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Tourette disorder and sleep

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ABSTRACT

Healthy sleep is of utmost importance for growth, development, and overall health. Strong evidence shows that sleep is affected negatively in patients and particularly children with Tourette Disorder (TD). There is also a frequent association of TD with Attention Deficit Hyperactivity Disorder (ADHD) which alone has negative effects on sleep and cumulatively worsens the associated sleep findings. The most consistent polysomnographic findings in patients with TD is decreased total sleep time, lower sleep efficiency and an elevated arousal index. Polysomnography studies have confirmed the presence of movements and persistence of tics during both Rapid Eye Movement (REM) and NREM sleep [1]. In general Patients with TD are found to have an increased incidence of sleep onset and sleep maintenance insomnia. Some studies have shown increased incidence of parasomnias (including sleepwalking, sleep talking and night terrors), but this may be confounded by the increased underlying sleep disruptions seen in TD. The hypersomnolence found in patients with TD is also suggested to be secondary to the underlying TD sleep disruption. There is not a significant association with sleep disordered breathing or circadian rhythm disorders and TD. Treatment of underlying TD is important for the improvement of sleep related TD manifestations and is outlined in this review.

Giles 'de la Tourette or more commonly known as Tourette Syndrome or Tourette Disorder (TD) was first published in the literature in 1885 [1]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifies TD as a motor disorder characterized by both motor and vocal tics that persist for more than a year [2]. The onset of the disorder is usually prior to 18 years old and is more prevalent in boys [3]. The overall worldwide prevalence is 0.9% [3]. The frequency of tics usually increases in the second decade of life and starts decreasing during adolescence, but still tics persist into adulthood in a third of patients [3]. There is strong evidence that sleep is affected negatively in patients and particularly children with TD, with some studies suggesting a direct correlation between tic severity and sleep disruption [4]. Furthermore, motor tics have been reported to persist during sleep. Up to 65% of children with TD have shown sleep

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disturbances of various types including but not limited to difficulty with sleep initiation, increased sleep disruption with associated decreased sleep efficiency [5]. The exact mechanism of this effect in sleep is not fully understood. Furthermore there in a high prevalence of comorbidities in children with TD, in particular 55% of children with TD also are diagnosed with attention deficit hyperactivity disorder [6] and 27% are diagnosed with Obsessive Compulsive Disorder (OCD) (rage 2–66%) along with other conditions including anxiety and depression [7]. Freeman et al. and others have demonstrated that children with TD and comorbidities have worse sleep problems than children with TD alone [7]. Also notable, is the finding that effective management of sleep problems has been reported to improve tic control in both severity and impact on life [8,9] emphasizing the importance of adequately identifying and treating sleep complaints in children with TD. In this manuscript we will summarize the most important findings associated with the presence of sleep disorders in children with TD.

Sleep and Tourette Disorder (TD)

Healthy sleep is of utmost importance for growth, development, and overall health. Healthy sleep includes obtaining the right amount of sleep for age, with good quality of sleep, appropriate consolidation, continuity, and absence of a sleep disorder. Adequate sleep is important for brain development, learning, memory consolidation, emotion regulation, executive function, among other important functions [10]. Lack of sleep, sleep disruption or sleep disorders have been associated with cognitive deficits, executive dysfunction, emotional dysregulation, increased sympathetic activation, hormone dysregulation, decreased seizure threshold among other consequences [11].

The American Academy of Sleep Medicine (AASM) has published an expert consensus on sleep requirements for adults and children [Table 1] [12,13]. The AASM also has published the international classification of sleep disorders that divides sleep disorders into 6 main group categories: insomnia, parasomnias, hypersomnias, sleep related movement disorders, sleep related breathing disorders (SRBD) and circadian rhythm disorders [14]. Polysomnography is the gold standard for evaluation of sleep disorders. Polysomnography assesses sleep latency, sleep continuity, arousal index, among other parameters that help identify disturbances in sleep quality or quantity [15]. These parameters are calculated from a total sleep time which is the time (in minutes) from lights off to lights on in the sleep lab during which the patient is asleep. Sleep latency is the time from lights off to the start of the first epoch of any stage of sleep, and the sleep efficiency index is the total time spent sleeping divided by the total recorded time in bed (from lights out to lights on). The time spent awake during the night after initially falling asleep detracts from the sleep efficiency index. People who are tired or have a significant sleep debt may spend more time in bed in an attempt to increase their total sleep time, but oftentimes if there is a comorbid sleep disorder or medication effect, they may not be able to fall asleep quickly despite sleepiness, or may wake up through the night, resulting in prolonged sleep latency, lower sleep efficiency and lack of resolution of daytime sleepiness symptoms. Polysomnography can identify sleep disorders such as obstructive sleep apnea (OSA) and periodic leg movement disorders and the addition of video can help in the recognition of movements and tics which may be disrupting sleep. Other methods to assess sleep include objective actigraphy which estimates total sleep time and sleep disruption, and subjective sleep diaries and questionnaires.

Studies have demonstrated that children with TD get less sleep than children without TD and sleep disruption gets worse with age. In fact, older adolescents have less nights of good sleep than younger children with TD; in a recent study neither medications or comorbidities appear to predict adequate amount of sleep in children with TD suggesting that sleep disruption is inherent to TD and not only secondary to comorbidities or medications [16]. Lee et al. found that comorbid anxiety was associated with the highest risk of sleep disorders, followed by ADHD, and allergic rhinitis [17]. A study using sleep diaries showed that sleep initiation affects approximately 48% of children with TD and 56% of children with TD with Attention Deficit Hyperactivity Disorder (ADHD) while sleep maintenance is affected in 27% of children in the former group and 47% in the latter [5]. Fig. 1 illustrates the contribution of comorbidities and medications to the sleep disturbance seen in patients with TD.

Sleep architecture which is the distribution of sleep into different sleep stages and frequency of sleep disruption (arousals and awakenings), has been studied if patients with TD using polysomnography and important differences have been identified, although findings have been variable. The most consistent findings are decreased total sleep time, lower sleep efficiency and elevated arousal index [18]. There is inconsistency in the literature with regard to the effect of TD on percentage of REM and N3 delta wave sleep. Most polysomnographic studies assessing sleep parameters in children with TD also include children with comorbidities, particularly ADHD. It is difficult to identify TD specific effects on sleep architecture besides the increase numbers of arousals and effect in sleep continuity. Studies have also shown increased periodic limb movements (PLM) during sleep which appear to be additive and worse in the context of comorbid ADHD [1,19,20].

Pathophysiology of sleep disorders in TD

The pathophysiology of sleep disruption in children with TD is not completely understood but several potential mechanisms have been postulated. Early studies have pointed toward a dopaminergic dysfunction with likely increase in dopaminergic activity as evidenced by improvement of symptoms with medications that produce dopamine depletion (tetrabenazine) [21].

Most recently an epigenetic basis of environmental influences over genetic predisposition has been postulated. There are currently no consistent neuroimaging markers of TD but studies with magnetic resonance spectroscopy and

Table 1 Recommended Amount of Sleep for Pediatric & Adult Populations to promote optimal health AASM Consensus Recommendations [12,13].

• Infants 0–4 months	Not well established with wide variation & insufficient evidence for associations with health outcomes
• Infants 4–12 months	12 to 16 h per 24 h (including naps)
• Children 1–2 years	11 to 14 h per 24 h (including naps)
• Children 3–5 years	10 to 13 h per 24 h (including naps)
• Children 6–12 years	9 to 12 h per 24 h
• Teenagers 13–18 years	8 to 10 h per 24 h
• Adults 18–60 years	7 or more hours per night on a regular basis

positron emission tomography suggest that other neurotransmitters are also implicated including GABA and glutamate [22]. Overall, there is strong evidence to support involvement of the cortical-basal ganglia-thalamocortical circuits which are crucial for regulation and control of movement. This may indicate involved neurotransmitters including serotonin, histamine, acetylcholine, norepinephrine, endogenous cannabinoids, opioids, and adenosine may form a dynamic interplay in the pathophysiology of tics [8]. Many of these neurotransmitters (most significantly acetylcholine, norepinephrine, serotonin, histamine, and GABA) have important implications in the regulation of sleep and wakefulness supporting a pathologic explanation for increased sleep disruption in TD.

Findings related to sleep

As discussed, the international classification of sleep disorders third edition (ICSD-3) [14] classifies sleep disorders in 6 major groups. In this section we discuss the findings associated with each group in children with TD.

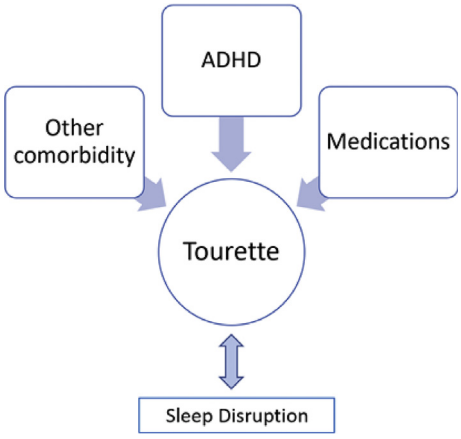

Fig. 1 Contribution of ADHD, other comorbidities and medication effect to sleep disruption in patients with Tourette Disorder.

Insomnia

Insomnia is defined as a frequent and persistent difficulty initiating or maintaining sleep that results in general sleep dissatisfaction despite having adequate time and circumstances each night to obtain necessary sleep. This sleep complaint is accompanied by distress about poor sleep and/or impairment in important areas of functioning and can occur in isolation or comorbidly [23]. The classically used Spielman model of chronic insomnia "the 3P model" describes an implication of predisposing, precipitating, and perpetuating factors which all contribute to the development and maintenance of chronic insomnia [24].

As described above, there is a pathophysiologic neurochemical disruption of sleep wake regulation which predisposes TD patients to develop insomnia. Precipitating factors "push" someone to the state of clinically significant insomnia and can be the result of a single or multiple recurrent events. In patients with TD, negative effects of tic symptoms on school, work, or other performance can for example lead to reduced sleep opportunity from compensating with late nights. Patients with comorbid ADHD have also been shown to have an increased incidence of insomnia over TD alone [5]. Finally, perpetuating factors further contribute to the maintenance of chronic insomnia. Patients often report distress, anxiety and fear during drowsiness [25], reluctancy to going to bed, and presence of myoclonic jerks or startle episodes on falling asleep [26]. This high prevalence of sleep onset and sleep maintenance insomnia have been described in both studies using subjective questionnaires and objective polysomnographic and actigraphy data [27].

Parasomnias

Parasomnias are defined as undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep. This abnormal activity may occur during transitions to and from sleep, during NREM sleep (sleepwalking, sleep talking, night terrors or confusional arousals) or REM sleep (nightmares or REM behavior disorder) [23].

The NREM sleep disorders are viewed as a state of sleep-wake consciousness that is not fully declared and may be consciously disassociated with motor function retained. Other sleep disorders such as OSA have demonstrated an increase in comorbid night terrors or sleepwalking due to the increase sleep disruption [28]. One can speculate that movements during TD & the biochemical factors described could affect sleep continuity predisposing to increase in parasomnias. This was seen with a report of 14.3% of 56 young patients with TD or chronic tic disorder talking or walking during sleep [29].

Sleepwalking (somnambulism) is defined as ambulation and other complex behaviors out of bed while meeting NREM disorder criteria. One study of 247 children with TD and 47 random controls showed a threefold increased frequency of sleepwalking compared to controls [30]. A threefold increase was also seen in younger patients with TD age 6–17 compared to TD age >18 [31]. A defined prevalence of parasomnias in patients with TD is not clearly established.

There is also a confounding known age association with general population of some parasomnias (such as confusional arousals, sleep walking or sleep talking) which are generally more common in childhood and tend to decrease with age.

Sleep terrors (night terrors) are characterized by sudden scream from sleep usually during slow wave sleep (N3), with signs of autonomic arousal. Like in sleepwalking, there is dissociation and patients are not aware of the surroundings and do not recall of the event. Although the evidence is similarly not robust, Comings et al. also showed that 15.8%–49% of patients with TD had night terrors, and was higher than that found in controls [30].

REM sleep behavior disorder (RBD) is rare in children and always associated with a pathological process. RBD is characterized by dream enacting behaviors arising from REM sleep when atonia should occur. The pathophysiology of RBD is based on disruption this atonia mechanism during REM and is found commonly in neurodegenerative conditions particularly synnucleopathies [32]. The prevalence is therefore higher in older individuals and very rare in children unless associated with other neurologic disorder (i.e. narcolepsy) [33]. There was only one case report found of a 7-year-old with the co-existence of Tourette's syndrome with RBD confirmed after polysomnographic studies [34]. The authors proposed possible overlap in the pathophysiological mechanisms underlying the two disorders.

Central disorders of hypersomnolence

Hypersomnia refers to excessive daytime sleepiness (inability to stay awake or alert during wakeful portions of the day) and as a primary diagnosis is defined as not being caused by disturbed nocturnal sleep or misaligned circadian rhythms. Other sleep disorders may be present, but these must be adequately treated before a hypersomnia diagnosis can be established [23].

Disorders of hypersomnolence include narcolepsy type 1 or 2 (with physiologic basis on absence of neurons containing the sleep and wake regulating hormone orexin/hypocretin), idiopathic hypersomnia (diagnosis of exclusion with objective decreased sleep latency as seen on MSLT), Kleine-Levin syndrome and secondary hypersomnia.

There are no studies reporting cases of Kleine-Levin syndrome in children with TD. There are very few reported cases of TD and narcolepsy including 2 comorbid cases of TD & narcolepsy by Ghosh et al. [5] and one case of a patient with TD with a gene mutation of the orexin system implicated in narcolepsy [35]. The association with TD and narcolepsy is unknown at this time.

Results of questionaries used to evaluate other disorders of hypersomnolence in patients with TD vary in the literature. Modafferi et al. [26] described a significantly higher frequency of "daytime somnolence" and "falling asleep at school" in patients with tic disorders compared to healthy controls, but as described above also found significant sleep disruption reported in these patients. Other studies did not find significant difference from controls in patients with TD alone [5,36]. The hypersomnolence found in patients with TD is likely secondary to the sleep disruption associated with the disorder and comorbid ADHD, and it is unlikely to be a correlation with a primary central hypersomnolence condition.

Sleep related movement disorders

Sleep related movement disorders are primarily characterized by relatively simple, usually stereotyped, movements that disturb sleep or its onset [23]. There are several diagnosable movement disorders including periodic limb movement disorder, restless leg syndrome, restless sleep disorder (RSD), bruxism, sleep related rhythmic movement disorder and secondary sleep related movement disorders.

Early studies from 1980 have demonstrated that patients with Tourette syndrome exhibit more movements during sleep, across all sleep stages including REM sleep, showing poor sleep quality in patients with Tourette syndrome when compared to normal controls [1]. Polysomnography studies have confirmed the presence of movements and persistence of tics during both REM and NREM sleep [4].

PLM are characterized by repetitive, highly stereotyped limb movements that clinically disturb sleep. Some studies have found increased numbers of PLMs [20] while others have not confirmed this finding [37].

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an irresistible desire to move legs due to uncomfortable and unpleasant sensations that are worse at rest, symptom relief with movement and symptoms occurring/worsening in the evening/night prior to sleep. There is not significant evidence of increased RLS in TD. One study found increased prevalence of RLS in children with TD but the generalizability is limited [38]. There is also a potential reported genetic association with RLS and TD although evidence is limited [39].

The frequency of subjective "restless sleeper" has been shown to be significantly higher than controls (38.9% of 36 patients with TD vs 2.18% of 266 controls) [26]. The same study reported increased incidence of sleep-induced bruxism which is characterized by repetitive jaw–muscle activity characterized by clenching or grinding of the teeth (19.4% of 36 TD vs 4.1% of 266 controls) [26].

Sleep-related rhythmic movements disorder (SRRMD) is characterized by repetitive, stereotyped, and rhythmic motor behaviors (not tremors) that occur predominantly during drowsiness or sleep and involve large muscle groups [23]. There are no studies reporting rhythmic movements in children with TD.

Sleep related breathing disorders

SRBD which include OSA, central sleep apnea, sleep-related hypoventilation, and sleep-related hypoxemia disorder [23] have been infrequently reported in patients diagnosed with TD [40]. Rare cases describing the presence of OSA and sudden infant death in children belonging to TD families led to the postulation of an increased risk of life-threatening apnea in infancy for TD gene carriers [41].

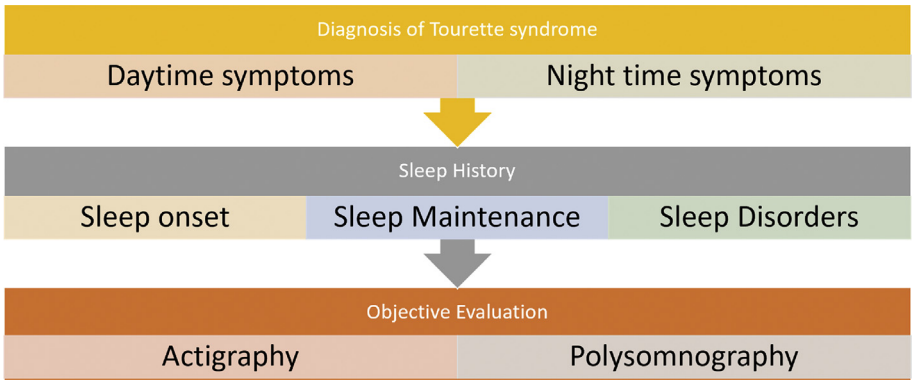

Fig. 2 Proposed evaluation of sleep disorders in children with tourette syndrome including assessment of sleep complaints, assessment of comorbid sleep disorders and consideration to use actigraphy and polysomnography.

Circadian rhythm sleep-wake disorders

Circadian rhythm sleep wake disorders are characterized by a chronic pattern of sleep and wake disturbance due to incongruence of the individual's circadian sleep-wake propensity and the 24-h social and physical environment [23]. Presence of circadian rhythm sleep-wake disorders were reported in 3 of 31 (9.7%) of patients with TD-only and in 2 of 48 (4.2%) TD + ADHD patients [5]. There are no other reported associations found to date.

Treatment options

There are currently no guidelines on the approach to treatment of sleep complaints in children with Tourette syndrome. As described through this review, sleep disruptions and increased overnight arousals secondary to the underlying TD can elicit or exacerbate other sleep conditions such as symptoms of insomnia, parasomnias, and daytime somnolence. It is therefore of utmost importance to assess sleep habits and sleep behaviors in children with TD. Comorbidities can further worsen sleep disruption and exacerbate effects on cognition, executive function, emotional regulation, and other associated consequences. Fig. 2 illustrates a potential algorithm for evaluation of sleep in children with TD. As is seen with improvement of sleep with treatment of underlying OSA or ADHD, treatment of underlying TD is important for the improvement of sleep related TD manifestations.

In general, the interventions recommended for treatment of tics include neuropsychological interventions (habit reversal training, exposure and response prevention, and comprehensive behavioral intervention), and medications. Medical treatment should be considered when tics cause emotional, physical, or social problems and consists mainly of antipsychotics. Atypical antipsychotics have been used for their antidopaminergic activity and potential benefit in both symptoms of Tourette and sleep complaints. A single case report of a 12 year old treated with risperidone showed benefit in sleep latency and sleep efficiency [42]. Most recently aripiprazole has shown some promising results [43].

Interestingly, studies have shown that iron deficiency has been associated with more severe tics in children with TD with iron supplementation improving tic severity [44]. Iron supplementation poses an interesting potential pathophysiology of brain iron deficiency in TD [45], which is also present in children with ADHD and some sleep related movement disorders (RLS and RSD) [46–48].

Although not studied specifically for sleep complaints in children with TD, some medicines commonly used for improvement of tics can potentially improve sleep complaints (clonidine, clonazepam, iron, among other). Table 2 lists a review of treatment options in TD with medicines potentially improving sleep marked with (*).

Illustrative case:

A 12 year old boy with TD presents for evaluation of sleep disruption and daytime sleepiness. The child does not have any comorbidities. Tics are frequent and brief presenting as both motor and vocal, but he does not feel they interfere with daytime activities, school, or interactions. The child does not snore, does not have symptoms of RLS, and does not report difficulty falling asleep, however during sleep the parents report he is restless, with bedsheets very disrupted in the morning. His bedtime is 9 PM and wake up time is 7 AM. He also reports waking up at least 3–4 times each night without any apparent precipitant. In the morning he wakes up sleepy and has difficulty focusing during school. When he comes home, he feels like taking a nap but is not able to fall asleep. The child does not take any medication.

A sleep study is performed to identify the unknown causes for frequent nocturnal awakening. A segment of the sleep study is shown in Fig. 3. Frequent tics were found throughout the night in all sleep stages; some associated with awakenings and sleep disruption.

Treatment of tics was recommended and discussed with the family. Ferritin levels were found to be low and iron supplementation started with improvement in tic frequency and improvement in sleep quality with subsequent resolution in daytime symptoms.

Table 2 Summary of Treatment (* means potential use in sleep).

Treatment	Subjects	Methods	Findings	Cite
Alpha Agonists				
Clonidine*	N = 27	Retrospective uncontrolled open-label study	9 (33%): Excellent Response 9 (33%): Moderate Response 9 (33%): Poor Response	[49]
	Expert Opinion from National Guideline of Traditional Chinese Medicine		First Line Therapy	[50]
Antiepileptics				
Topiramate *	Expert Opinion from National Guideline of Traditional Chinese Medicine		Second Line Off Label	[50]
Dopamine Depletors				
Tetrabenazine	9 patients	Retrospective uncontrolled open-label study	4 (44%): Marked/Lasting improvement 3 (33%): Mild/Transient improvement 2 (22%): Minimal/No response	[21]
	N = 15	Retrospective uncontrolled open-label study	7 (47%): Excellent Response 5 (33%): Moderate Response 3 (20%): Poor Response	[49]
D2 Blocker				
Tiapride	Expert Opinion from National Guideline of Traditional Chinese Medicine		First Line Therapy	[50]
	603 Patients age 5-18	Multisite, double-blind, double-dummy, randomized, placebo-controlled trial	68.3% in the tiapride arm had clinical response and these rates of response were significantly higher than those on placebo	[51]
Dopamine Precursor				
Very-low-dose levodopa therapy (VLDT)	Japanese pediatric neurologists	Questionnaire to providers	14 providers reported treating with VLDT for tics. VLDT was 30–50% effective for all types of tics	[52]
Benzodiazepine				
Clonazepam *	N = 13	Retrospective uncontrolled open-label study	5 (38%): Excellent Response 5 (38%): Moderate Response 3 (24%): Poor Response	[49]
Monoamine Oxidase Inhibitor				
Selegiline (Deprenyl)	25 boys, 4 girls with mean age 11.2 years old (range 6–18) with ADHD + TD	Open Trial	26 patients reported improvement of ADHD with 2 patients reporting exacerbation of tics	[53]
Antipsychotic				
Aripiprazole *	44 patients aged 18–58 Mean dose 12.2 mg	Prospective uncontrolled open-label study	Results suggest that aripiprazole may improve associated comorbid conditions in addition to tics in patients with TD	[54]
	Expert Opinion from National Guideline of Traditional Chinese Medicine		First Line Therapy	[50]
	78 Patients	Case Series	Aripiprazole is effective and safe in most patient	[55]
Sulpiride	114 patients reviewed	Retrospective analysis	Worthwhile beneficial effects occurred in 59% of patients	[56]
Fluphenazine	N = 28	Retrospective uncontrolled open-label study	15 (54%): Excellent Response 9 (32%): Moderate Response 4 (14%): Poor Response	[49]
Haloperidol	N = 24		11 (32%): Excellent Response 19 (56%): Moderate Response 4 (12%): Poor Response	[49]
	Expert Opinion from National Guideline of Traditional Chinese Medicine		Second Line Therapy	[50]
Pimozide	N = 9	Retrospective uncontrolled open-label study	5 (56%): Excellent Response 2 (22%): Moderate Response 2 (22%): Poor Response	[49]
Risperidone *	12 year old boy	Pre & Post PSG	Blockage of dopaminergic systems with antipsychotic risperidone reverts both TD symptoms and disturbances	[42]

(continued on next page)

Table 2 – (*continued*)

Treatment	Subjects	Methods	Findings	Cite
	Expert Opinion from National Chinese Medicine	Guideline of Traditional	Second Line Off Label	[50]
SSRI (Selective Serotonin Reuptake Inhibitor)				
Fluoxetine	21 year old 32 year old	Observational study	Significant reduction (at least 50%) of abnormal movements and objective improvements	[57]
Nonpharmacologic Therapy				
Comprehensive Behavioral Intervention for Tics (CBIT) *	126 children aged 9–17 from Dec 2004–May 2007 randomized to CBIT or supportive therapy and education.	RCT Observer Blind	Behavioral intervention led to a significantly greater decrease on the Yale Global Tic Severity Scale	[58]
Diet, Exercise and Sleep	6 Electronic Databases	Scoping Review	Study in Progress	[59]
Morning Light Therapy *	34 Adults with tick disorder		Findings showed some benefits following brief light therapy in tic disorder, but significantly greater eveningness and sleep disturbance	[60]
Alternate Therapy				
Cannabis/Cannabidiol (CBD)/ Cannabimovone (CBM)	10,000 Abstracts	Systematic Review	The evidence supporting improvement Tourette syndrome was described as limited, insufficient, or absent.	[61]
	98 patients	Retrospective analysis	CBM resulted in a subjective improvement of tics (of about 60% in 85% of treated cases), comorbidities (55% of treated cases, most often OCB/OCD, ADHD, and sleeping disorders), and quality of life (93%).	[62]
	42 patients	Interview	MC seems to hold promise in the treatment of TD as it demonstrated high subjective satisfaction by most patients however not without side effects and should be further investigated as a treatment option for this syndrome.	[63]
Nicotine	Expert opinion		When chronically taken, nicotine may result in protection against TD	[64]
Procedural Intervention				
Botulinum toxin	Expert Opinion		Botulinum toxin may be helpful in the treatment of focal motor tics and in some simple and complex phonic tics (including coprolalia)	[65]
Deep Brain Stimulation (DBS)	Expert Opinion		DBS for TD is a valid option for medically intractable patients	[66]
Supplement				
Iron Replacement *	Children <18 year old diagnosed with TD during 2009–2015 with recorded ferritin levels	Retrospective analysis	Iron supplementation showed a trend towards improvement of tic severity upon follow-up.	[44]
Changma Xifeng Tablets	Expert Opinion from National Chinese Medicine	Guideline of Traditional	First Line Therapy	[50]
Jiuwei Xifeng Granules	Expert Opinion from National Chinese Medicine	Guideline of Traditional	First Line Therapy	[50]
5-Ling Granule	603 Patients age 5-18	Multisite, double-blind, double-dummy, randomized, placebo-controlled trial	The clinical efficacy of 5-LGr is comparable to tiapride in reducing tics. Its safety profile is better than tiapride. 5-LGr can be considered a safe and effective therapy for TD.	[51]

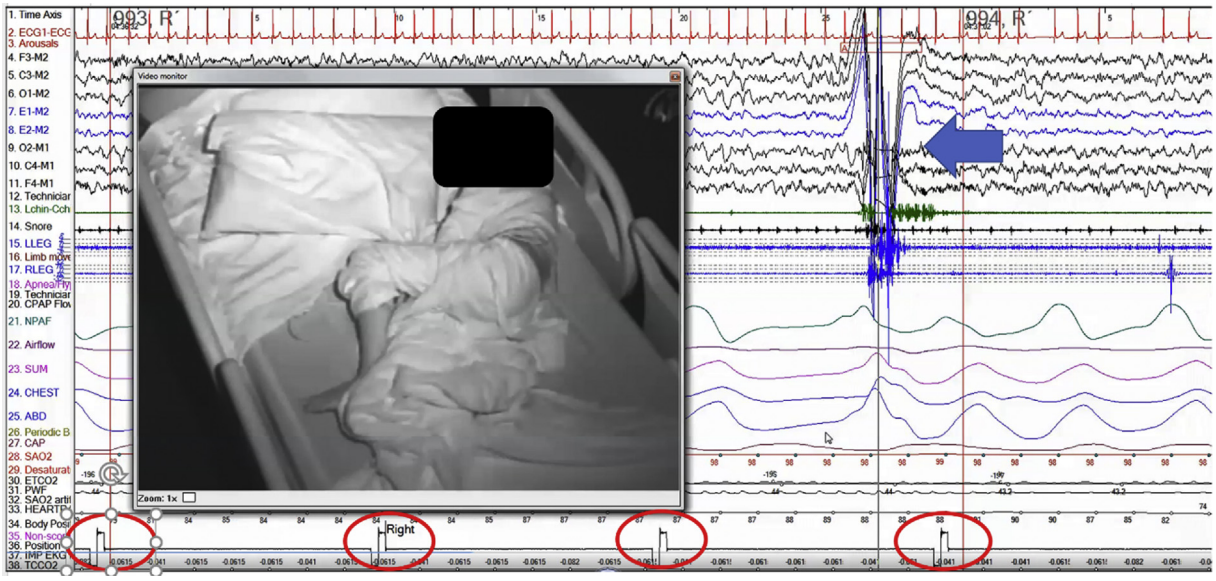

Fig. 3 Video-polysomnography segment demonstrating a tic during sleep stage REM (blue arrow). Red circles highlight position changes after tics resulting in sleep disruption. On left column from top down 1. Time axis, 2. Single lead electrocardiogram, 3. Scoring of arousals, 4–6 and 9–11 electroencephalogram, 7–8 electro oculogram, 12 technician notes, 13 chin electromyogram, 14 snore sensor, 15–17 leg electromyogram, 18–27 breathing sensors, 28–29 and 31–32 oxyhemoglobin saturation, 30 and 38 capnography, 33 heart rate, 34–36 body position sensor, 37 EKG.

Conclusion

As we have reviewed in this manuscript, children with TD are at high risk of sleep disruption and increase prevalence of some sleep disorders such as movement disorders during sleep. It is very important to remember that tics can persist in all stages of sleep and contribute to sleep disruption.

There is compelling need for the diagnosis and treatment of any sleep disorders in children with TD and/or ADHD to facilitate better management of problem behaviors. Through the review, we have also identified areas of that remain under further investigation with limited and inconclusive data to date.

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Conflicts of interest

There is no conflicts of interest to report for any of the authors.

REFERENCES

[1] Hashimoto T, Endo S, Fukuda K, Hiura K, Kawano N, Suzue J, et al. Increased body movements during sleep in Gilles de la Tourette syndrome. Brain Dev 1981;3:31–5.

[2] Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. Washington, DC: Washington, DC: American Psychiatric Publishing; 2013.

[3] Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 1: the epidemiological and prevalence studies. J Psychosom Res 2008;65:461–72.

[4] Cohrs S, Rasch T, Altmeyer S, Kinkelbur J, Kostanecka T, Rothenberger A, et al. Decreased sleep quality and increased sleep related movements in patients with Tourette's syndrome. J Neurol Neurosurg Psychiatry 2001;70:192–7.

[5] Ghosh D, Rajan PV, Das D, Datta P, Rothner AD, Erenberg G, et al. Sleep disorders in children with Tourette syndrome. Pediatr Neurol 2014;51:31–5.

[6] Freeman RD. Tic disorders and ADHD: answers from a world-wide clinical dataset on Tourette syndrome. Eur Child Adolesc Psychiatr 2007;16:15–23.

[7] Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P, et al. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. Dev Med Child Neurol 2000;42:436–47.

[8] Singer HS. Tics and tourette syndrome. Continuum (Minneap Minn) 2019;25:936–58.

[9] GHosh D. 47th annual meeting of the child neurology society. Ann Neurol 2018;84:S370–1.

[10] Goldstein AN, Walker MP. The role of sleep in emotional brain function. Annu Rev Clin Psychol 2014;10:679–708.

[11] Brand S, Kirov R. Sleep and its importance in adolescence and in common adolescent somatic and psychiatric conditions. Int J Gen Med 2011;4:425–42.

[12] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. Sleep 2015;38:843–4.

[13] Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, et al. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. J Clin Sleep Med 2016;12:785–6.

[14] International classification of sleep disorders. 3rd ed. Darien: IL American Academy of Sleep Medicine; 2014.
[15] Aurora RN, Zak RS, Karippot A, Lamm CI, Morgenthaler CI, Auerbach SH, et al. Practice parameters for the respiratory indications for polysomnography in children. Sleep 2011;34:379–88.
[16] Ricketts EJ, Rozenman M, Choy C, Goldberg HB, Kim JS, Colwell CS, et al. Sleep sufficiency in pediatric and adolescent tourette's disorder: national survey of children's health. J Dev Behav Pediatr 2018;39:72–6.
[17] Lee WT, Huang HL, Wong LC, Weng WC, Vasylenko T, Jong YJ, et al. Tourette syndrome as an independent risk factor for subsequent sleep disorders in children: a nationwide population-based case-control study. Sleep 2017;40:zsw072.
[18] Kirov R, Kinkelbur J, Banaschewski T, Rothenberger A, et al. Sleep patterns in children with attention-deficit/hyperactivity disorder, tic disorder, and comorbidity. JCPP (J Child Psychol Psychiatry) 2007;48:561–70.
[19] Stephens RJ, Chung SA, Jovanovic D, Guerra R, Stephens B, Sandor P, et al. Relationship between polysomnographic sleep architecture and behavior in medication-free children with TS, ADHD, TS and ADHD, and controls. J Dev Behav Pediatr 2013;34:688–96.
[20] Voderholzer U, Müller N, Haag C, Riemann D, Straube A, et al. Periodic limb movements during sleep are a frequent finding in patients with Gilles de la Tourette's syndrome. J Neurol 1997;244:521–6.
[21] Jankovic J, Glaze DG, Frost Jr JD. Effect of tetrabenazine on tics and sleep of Gilles de la Tourette's syndrome. Neurology 1984;34:688–92.
[22] Martino D, Ganos C, Worbe Y. Neuroimaging applications in tourette's syndrome. Int Rev Neurobiol 2018;143:65–108.
[23] American Academy of Sleep M. International classification of sleep disorders. 2014.
[24] Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin 1987;10:541–53.
[25] Romano A, Cundari G, Bruni O, Cardona F, et al. Tic disorders and arousal dysfunction: clinical evaluation of 49 children and adolescents. Minerva Pediatr 2004;56:327–34.
[26] Modafferi S, Stornelli M, Chiarotti F, Cardona F, Bruni O, et al. Sleep, anxiety and psychiatric symptoms in children with Tourette syndrome and tic disorders. Eur J Paediatr Neurol 2016;20:696–703.
[27] Isomura K, Sidorchuk A, Sevilla-Cermeño L, Åkerstedt T, Silverberg-Morse M, Larsson H, et al. Insomnia in tourette syndrome and chronic tic disorder. Mov Disord 2021;37:392–400.
[28] Lundetrae RS, Saxvig IW, Pallesen S, Aurlien H, Lehmann S, Bjorvatn B, et al. Prevalence of parasomnias in patients with obstructive sleep apnea. A registry-based cross-sectional study. Front Psychol 2018;9:1140.
[29] Storch EA, Merlo LJ, Lack C, Milsom VA, Geffken GR, Goodman WK, et al. Quality of life in youth with tourette's syndrome and chronic tic disorder. J Clin Child Adolesc Psychol 2007;36:217–27.
[30] Comings DE, Comings BG. A controlled study of Tourette syndrome. VI. Early development, sleep problems, allergies, and handedness. Am J Hum Genet 1987;41:822–38.
[31] Wand RR, Matazow GS, Shady GA, Furer P, Staley D, et al. Tourette syndrome: associated symptoms and most disabling features. Neurosci Biobehav Rev 1993;17:271–5.
[32] Barone DA, Henchcliffe C. Rapid eye movement sleep behavior disorder and the link to alpha-synucleinopathies. Clin Neurophysiol 2018;129:1551–64.
[33] Nevsimalova S, Prihodova I, Kemlink D, Lin L, Mignot E, et al. REM behavior disorder (RBD) can be one of the first symptoms of childhood narcolepsy. Sleep Med 2007;8:784–6.
[34] Trajanovic NN, Voloh I, Shapiro CM, Sandor P, et al. REM sleep behaviour disorder in a child with Tourette's syndrome. Can J Neurol Sci 2004;31:572–5.
[35] Thompson MD, Comings DE, Abu-Ghazalah R, Jereseh Y, Lin L, Wade J, et al. Variants of the orexin2/hcrt2 receptor gene identified in patients with excessive daytime sleepiness and patients with Tourette's syndrome comorbidity. Am J Med Genet B Neuropsychiatr Genet 2004;129b:69–75.
[36] Allen RP, Singer HS, Brown JE, Salam MM, et al. Sleep disorders in Tourette syndrome: a primary or unrelated problem? Pediatr Neurol 1992;8:275–80.
[37] Kostanecka-Endress T, Banaschewski T, Kinkelbur J, Wüllner I, Lichtblau S, Cohrs S, et al. Disturbed sleep in children with Tourette syndrome: a polysomnographic study. J Psychosom Res 2003;55:23–9.
[38] Lespérance P, Djerroud N, Diaz Anzaldua A, Rouleau GA, Chouinard S, Richer F, et al. Restless legs in Tourette syndrome. Mov Disord 2004;19:1084–7.
[39] Rivière JB, Xiong L, Levchenko A, St-Onge J, Gaspar C, Dion Y, et al. Association of intronic variants of the BTBD9 gene with Tourette syndrome. Arch Neurol 2009;66:1267–72.
[40] Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG, et al. Sleep disorders in tourette syndrome. Sleep Med Rev 2020;53:101335.
[41] Sverd J, Montero G. Is Tourette syndrome a cause of sudden infant death syndrome and childhood obstructive sleep apnea? Am J Med Genet 1993;46:494–6.
[42] Arana-Lechuga Y, Sanchez-Escandón O, de Santiago-Treviño N, Castillo-Montoya C, Terán-Pérez G, Velázquez-Moctezuma J, et al. Risperidone treatment of sleep disturbances in Tourette's syndrome. J Neuropsychiatry Clin Neurosci 2008:375–6.
[43] Cavanna AE, Selvini C, Termine C, Luoni C, Luoni CM, Rickards H, et al. Tolerability profile of aripiprazole in patients with Tourette syndrome. J Psychopharmacol 2012;26:891–5.
[44] Ghosh D, Burkman E. Relationship of serum ferritin level and tic severity in children with Tourette syndrome. Childs Nerv Syst 2017;33:1373–8.
[45] Cortese S, Lecendreux M, Bernardina BD, Mouren MC, Sbarbati A, Konofal E, et al. Attention-deficit/hyperactivity disorder, Tourette's syndrome, and restless legs syndrome: the iron hypothesis. Med Hypotheses 2008;70:1128–32.
[46] Konofal E, Lecendreux M, Arnulf I, Mouren MC, et al. Iron deficiency in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2004;158:1113–5.
[47] Dosman C, Witmans M, Zwaigenbaum L. Iron's role in paediatric restless legs syndrome - a review. Paediatr Child Health 2012;17:193–7.
[48] DelRosso LM, Picchietti DL, Ferri R. Comparison between oral ferrous sulfate and intravenous ferric carboxymaltose in children with restless sleep disorder (RSD). Sleep 2021;44:zsaa155.
[49] Jankovic J, Rohaidy H. Motor, behavioral and pharmacologic findings in Tourette's syndrome. Can J Neurol Sci 1987;14:541–6.
[50] Liu ZS, Cui YH, Sun D, Lu Q, Jiang YW, Jiang L, et al. Current status, diagnosis, and treatment recommendation for tic disorders in China. Front Psychiatr 2020;11:774.
[51] Zheng Y, Zhang ZJ, Han XM, Ding Y, Chen YY, Wang XF, et al. A proprietary herbal medicine (5-Ling Granule) for Tourette syndrome: a randomized controlled trial. JCPP (J Child Psychol Psychiatry) 2016;57:74–83.
[52] Hoshino K, Hayashi M, Ishizaki A, Kimura K, Kubota M, Nezu A, et al. Very-low-dose levodopa therapy for pediatric neurological disorders: a preliminary questionnaire in Japan. Front Pediatr 2021;9:569594.
[53] Jankovic J. Deprenyl in attention deficit associated with Tourette's syndrome. Arch Neurol 1993;50:286–8.

[54] Gerasch S, Kanaan AS, Jakubovski E, Müller-Vahl KR, et al. Aripiprazole improves associated comorbid conditions in addition to tics in adult patients with gilles de la Tourette syndrome. Front Neurosci 2016;10:416.
[55] Wenzel C, Kleimann A, Bokemeyer S, Müller-Vahl KR, et al. Aripiprazole for the treatment of tourette syndrome: a case series of 100 patients. J Clin Psychopharmacol 2012;32:548–50.
[56] Robertson MM, Schnieden V, Lees AJ. Management of Gilles de la Tourette syndrome using sulpiride. Clin Neuropharmacol 1990;13:229–35.
[57] Silvestri R, Raffaele M, De Domenico P, Tisano A, Laganà A, Di Perri R, et al. Serotoninergic agents in the treatment of Gilles de la Tourette's syndrome. Acta Neurol 1994;16:58–63.
[58] Piacentini J, Woods DW, Scahill L, Wilhelm S, Peterson AL, Chang S, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA 2010;303:1929–37.
[59] Nosratmirshekarlou E, Shafiq S, Goodarzi ZS, Martino D, Pringsheim T, et al. Effect of diet, exercise and sleep on tic severity: a scoping review protocol. BMJ Open 2019;9:e024653.
[60] Ricketts EJ, Burgess HJ, Montalbano GE, Coles ME, McGuire JF, Thamrin H, et al. Morning light therapy in adults with Tourette's disorder. J Neurol 2022;269:399–410.
[61] Abrams DI. The therapeutic effects of cannabis and cannabinoids: an update from the national academies of sciences, engineering and medicine report. Eur J Intern Med 2018;49:7–11.
[62] Milosev LM, Psathakis N, Szejko N, Jakubovski E, Müller-Vahl KR, et al. Treatment of gilles de la Tourette syndrome with cannabis-based medicine: results from a retrospective analysis and online survey. Cannabis Cannabinoid Res 2019;4:265–74.
[63] Thaler A, Arad S, Schleider LB, Knaani J, Taichman T, Giladi N, et al. Single center experience with medical cannabis in Gilles de la Tourette syndrome. Park Relat Disord 2019;61:211–3.
[64] Jarvik ME. Beneficial effects of nicotine. Br J Addict 1991;86:571–5.
[65] Thenganatt MA, Jankovic J. Recent advances in understanding and managing tourette syndrome [version 1 peer review: 3 approved]. F1000 research 2016;5:152.
[66] Baldermann JC, Schüller T, Huys D, Becker I, Timmermann L, Jessen F, et al. Deep brain stimulation for tourette-syndrome: a systematic review and meta-analysis. Brain stimulation 2015;9:296–304.