient detail, and use sufficiently large samples or increase the duration of the study to create greater testing power by generating more data points.

Future Research Priorities

This review demonstrates that there is a need for more high quality research on sleep in patients with dystonia. First, characteristics of self-reported and PSG determined sleep and sleep disturbance need to be assessed more rigorously in larger drug-free samples compared to age- and sex-matched healthy subjects. For example, it needs to be further investigated whether self-reported sleep disturbances in patients with focal cranial dystonia are reflected in PSG determined sleep continuity, architecture or microstructure. The preliminary findings indicating a marked decrease of abnormal movement during sleep in focal dystonia, abnormal movement during REM sleep in dopa responsive dystonia and well maintained REM atonia in generalised torsion dystonia need replication. Studies on self-reported sleep in generalised dystonia and sleep studies in patients with other forms of dystonia, such as writer's cramp, musician's cramp or spasmodic dysphonia need to be conducted.

Second, the hypotheses concerning the aetiology of sleep disturbances outlined in this review need to be tested. The role of abnormal brain functioning, abnormal movement, pain, and psychological distress as mediators of sleep disturbance needs further investigation. Daily process studies[64] would be suitable to tease apart the temporal associations between these constructs.

Third, sleep needs to be targeted in therapy. Preliminary evidence suggests that sleep is not sufficiently improved after botulinum toxin treatment, thus sleep quality should be included as an outcome in treatment studies. If the finding that sleep is not improved after state of the art treatment is replicated, standard sleep treatments such as cognitive behavioural therapy for insomnia need to be evaluated and, if necessary, adapted for patients with dystonia. It has been shown that cognitive behavioural therapy is effective in patients with insomnia and comorbid medical disorders,[65,66] thus it can be speculated that this treatment may also improve sleep in patients with dystonia. A first step, however, is to evaluate the efficacy of 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.

- Research into the aetiology of sleep disturbances in patients with dystonia is needed. More specifically, the role of abnormal brain functioning, abnormal movement, pain, and psychological distress as mediators of sleep disturbance needs further investigation.
- Psychological processes potentially linked to insomnia in dystonia such as dysfunctional beliefs and attitudes about sleep, anxiety and preoccupation, sleep effort, and sleep hygiene practice need to be assessed.
- Sleep quality should be included as an outcome in treatment studies.
- Preliminary results suggest that botulinum toxin is ineffective for the improvement of sleep in cervical dystonia despite a significant improvement of dystonia symptoms, thus targeted sleep interventions should be developed and evaluated.

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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

	(DU 18.7±14.7y) medicated N=55 healthy controls matched for age and sex	HAM-A, TWSTRS, CDIP-58		quality↑ (65%) mean PSQI score↑ (baseline 7.5±4.2) **<u>normal daytime sleepiness</u>** normal % with excessive daytime sleepiness normal mean ESS score (baseline 5.04±4.0)	improvement in dystonia severity
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

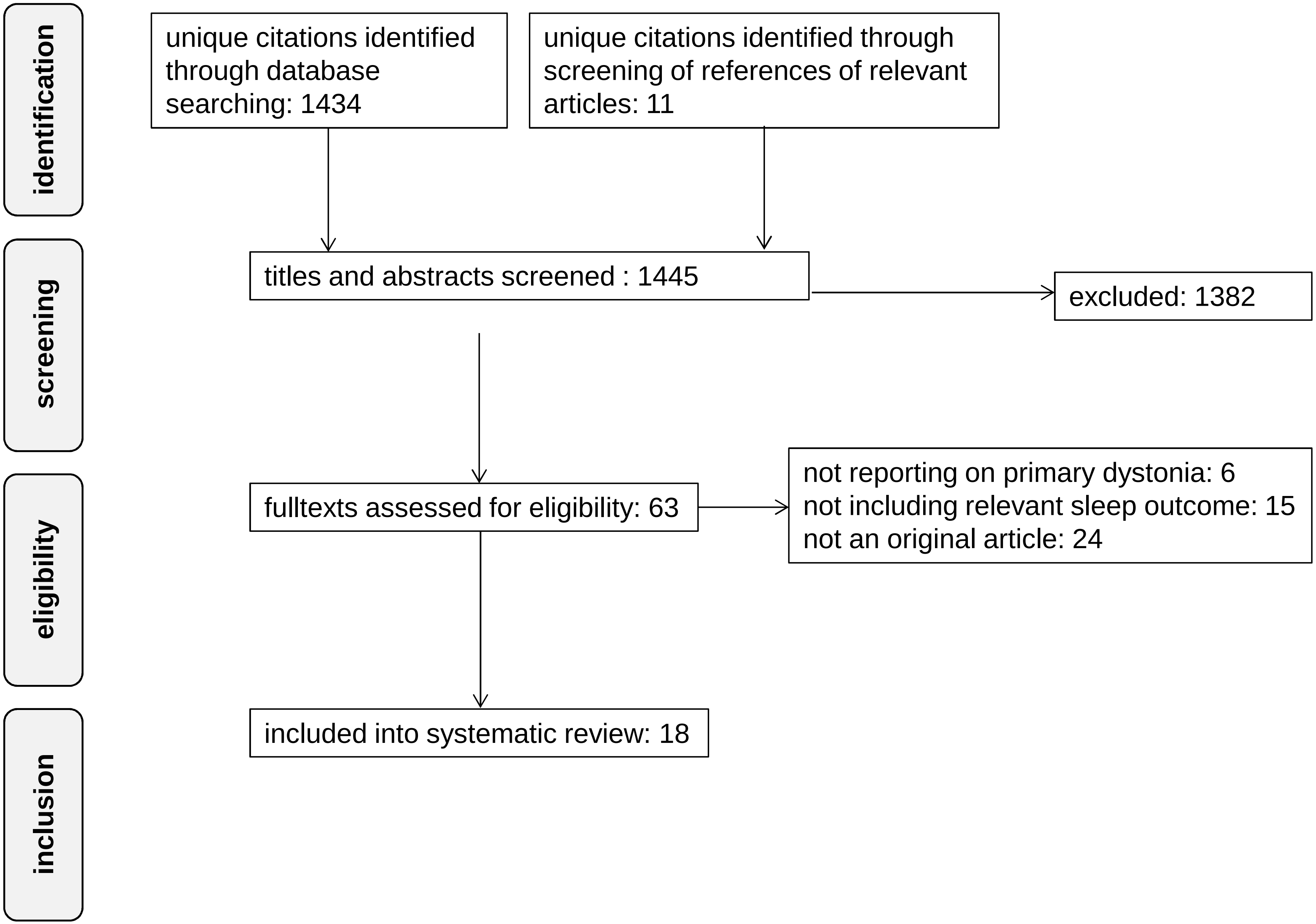
"normal" and "abnormal" refer to comparisons with the respective control groups.

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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screening
eligibility
inclusion
unique citations identified through database searching: 1434
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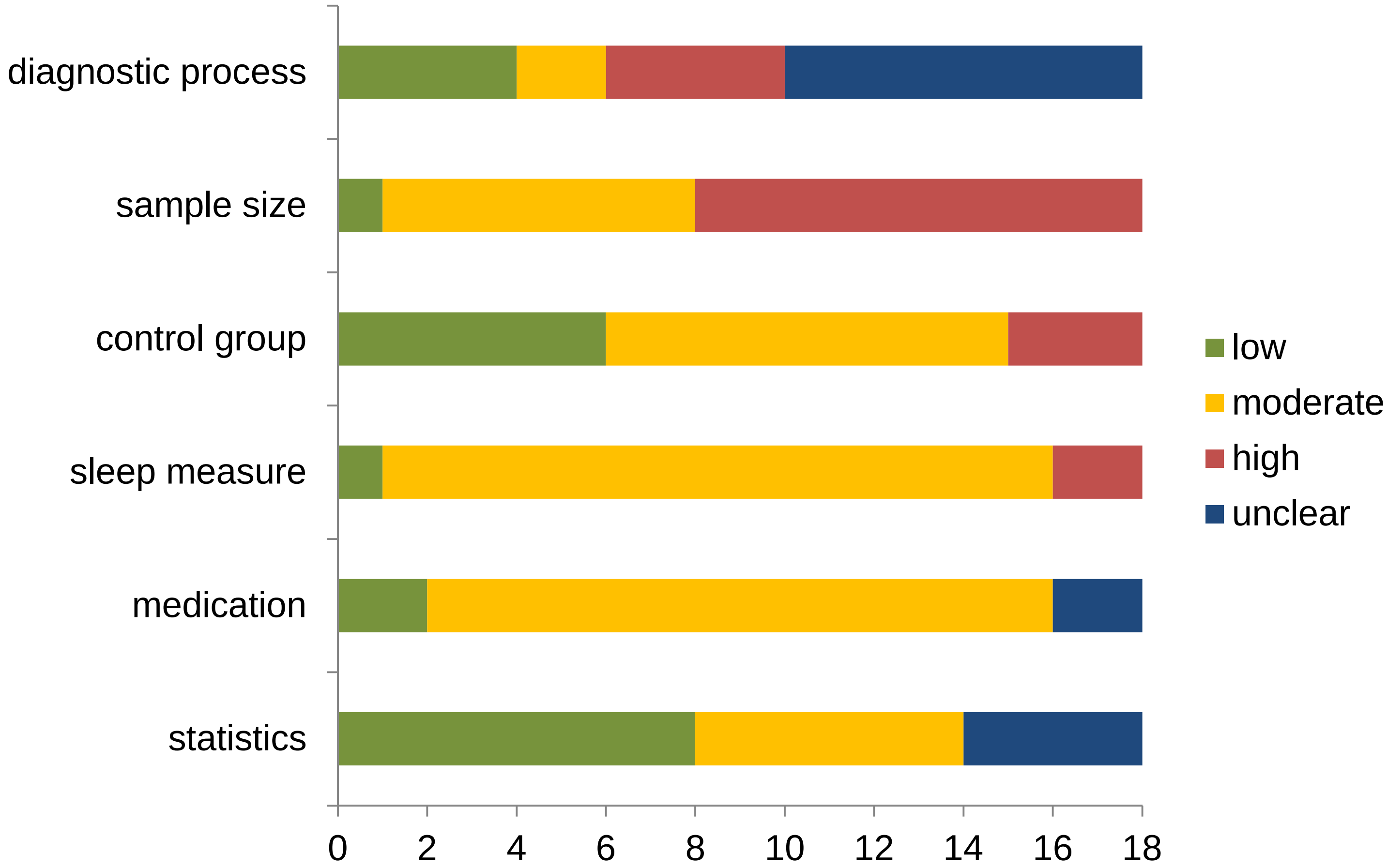
not reporting on primary dystonia: 6
not including relevant sleep outcome: 15
not an original article: 24
included into systematic review: 18


diagnostic process
sample size
control group
sleep measure
medication
statistics
0
2
4
6
8
10
12
14
16
18
low
moderate
high
unclear