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REVIEW ARTICLES

Associations Between Neuropsychological, Neurobehavioral and Emotional Functioning and Either Narcolepsy or Idiopathic Hypersomnia in Children and Adolescents

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Study Objectives: Narcolepsy and idiopathic hypersomnia are chronic neurological sleep disorders characterized by hypersomnolence or excessive daytime sleepiness. This review aims to systematically examine the scientific literature on the associations between narcolepsy and idiopathic hypersomnia and their effect on intellectual functioning, academic achievement, behavior, and emotion.

Methods: Published studies that examined those associations in children and adolescents were included. Studies in which children or adolescents received a clinical diagnosis, and in which the associated function was measured with at least one objective instrument were included. Twenty studies published between 1968 and 2017 were eligible for inclusion in this review.

Results: There does not appear to be a clear association between intellectual functioning and narcolepsy or idiopathic hypersomnia; however, limited research is an obstacle to obtaining generalizability. The variability in results from studies investigating associations between academic achievement and these two hypersomnolence disorders suggests that further research using standardized and validated assessment instruments is required to determine if there is an association. Behavior and emotion appear to be significantly affected by narcolepsy. Only two studies included populations of children and adolescents with idiopathic hypersomnia.

Conclusions: Further research using larger populations of children and adolescents with narcolepsy or idiopathic hypersomnia while utilizing standardized and validated instruments is required, because the effect of these conditions of hypersomnolence varies and is significant for each individual.

Keywords: academic achievement, behavior, emotion, excessive daytime sleepiness, hypersomnolence, idiopathic hypersomnolence, intellectual functioning, narcolepsy

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INTRODUCTION

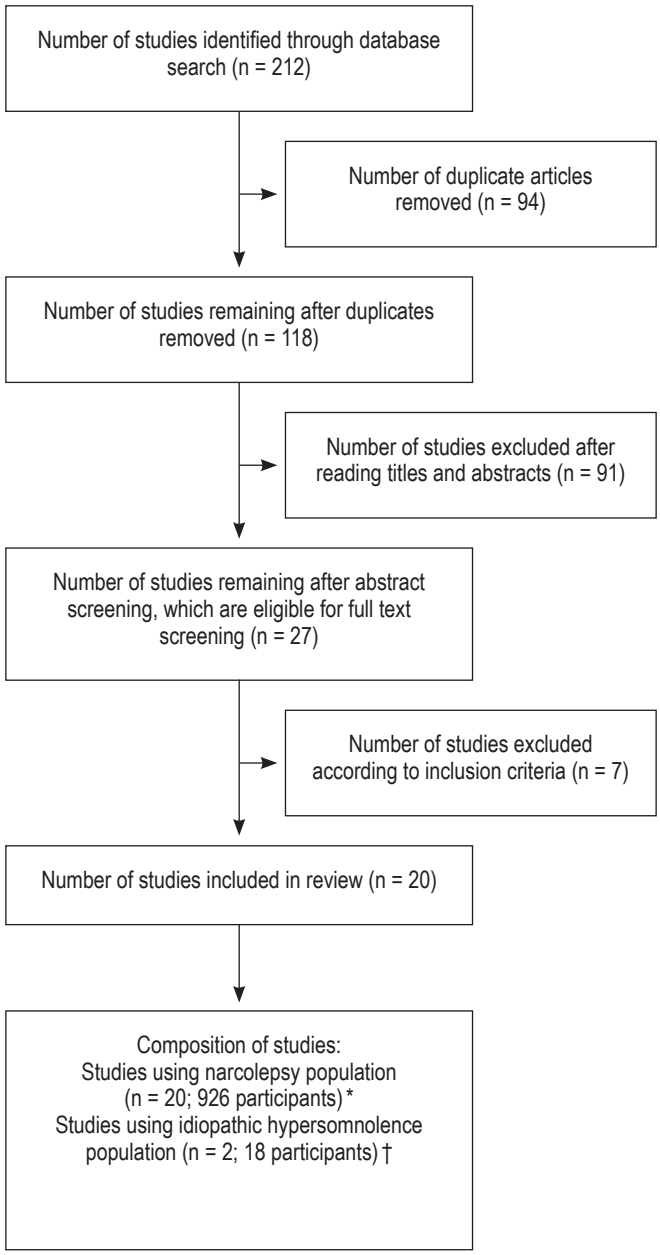
Daytime sleepiness has a profound effect on everyday function in children and adolescents. Excessive daytime sleepiness (EDS), or hypersomnolence, is frequently seen in association with sleep disorders such as obstructive sleep apnea (OSA). Hypersomnolence in the pediatric population with OSA and its association with learning difficulties, behavior, and psychological well-being have been studied extensively.[1–4] However, other causes of hypersomnolence have not been investigated as thoroughly. Hypersomnolence is the primary symptom for the group of sleep disorders known as central disorders of hypersomnolence, of which narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia are possibly the most well known.[5] These conditions frequently present in childhood and adolescence, but often take some time to be diagnosed.[6–8] A recent review by Blackwell et al.[9] sought to identify to what extent research had focused on the effects of narcolepsy in children, in particular in their cognitive functioning and psychosocial well-being. The reviewers were responding to concerns regarding an increase in the incidence of narcolepsy diagnoses, and the necessity for monitoring these children and adolescents to enable management of the effects of this disorder. They were only able to identify eight studies that met their criteria for inclusion. The authors noted that restrictions such as small sample sizes and lack of control groups limited understanding of the consequences of narcolepsy. This analysis seeks to build on their review: (1) by widening the criteria to include both narcolepsy and idiopathic hypersomnolence as central disorders of hypersomnolence, (2) through an examination of a broader range of outcomes including intellectual functioning, academic functioning, executive functioning, behavior, and mood, and (3) by including papers from 1968 through to 2017.

METHODS

Literature Search

Published studies that examined the associations between neuropsychological, neurobehavioral, and emotional functioning and either narcolepsy or idiopathic hypersomnia in children and adolescents were included. Studies in which children or adolescents received a clinical diagnosis, and in which the

Figure 1—Research populations.



Flow diagram for identification of studies and research populations. * = not all studies identified whether the children had narcolepsy with or without cataplexy. † = populations of children with idiopathic hypersomnolence were included in studies with populations of children with narcolepsy.

associated function was measured with at least one objective instrument were included. The search parameters were confined to papers published in English. MEDLINE and Embase databases were accessed to search articles from 1960 through June 2017 using combinations of the following subject terms: narcolepsy OR idiopathic hypersomnia, AND children OR pediatric OR paediatric, AND cognition OR memory OR learning OR cognitive OR neuropsychological OR neurobehavioural OR neurobehavioral OR behaviour OR behavior. This yielded a total of 118 articles.

Inclusion Criteria

Titles and abstracts were scanned for the inclusion criteria, with the full-text version (if available) being collected when further information was required to assess suitability, or if it was determined the article fulfilled criteria. Criteria included articles written in English and published in peer-reviewed journals. Quantitative studies gave sound data on the effect of hypersomnolence whereas the selected case studies gave qualitative information, which is significant in gaining real-world perspectives of the implications. A total of 20 articles were included for this review (Figure 1).

Quality Assessment

To assess the quality of studies, a set of criteria was developed based on criteria utilized in recent similar reviews. Unique criteria were developed due to the specificity of this field of research and the understanding that research in this area is generally unable to utilize randomized controlled trials (RCTs). Each article was rated according to these criteria (Table 1 and Table S1 in the supplemental material). Studies were excluded if they did not provide details on demographic and diagnostic details of participants or if there was a high risk of bias according to the Cochrane risk of bias tool.[10]

RESULTS

Study Characteristics

Study characteristics for each of the 20 articles included in this review are summarized in Table 2. This gives information on sample size and origin (such as the inclusion of narcolepsy with and without cataplexy and the use of matched control groups), country, design (six studies were case studies providing a wealth of qualitative information on the more personal effect of narcolepsy on individuals), diagnostics, and psychometric measures used. Results for each are reported and the strengths and weaknesses for each study identified.

Nine studies used relatively large groups, ranging in size from 29 (narcolepsy type 1) through to 243 (narcolepsy with and without cataplexy). Access to these larger groups was due to the increase in the number of cases of children with narcolepsy following the 2009 Pandemrix vaccination used in several European countries. This vaccine triggered what is thought to be an autoimmune reaction, causing narcolepsy to develop in people who were genetically at risk.[11–13]

Methodological Quality of Studies

A full overview of the quality ratings of the included studies can be found in Table S1, with the criteria for this table outlined in Table 1. Table S1 also contains the bias and Strength of Recommendation Taxonomy (SORT) levels that contain three levels for study quality (level 1 being good-quality patient-oriented evidence) and three levels for strength of recommendation (level A representing consistent evidence). The screening for bias used the Cochrane bias method, and all studies were identified as having a low risk of bias. The SORT criteria were used to identify the quality, quantity, and consistency of evidence. Level 1 studies require good-quality, patient-oriented

Table 1—Scale for methodological quality assessment.

Study Sample
A. Inclusion and exclusion criteria are reported.
B. Diagnosis information including polysomnographic included.
C. Demographic variables of participants described (age range, sex).
Study Design
D. Data collection is sufficiently described to enable study replication.
E. The neuropsychological, neurobehavioral or emotional area is a primary or secondary outcome measure.
F. The neuropsychological, neurobehavioral or emotional area is objectively measured using a validated and standardized instrument.
Results
G. Recognized statistical techniques are used for analysis of results.

Each item is scored 1 (present) or 0 (absent). Best possible score is 7.

Table 2—Summary of papers included within the review.

Study, Year	Quality*	Sample	Country	Design	Diagnostics	Psychometric Measures	Results	Comments
Aran et al. 2010[23]	5	Narcolepsy with cataplexy (n = 51) •Prepubertal onset (n = 27) •Peripubertal onset (n = 15) •Postpuberty onset (n = 9) •Age at first symptom 10.3 ± 0.5 years •Age at diagnosis 11.8 ± 0.5 years •Male = 57%	USA	•Retrospective cohort study •Prospective cohort study	•SSI •HLA-DQB1*0602 typing •PSG or MSLT •MSL: min: 2.8 ± 0.6 •CSF Hypocretin-1 measurements	Clinical interview	•72% reported a decrease in the academic performance after disease onset, with significant improvement in academic performance but not for social problems with appropriate treatment. •25% identified with ADD or learning disabilities after onset of narcolepsy symptoms. •40% had depression or anxiety after onset of narcolepsy symptoms, with the percentage of children experiencing depression or anxiety increasing with age.	Strengths: •Relatively large sample size. •Large amount of quantitative data produced. Weaknesses: •Parent questionnaire designed for this study so not validated and standardized. •Lack of a control group. •Reliant on parent observations.
Avis et al. 2015[28]	7	•Narcolepsy with cataplexy (n = 7) •Narcolepsy without cataplexy (n = 11) •Idiopathic hypersomnia (n = 15) •Hypersomnolence male = 49% •HC = 33	USA	CCS	•ESS for children with central hypersomnia: 12.3 (SD = 5.7) •ESS for HC: 6.9 (SD = 3.8)	•Wolfson and Carskadon's School Sleep Habits Survey (academic grades extracted) •PedsQL	Children with central hypersomnia scored significantly lower on academic grades (P < .05) and were significantly sleepier (P < .001)	Strengths: •Matched case control design. •Relatively large sample size and equivalent control group size. Weaknesses: •Children previously diagnosed but time of diagnosis and length of treatment was unknown. •Child self-report and parent report measures for psychosocial functioning can be biased. •ESS not established as fully valid with children.
Dias Costa et al. 2014[27]	6	Narcolepsy (n = 8) •With cataplexy (n = 5) •Male = 63%	Portugal	CS	•PSG •MSLT •HLA-DQB1*0602 allele testing	Parent report	•There was impact on school performance in 5 cases and psychosocial difficulties in 3 of them. •Following behavioral therapy, nutritional counseling and pharmacological support: there was an improvement in school performance and social integration skills in all cases. •In two 12-year-old teenagers, it was necessary to add psychiatric support due to behavioral problems and depressive symptomatology.	Strengths: •Large amount of in-depth quantitative and qualitative data produced. •Diagnostics were detailed and deeply investigative. Weaknesses: •Small group. •Parent report measure used so could be biased.

* = quality score out of 7. ADHD-RS = attention deficit hyperactivity disorder-rating scale, ADHD = attention deficit hyperactivity disorder, AESS = adapted Epworth Sleepiness Scale, ASSQ = Autism Spectrum Screening Questionnaire, CBCL = Achenbach Child Behavior Checklist, CCS = case control study, CDI = Children's Depression Inventory, CPRS-R = Conners Parent Rating Scale-revised, CS = cross-sectional, DAWBA = development and well-being assessment, DSM = Diagnostic and Statistical Manual of Mental Disorders, EDS = excessive daytime sleepiness, EF = executive functioning, ESS = Epworth Sleepiness Scale, FSIQ = full scale intelligence quotient, HC = healthy controls, ISI = Insomnia Severity Index, K-ABC = Kaufman Assessment Battery for Children, MSLT = Multiple Sleep Latency Test, MWT = Maintenance of Wakefulness Test, NEPSY-II = Developmental NEuroPSYchological Assessment, NVIQ = nonverbal intelligence quotient, NT1 = narcolepsy type 1, NT2 = narcolepsy type 2, PANSS = Positive and Negative Syndrome Scale, PDSS = Pediatric Daytime Sleepiness Scale, PedsQL = Pediatric Quality of Life Inventory, PIQ = performance intelligence quotient, PRI = Perceptual Reasoning Index, PSG = polysomnography, SD = standard deviation, SDQ = Strengths and Difficulties Questionnaire, SES = socioeconomic status, SSI = Stanford Center for Narcolepsy Sleep Inventory, VCI = Verbal Comprehension Index, VIQ = verbal IQ, VSP-A = Vécu et Santé Perçue de l'Adolescent [perceived health-related quality of life in adolescents], WAIS = Wechsler Adult Intelligence Scale, WISC = Wechsler Intelligence Scale for Children, WMI = Working Memory Index, WPPSI = Wechsler Preschool and Primary Scale of Intelligence, WRAML = Wide Range Assessment of Memory and Learning.

Table 2 continues on the following page

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Dorris et al. 2008 [14]	7	•Narcolepsy with cataplexy (n = 12) •Age range: 7–16 years	UK	CS	MSLT	•WISC-III •CBCL •Clinical interview with clinical psychologist	•11 of 12 participants had FSIQ within normal range; but 3 had VIQ > NVIQ and 2 had NVIQ > VIQ. •10 out of 12 children scored in the clinically significant range on the CBCL Total Score Index. •Only one child's score for Aggressive Behavior was in the clinically significant range.	Strengths: •Assessment instruments are well-validated and reliable measures with normative data. •Large amount of quantitative and qualitative data produced on each individual. Weaknesses: •Lack of a control group. •Reliant on parent observations. •Seven children were medicated (modafinal) and five untreated prior to the assessment. •Small group.
Frolich et al. 2001 [29]	6	•Group 1: ADHD with impaired nighttime sleep (n = 15) •Group 2: ADHD without impaired nighttime sleep (n = 8) •Group 3: narcolepsy (n = 3) and idiopathic hypersomnia (n = 3) •Four of six hypersomnolence children also had diagnosis of ADHD. •Males = 90% (one female in each group)	Germany	CS	MWT: three trials	MWT used as vigilance/alertness measure	Children with increased daytime sleepiness (narcolepsy and idiopathic hypersomnia) presented a shortened mean sleep latency during the trials: MWT: mean sleep latencies (minutes ± SD) for excessive somnolence group: •Trial 1: 8.5 ± 9.3 •Trial 2: 7.0 ± 9.0 •Trial 3: 11.2 ± 10 Children with ADHD: •with impaired nighttime sleep, average over 3 trials = 17.2 minutes. •without impaired nighttime sleep, average over 3 trials = 16.3 minutes. More children with narcolepsy and idiopathic hypersomnia fell asleep during MWT than ADHD children (72% versus 40.6%).	Strengths: •Validated assessment instrument used. •Data indicates MWT would be a valid instrument for assessment of vigilance and alertness. •All children were drug free for one week prior to assessments. Weaknesses: •Small group sizes, particularly the hypersomnolence group. •Narcolepsy children were not identified as having/not having cataplexy.
Guilleminault and Pelayo 1998 [25]	5	•Narcolepsy with cataplexy (n = 51) •Male = 57%	USA	Prospective study	•PSG •MSLT (in children ≥ 7 years) •HLA-DQB1*0602 allele testing (46 children)	•Brief psychiatric interviews •Parent reports	•Parents of 60% of children had been contacted by the school regarding "laziness". •62% of children had poor academic performance. •61% of children had periods of non-compliance with pharmacological treatment. •80% reported feelings of helplessness. •80% reported feeling depressed at not being same as peers. •20% symptoms of reactive depression.	Strengths: •Relatively large sample. •Large amount of data collected on each child and collectively on the group. Weaknesses: •No control group. •Lack of use of validated and reliable instruments with normative data for assessing psychological well-being.
Hansen 1997 [31]	7	•Sleep apnea (n = 7) •Narcolepsy (n = 7) •HC (n = 6) •Male = 65%	USA	CS	•PSG •MSLT	•Auditory attention: WISC-R (digit span) •Visual attention: Finger windows from WRAML •General memory: 4 tests from WRAML	•Re-tested after 5 months to lessen potential practice effects. •Cognitive deficits for both apnea and narcolepsy groups. •Mild cognitive difficulties amongst children in narcolepsy group. •Posttreatment in failed to confirm significant improvement for narcolepsy or apnea groups, but there was a significant improvement for control group.	Strengths: •Use of validated and reliable instruments with normative data used. •As a preliminary study, identified processes that would work well with larger groups. Weaknesses: •Relatively small groups. •Number of factors such as sleep fragmentation, and differential effects of age, sex and SES were unable to be controlled for given the small numbers.

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Inocente et al. 2014 [22]	7	Narcolepsy (n = 117) •Age range 5–17.5 years •Cataplexy present = 81% •Male = 56% HC (n = 69) •Age range 7–17.8 years •Male = 42%	France	CS	•PSG •MSLT •AESS (narcolepsy = 73, HC = 37) •PDSS (narcolepsy = 72, HC = 58) •Both AESS & PDSS (narcolepsy = 44, HC = 35) •Cataplexy = Cataplexy Severity Rating Score	•CDI (narcolepsy = 88, HC = 64) •ISI (narcolepsy = 93, HC = 66) •Conners Parents Rating Scale-Revised (narcolepsy = 85, HC = 61) •Chalder's fatigue scale (narcolepsy = 89, HC = 65) •Parent questionnaire on school difficulties, etc. •Health-related quality of life questionnaire	•Narcolepsy children were significantly more obese, significantly sleepier, significantly more fatigued, had significantly more insomnia, significantly more depressed, had significantly more school difficulties (P < .001). •41% of children with narcolepsy reported school difficulties compared to 7.5% of HC (P = .002) [parent report]. •28% of children with narcolepsy did not pass a school year and repeated it prior to narcolepsy diagnosis compared to 7.5% of HC (P < .001). •30% of children with narcolepsy compared with 8.9% of HC had high levels of absenteeism (P = .002). •25% of children with narcolepsy have clinically significant depressive feelings on CDI (CDI ≥ 16) compared to 15.6% of HC.	Strengths: •Relatively large sample. •Assessment instruments are well-validated and reliable measures with normative data. •Large amount of quantitative data produced on each child. •Control group. Weaknesses: •Narcoleptic group were the more seriously affected patients and possibly not reflective of all individuals with narcolepsy.
Inocente et al. 2014 [34]	7	•Narcolepsy (n = 88) •Age 11.9 ± 3.1 years •Cataplexy present = 80.7% •Male = 50%	France	CS	•MSLT •AESS (60 children) •PDSS (69 children) •Both AESS & PDSS (43 children)	•Conners' Parent Rating Scale, Revised •CDI	•Conduct: median T-score = 49 (range: 38–111). •Impulsivity: median T-score = 48 (range: 35–94). •Absenteeism: 30/88 (35.3%). •Hyperactivity significantly associated with depressive symptoms in children with narcolepsy. •7% of children with narcolepsy had a high level of ADHD symptoms (CPRS-R > 75). •Conduct significantly associated with depressive symptoms. •Depression score positively correlated with EDS (14% by AESS & 24% by PDSS). •High levels of depressive symptoms affect 25% of children with narcolepsy.	Strengths: •Relatively large sample. •Assessment instrument is a well-validated and reliable measure with normative data. •Large amount of quantitative data produced on each child. •In-depth analysis of depression and relationship to other aspects of manifestations of narcolepsy. Weaknesses: •No control group. •Behavior data and concerns not discussed in depth.
Ito et al. 2014 [30]	7	Narcolepsy with cataplexy in a monozygotic twin	Japan	CCS	PSG	•WISC-III subtests •K-ABC	•FSIQ = average, with significant difference between VIQ and PIQ. •Poor memory •Slow processing speed on both WISC-III and K-ABC. •Poor knowledge, vocabulary, planning, attention. •Average comprehension, object assembly, and maze scores.	Strengths: •Assessment instruments are well-validated and reliable measures with normative data. •Large amount of quantitative data produced with comparisons to monozygotic twin. •Qualitative comparisons made between sisters with only difference being the head injuries. Weaknesses: •Not all assessments were administered to the twin so enable quantitative comparisons.
Jennum et al. 2017 [36]	7	Narcolepsy (n = 243) •Age range 0–19 years •Male = 52.7% HC (n = 970, matched by age, sex, geography) •Male = 52.8%	Denmark	CS	Not stated – Danish National Patient Registry uses several international classification systems including International Classification of Disorders (ICD-10)	•21 WHO areas investigated •ICD-10 criteria used to identify co-morbidities	•In the year before first narcolepsy diagnosis: 10.8% of narcolepsy and 2.4% of HC had diagnoses of mental and psychiatric disorders. •Three years after narcolepsy diagnosis: 11.4% of narcolepsy and only 2.1% of HC had diagnoses of mental and psychiatric disorders. •Summary finding: childhood- and adolescence-onset narcolepsy is associated with a wide range of comorbidities: 59.5% had 3+ comorbidities 3 years after diagnosis.	Strengths: •Large sample. •Diagnoses utilized internationally recognized criteria. •Large amount of quantitative data available on each child/adolescent. •Large control group. Weaknesses: •Diagnostic process for narcolepsy was not identified in the national register. •National register did not distinguish between narcolepsy with and without cataplexy.

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Karjalainen et al. 2014 [26]	6	Narcolepsy (n = 6)	Finland	CCS with mixed methods research	Not stated	•SDQ •Parent and teacher questionnaires	•Parent reports of problems with concentration and attention following getting narcolepsy. •Skills that were learned previously were lost at the beginning of the illness •Five out of six children had behavioral, social, and emotional problems. •Parent reports of problems with depression and stress.	Strengths: •Large amount of qualitative and quantitative data produced on each child. •Detailed investigation into each child. •SDQ is a commonly used assessment instrument. Weaknesses: •Small sample size. •Lack of objective measures meaning a reliance on parent and teacher observations and interviews. •SDQ is widely used but not well validated. •Authors did not identify whether cataplexy was present in each child.
Kotagal et al. 1990 [35]	5	•Narcolepsy (n = 4) •Age range 8–12 years	USA	CCS	•PSG •MSLT	Clinical interview	Significant behavioral problems were present in all four patients; these could result from the frustrations associated with chronic sleepiness.	Strengths: •Large amount of qualitative data produced on each child. •Detailed investigation into each child. Weaknesses: •Small sample size. •Lack of objective measures [for behavior] meaning a reliance on parent observations and interviews.
Lecendreux et al. 2015 [32]	7	Narcolepsy with cataplexy (n = 86) •Age range 5.9–17.4 years •Males = 55.8% Narcolepsy without cataplexy (n = 22) •Age range 6.6–17.8 years •Males = 45.5% HC (n = 67) •Age range 7.0–17.9 years •Males = 40.3%	France	CS	•MSLT •PDSS •HLA-DQB1*0602 allele testing	•ADHD-RS •CDI •VSP-A	•Total ADHD symptoms were two-fold higher in narcolepsy without cataplexy than in controls, and 1.8 higher in narcolepsy with cataplexy than in controls. •Prevalence of ADHD in controls was similar to general populations in previous studies (3.5–7.1%). •EDS was associated with ADHD. •Individuals with narcolepsy were at a greater risk for depressive symptoms, and also had poorer quality of life.	Strengths: •Relatively large sample. •Use of a control group. •Assessment instruments are well-validated and reliable measures with normative data. •Large amount of quantitative data produced on each child. Weaknesses: •ADHD not formally diagnosed.
Partinen et al. 2012 [11]	6	•Narcolepsy (n = 50) •All under age of 17 •Cataplexy = 94%	Finland	Retrospective cohort study; structured interview	MSLT	Parent interview with a child neurologist	Behavioral problems in 24 of 50 children (48%).	Strengths: •Relatively large sample. •Interviews conducted by child neurologist. Weaknesses: •No control group. •Assessment instruments not identified.
Posar et al. 2014 [15]	7	•Narcolepsy with cataplexy (n = 13) •Age range 6–13 years	Italy	CCS	MSLT	•SDQ •WISC-R •Academic performance according to anamnestic history	•Average FSIQ for all 13 but 3 had VIQ > NVIQ and 2 had NVIQ > VIQ. •Conduct problems: 3 abnormal and 2 borderline scores. •Hyperactivity: 1 abnormal and 3 borderline scores. •Emotional problems: 3 of 13 had an abnormal score. •7 of 13 children had a history of academic failure.	Strengths: •Large amount of quantitative data produced on each child. •SDQ is a commonly used assessment instrument. Weaknesses: •No control group. •Small sample. •SDQ is widely used but not well validated. •ADHD not formally diagnosed.

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Study, Year	Quality*	Sample	Country	Design	Diagnostics	Psychometric Measures	Results	Comments
Rocca et al. 2016[24]	7	Narcolepsy type 1 (n = 29) •Age range 7–16 years Idiopathic epilepsies (n = 39) •Age range 7–15 years HC (n = 39) •Age range 6–18 years	Italy	CCS	•PSG •MSLT •PDSS	•CBCL •PedsQL	•NT1 school functioning was significantly lower than HC. •NT1 group had higher aggressive behavior scores. •Both NT1 and idiopathic epilepsies groups had higher scores for social and attention problems, and scores for ADHD and ODD were higher. •NT1 had lowest scores for social activities. •NT1 had highest scores (more frequently pathological) for withdrawn/depressed and somatic complaints. •Both NT1 & Idiopathic epilepsies groups had higher scores for anxious/depressed, social and attention probs. •NT1 had pathological scores for anxious/depressed.	Strengths: •Moderate sample size. •Control group used. •Assessment instruments are well-validated and reliable measures with normative data. •Large amount of quantitative data produced and analyzed. Weaknesses: •Parent report only without child self-report data.
Stores et al. 2006[21]	7	Narcolepsy (n = 42) •Age range 7.3–17.9 years EDS (n = 18) •Age range 5.1–18.8 years HC (n = 23) •Age range 6.0–16.8 years	UK	CS	•Narcolepsy Scale •ICSD 1997 diagnostic criteria for narcolepsy •Ullanlinna Narcolepsy Scale	•Information from teachers using international questionnaire asking teachers to provide information about a number of school-based areas. •SDQ •CDI •Child Health Questionnaire for QoL	•Composite educational difficulties score was significantly higher in narcolepsy and EDS groups. •Children with narcolepsy and EDS reported significantly higher rates of behavioral problems, hyperactivity, and conduct problems. •A range of psychosocial problems can be identified in children with narcolepsy. •Both narcolepsy and EDS groups scored significantly higher on CDI. •Both groups scored significantly higher on mental health subscale of QoL. •The similar profiles of difficulties in the narcolepsy and EDS groups suggest that excessive sleepiness is the main cause.	Strengths: •Moderate sample size. •Control group used. •SDQ is a commonly used assessment instrument. •CDI and QoL are well-validated and reliable measures with normative data. Weaknesses: •SDQ is widely used but not well validated. •No information given on how many narcolepsy children had cataplexy.
Szakács et al. 2015[16]	7	Post-H1N1 vaccination narcolepsy group (PHV) (n = 31) •Cataplexy = 84% Non-post-H1N1 vaccination narcolepsy group (nPHV) (n = 7) Cataplexy = 100% Age range 5.7–25.0 years Age range at onset 3.0–17.0 years	Sweden	CS	MSLT	•DAWBA •ICD-10 and DSM-IV •ASSQ •ADHD-RS •PANSS •WPPSI-III •WISC-IV •Adults: WAIS-IV •NEPSY-II	•FSIQ within average range. •VCI and WMI significantly lower in PHV group. •VCI and WMI lower mean scores but not significant in nPHV group. •17 of 38 patients had diff of ≥ SD between PRI and VCI VCI was lower. •EF on the 2 NEPSY-II subtests were within normal range. •More than 1 in 4 had ADHD, inattentive type (29%), which is higher than the incidence in the general population (estimated at 7%). •7 of 9 patients developed ADHD after age 7 and after narcolepsy onset a relationship between onset of narcolepsy and development of ADHD. •ODD occurred in 8% of the study population, which is higher than the incidence in the general population (3.3%). •Major depression present in 20% of PHV narcolepsy group.	Strengths: •Moderate sample size. •Assessment instruments are well-validated and reliable measures with normative data. •Large amount of quantitative data produced and analyzed. Weaknesses: •No control group. •Possibility of some underdiagnosis of psychiatric comorbidities due to strict application of DSM-IV criteria. •Number of children with nPHV is too small to establish differences between that group and the PHV group.
Szakács 2016[17]	7	•Narcolepsy (n = 32) •n = 28 following H1N1 influenza vaccination •Age range 6–25 years	Sweden	CS	•MSLT •Actigraphy •HLA-DQB1*0602 allele testing	•WPPSI-III •WISC-IV •Adults: WAIS-IV •NEPSY-II •Online-based DAWBA designed to generate psychiatric diagnoses according to the ICD-10 and the DSM-IV. Final assessment made by an experienced child and adolescent psychiatrist. •ADHD-RS was used to assign ADHD diagnoses.	•PHV group: a difference of > 1 SD in 17/35 patients when comparing PRI with VCI, where VCI was lower. •FSIQ was lower (P = .027) in patients with a concurrent psychiatric disorder compared with patients without a psychiatric diagnosis; i.e., P < .05. •Working memory on WISC-IV: for PHV group of 29 children, mean WMI was 89.5 with SD of 13.3. Although not statistically significantly lower than general population, is lower than mean of 100 with SD of 15. •7 of 32 (22%) patients developed ADHD after age 7 and after narcolepsy onset a relationship between onset of narcolepsy and development of ADHD. •3 of 37 (8%) patients identified with ODD. •Most frequent psychiatric symptom was temper tantrums: 94% of PHV and 71% of nPHV. •Comorbidity with major depression: 6/37 (16%). •Comorbidity with general anxiety disorder: 3/37 (8%). •That is, 13/30 (43%) of patients with PHV narc and 14% with nPHV had at least one psychiatric disorder	Thesis for Doctor of Philosophy Strengths: •Moderate sample size. •Assessment instruments are well-validated and reliable measures with normative data. •Large amount of quantitative data reportedly produced. Weaknesses: •No control group. •Number of children with nPHV is too small to establish differences between that group and the PHV group. •Limited amount of data reported – findings only reported. •No information given on how many narcolepsy children had cataplexy.

* = quality score out of 7. ADHD-RS = attention deficit hyperactivity disorder-rating scale, ADHD = attention deficit hyperactivity disorder, AESS = adapted Epworth Sleepiness Scale, ASSQ = Autism Spectrum Screening Questionnaire, CBCL = Achenbach Child Behavior Checklist, CCS = case control study, CDI = Children's Depression Inventory, CPRS-R = Conners Parent Rating Scale-revised, CS = cross-sectional, DAWBA = development and well-being assessment, DSM = Diagnostic and Statistical Manual of Mental Disorders, EDS = excessive daytime sleepiness, EF = executive functioning, ESS = Epworth Sleepiness Scale, FSIQ = full scale intelligence quotient, HC = healthy controls, ISI = Insomnia Severity Index, K-ABC = Kaufman Assessment Battery for Children, MSLT = Multiple Sleep Latency Test, MWT = Maintenance of Wakefulness Test, NEPSY-II = Developmental NEuroPSYchological Assessment, NVIQ = nonverbal intelligence quotient, NT1 = narcolepsy type 1, NT2 = narcolepsy type 2, PANSS = Positive and Negative Syndrome Scale, PDSS = Pediatric Daytime Sleepiness Scale, PedsQL = Pediatric Quality of Life Inventory, PIQ = performance intelligence quotient, PRI = Perceptual Reasoning Index, PSG = polysomnography, SD = standard deviation, SDQ = Strengths and Difficulties Questionnaire, SES = socioeconomic status, SSI = Stanford Center for Narcolepsy Sleep Inventory, VCI = Verbal Comprehension Index, VIQ = verbal IQ, VSP-A = Vécu et Santé Perçue de l'Adolescent [perceived health-related quality of life in adolescents], WAIS = Wechsler Adult Intelligence Scale, WISC = Wechsler Intelligence Scale for Children, WMI = Working Memory Index, WPPSI = Wechsler Preschool and Primary Scale of Intelligence, WRAML = Wide Range Assessment of Memory and Learning.

evidence with a high-quality individual RCT (6 studies). As such, the quality of 14 studies was identified as rating at a level 2 due to (1) not being RCTs and (2) by using smaller groups of children. Studies with a level 1 quality rating generally had a control group, but also used standardized assessments, meaning scores could be compared to a large population mean. The strength of recommendation was generally identified as level B, which is based on limited-quality, patient-oriented evidence. This was due to most studies being single investigations of a smaller population. One study did not report its design in sufficient detail to enable replication of data collection. That is, the interview questionnaires were not identified in the report. Although a number of studies relied on interviews or qualitative collection of information, they were included in this review. However, these studies gained low quality and strength of recommendation ratings. The inclusion of qualitative information is essential with disorders such as narcolepsy and idiopathic hypersomnia due to the significant effect on the individual's lives and the lives of those around him or her. All studies used recognized statistical techniques for data analysis.

Intellectual Functioning and Hypersomnolence

The four studies (20%) that looked at the intellectual implications of a hypersomnolence disorder all used one of the Wechsler assessments to determine intellectual functioning, with verbal IQ (VIQ) and nonverbal IQ (NVIQ) also reported. Two of the four studies[14,15] were case studies employing standardized assessments that yielded quantitative data that resulted in individual rather than group findings being reported. Eleven of 12 children in the study by Dorris et al.[14] and the 13 children in the study by Posar et al.[15] had a full-scale IQ (FSIQ) in the average range, although 5 children in each study had a discrepancy of more than one standard deviation between their VIQ and NVIQ, thus displaying disparate intellectual abilities. Both studies used standardized norms for the particular assessment instrument administered.

The two studies[16,17] that were conducted with larger groups of children and adolescents with narcolepsy also found that most subjects had a FSIQ in the average range, with a number having a FSIQ in the gifted range. These studies investigated groups of 38 and 37 participants respectively, allowing some generalizability of results. Again, many children and adolescents had a significant discrepancy between two or more of the four indices that compose the FSIQ in the Wechsler assessments. However, statistically significant discrepancies between factor indices included in the FSIQ are not unusual in the general population as explored and discussed by Kahana et al.[18] Their investigation using the Differential Ability Scales with a nationally representative sample of 1,185 children found that 31.5% had a significant discrepancy between the verbal and nonverbal reasoning indices. Overall, 80% of their sample had a significant discrepancy between factor or subtest scores. The Szakács[17] study also found a significant difference between the FSIQ of those with a concurrent, diagnosed psychiatric disorder and those without, whereas those with a concurrent psychiatric disorder had a lower FSIQ. The concurrent psychiatric disorders included major depression, attention deficit hyperactivity disorder, and general anxiety disorder.

In these four studies with 98 participants being assessed, almost all children and adolescents were identified as having a FSIQ within the average range, with most participants yielding significantly uneven cognitive profiles, thus being reflective of the general population. With so few studies, and relatively few participants, identification of any association between intellectual functioning and narcolepsy would be inconsistent and unreliable. In addition, there is a probability of underdiagnosis in less educated groups. A number of studies have identified the inequities associated with access to specialized medical care, with individuals with lower education seeing specialists less frequently than those with higher education levels.[19,20] No studies have been conducted with participants who have a diagnosis of idiopathic hypersomnia.

Academic Achievement and Hypersomnolence

There do appear to be some cognitive effects of EDS not reflected in FSIQ. Specifically, Stores et al.[21] identified an effect of the EDS associated with narcolepsy and EDS of uncertain origin on educational achievement (narcolepsy = 42, EDS = 18, healthy controls = 23). They developed a composite educational difficulties score using four items rated 0 or 1 and found that in comparison with their control group, the composite educational difficulties score was significantly higher in the narcolepsy and EDS groups. Additionally, in a larger study exploring the associations of narcolepsy with various intellectual, academic, and quality-of-life aspects, Inocente et al.[22] found that children with narcolepsy (n = 117) had significantly more school difficulties than matched healthy controls (n = 69). This association was also identified in other research with relatively large groups of children with narcolepsy. Aran et al.[23] (n = 51) determined that 72% of parents reported a decrease in academic performance following development of narcolepsy. However, this was somewhat alleviated with appropriate treatment. Rocca et al.[24] cited that parent reports identified school functioning was significantly lower in children with narcolepsy (n = 42) than that of the healthy controls (n = 23). Guilleminault and Pelayo[25] (n = 51) reported that more than half their participants indicated difficulties with academic achievement, with many children repeating a year of schooling.

Although not as compelling as investigations with large groups, the qualitative evidence gleaned from case studies provides insights often unavailable from data alone. Three case studies explored the association between narcolepsy and academic functioning. Karjalainen et al.[26] used mixed-methods research including parent and teacher questionnaires and the Strengths and Difficulties Questionnaire (SDQ) with the six children in whom narcolepsy was diagnosed. This real-life context yielded parent reports of problems with concentration and attention following the development of narcolepsy, and observations that skills that had been previously learned were lost following the onset of the disorder. Whole class work was reported as being particularly challenging, so that smaller group or individual teaching was required. Narcolepsy developed in all six children following the 2009 Pandemrix vaccination. Seven of the 13 children in the study by Posar et al.[15] were identified as having a history of academic failure. This is despite having a FSIQ within the average range for their age. In their

group of eight children, Dias Costa et al.[27] found that parents of five of those children reported an effect on school performance but that there was an improvement following behavioral therapy, nutritional counseling, and pharmacological support.

The Avis et al.[28] study included children with a variety of central disorders of hypersomnolence: narcolepsy with cataplexy (n = 7), narcolepsy without cataplexy (n = 11), idiopathic hypersomnia (n = 15), and 33 healthy controls. It found that all children with a central disorder of hypersomnolence scored significantly lower on academic grades with a Cohen effect size value suggesting a moderate practical significance. These children were also significantly sleepier. The academic grade scores were extracted from the Wolfson and Carskadon's School Sleep Habits Survey and the "sleepiness score" was determined using a modified Epworth Sleepiness Scale. This was the only study to clearly explore the association between academic functioning and hypersomnolence, while including a population with idiopathic hypersomnia.

Nine of the 20 studies (45%) in this review purported to explore an association between academic functioning and a central disorder of hypersomnolence, principally narcolepsy. Eight of the nine relied primarily on observational data. All nine reported significantly lower academic functioning, although in some studies it was acknowledged this had been somewhat alleviated through appropriate treatment. Only one study included a population of children with idiopathic hypersomnia (n = 15); therefore, no generalizations can be drawn from that small sample. As all nine studies relied on parent reports and questionnaires, information from teachers, or standardized checklists, there is no reliable information on the association between central disorders of hypersomnolence and academic achievement. The use of valid and reliable, normed and standardized assessment instruments such as the Wide Range Achievement Test would enable any effect of hypersomnolence to be more clearly identified. Scores within this population could be more readily compared to norms for a regular population.

Executive Functioning and Hypersomnolence

Seven studies (35%) explored the relationship between a central disorder of hypersomnolence and executive functioning (EF), with only one of those utilizing a population of children with idiopathic hypersomnia (n = 3).[29] Of the other six studies exploring the relationship between EF and hypersomnolence, two were case studies and one focused on a small group (n = 7). One case study investigated a twin who had developed narcolepsy.[30] The remaining three studies accessed groups ranging in size from 29 to 38—thus small populations overall. In all seven studies, the EF and hypersomnolence association was irregularly explored with inconsistent methodologies, multiple definitions of EF, and numerous choices of assessment instruments. These included subtests from the Wechsler scales,[16,17,30,31] Wide Range Assessment of Memory and Learning,[31] Developmental NEuroPSYchological Assessment,[16,17] and Child Behavior Checklist (CBCL).[24] One study utilized parent and teacher questionnaires with the SDQ.[26] The Frolich et al.[29] study explored vigilance as one of the executive functions associated with attention in a population with attention deficit hyperactivity disorder (ADHD) and in children with disorders of excessive somnolence. Research utilizing populations of participants with ADHD and participants with a central disorder of hypersomnolence is relatively common, as an association has been identified.[32,33] Frolich et al.[29] found all children with a disorder of excessive somnolence had significantly shorter sleep latency during the Maintenance of Wakefulness Test. This was used to identify vigilance. Although their data are consistent with some potential effects on vigilance, the small participant numbers do not allow for generalizability. Additional assessments of EF, particularly those associated with attention and vigilance, would enable further support of their findings.

No firm conclusions can be drawn from these data because (1) the wide variety of assessment instruments, (2) the differing aspects of EF each instrument assesses, and (3) the use of noncomparable parent and teacher interviews. Each individual study did identify problems such as a significantly lower mean score for working memory, and poor planning and attention.

Behavior and Hypersomnolence

Behavior problems, including increases in anger, aggression, impulsivity, and inattention, were reported in many children following the onset of narcolepsy. Of the 20 studies included in this review, 11 (55%) included behavior as one of the foci investigated by either standardized behavior assessments or interviews with parents, caregivers, the individuals themselves, and their educators. A number of studies reported that ADHD characteristics, including poor attention and focus, which led to a diagnosis of ADHD inattentive type, was identified after an investigation into the postnarcolepsy behaviors. Specifically, the Szakács et al.[16] study found more than 1 in 4 of the 31 children (29%) in the post-H1N1 vaccination group gained a comorbid diagnosis of ADHD inattentive type, which is significantly higher than the estimated incidence of 7% in the general population. Further, they found that one of the seven in whom narcolepsy developed without the vaccination trigger had gained comorbid diagnoses of ADHD inattentive type and oppositional defiant disorder (ODD). A later study by Szakács[17] found that 7 of the 32 children (22%) gained a comorbid diagnosis of ADHD. Of the 32 children in his study, narcolepsy developed in 28 following the H1N1 vaccination. These high incidences of ADHD in the narcolepsy population was also identified by Aran et al.[23] who noted that 22% of 40 children exhibited a comorbidity (some prior to the diagnosis of narcolepsy). Inocente et al.[34] also found that heightened hyperactivity as identified in the Conners Parent Rating Scale, Revised (CPRS-R) was identified in 22% of the 81 children screened. Lecendraux et al.,[32] who used the ADHD Rating Scale, which was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, found that clinically significant levels of ADHD symptoms were identified in 4.8% of controls ($n = 67$). However, they also reported a significantly higher incidence in patients with narcolepsy without cataplexy (35.3% of 22) than in patients with narcolepsy with cataplexy (19.7% of 86). It could be questioned, therefore, whether findings in those studies exploring the relationship between narcolepsy and ADHD constitute true comorbidity. A number of

the diagnostic items for ADHD overlap those for narcolepsy including sustaining attention difficulties and EDS.[32]

Other larger group studies had similar findings, with behavioral problems identified in significant percentages of children with narcolepsy. Partinen et al.[11] used parent interviews with a child neurologist to identify behavioral problems in 24 of the 50 children (48%) in their study. Rocca et al.[24] used a case-control study to explore the profiles of 29 children with narcolepsy type 1, comparing those findings with children with idiopathic epilepsies (n = 39) and healthy controls (n = 39). The children with narcolepsy were found to have increased attention deficit problems and aggressive behavior over children in either of the other two groups. ADHD behavior, ODD behavior, and conduct disorder were also found to be heightened in comparison with the control group. The study by Stores et al.[21] developed the association of these behaviors with EDS symptomatic of narcolepsy by including a group of children who exhibited EDS (n = 18). With 42 in the narcolepsy group and 23 healthy controls, participant numbers gave Stores et al. some strong data although they used the SDQ as their behavior assessment instrument. The mean scores for the narcolepsy and EDS groups were significantly higher for hyperactivity, conduct problems, and adverse effect on the family. The total SDQ score for these two groups was also significantly higher than the score for the control group. The Cohen effect-size values indicate a moderate to high practical significance, suggesting EDS is the cause for behavior issues in children with narcolepsy.

These latter group findings suggest that not only is inattention and poor focus found to be significantly more frequent in children with narcolepsy, but that other behavior problems may also present and that these identifiers could include hyperactivity and impulsivity, aggression, conduct problems, and oppositional behavior.

Other researchers have also taken a deep investigative approach using case studies which typically use smaller groups of children, enabling associations between narcolepsy and many other life aspects to be fully detailed for each child. Karjalainen et al.[26] found five of the six children in their study had behavioral and social problems; and Kotagal et al.[35] identified significant behavior problems in all four children they investigated. Two case studies used slightly larger groups. Dorris et al.[14] (n = 12) found 3 of the 12 children (25%) had a clinically significant score on the externalizing index of the CBCL, with only one having an aggressive behavior score in the clinical range. Posar et al.[15] (n = 13) used the SDQ to identify that 3 of the 13 children (23%) had a score in the clinical range for conduct problems, although 2 other children had borderline scores. There was only one child (8%) who gained a score in the clinical range for hyperactivity, whereas three other children had borderline scores. Although these incidences are similar to that identified in the larger groups investigated, the smaller numbers disallow any generalization.

In all 11 studies that investigated the association between behavior and narcolepsy, the numbers of children identified as displaying inattention, poor focus, impulsivity, aggressive behavior, conduct problems, and/or oppositional behavior was generally significantly higher than the incidence in the general population. A number of studies suggested the EDS of hypersomnolence disorders as the cause for these poor behaviors. All studies used parent reports to identify these behaviors, whether it was through standardized screeners such as the Conners, CBCL, or SDQ, or through in-depth parent interviews. Table 2 includes a summary of findings of associations explored between behavior and hypersomnolence.

Emotion and Hypersomnolence

Anxiety, depression, and/or other emotionally-based problems also appear to be strongly associated with hypersomnolence with 14 of 20 studies (70%) in this review exploring the association. In particular, depression has been identified as having a strong statistical association with hypersomnolence across a number of studies, many of which utilized the Children's Depression Inventory (CDI), an internationally recognized, reliable, and validated screener for depression in children. To incorporate observations from parents about their child's behavior and feelings in a range of situations, a variety of other instruments and/or parent questionnaires were also utilized. In many cases this revealed their child was experiencing a greater level of difficulty than other children in that age cohort.

An earlier study in this review by Guilleminault et al.,[25] noted that concerns regarding the association between depression and narcolepsy had already been identified up to 20 years ago. Their study utilized 51 prepubertal children, 40 of whom were age 7 years and older. The psychiatric interviews with those subjects found 32 (80%) were "depressed by their inability to be the same as their peers despite not having any physical signs" (p. 140), and eight (20%) were thought to have symptoms of reactive depression. These children displayed poor appetite, disinclination toward social activities or previously enjoyed activities, decline in self-esteem, and crying spells. A concern raised in this study was the lack of support for these children in the school setting where they were often labeled as "lazy," and were disciplined for falling asleep, being unmotivated, having poor attention or concentration, and exhibiting memory problems. Six families had been contacted on suspicion of their children using illicit drugs. During follow-up, all families reported occasions when their child presented with depressive symptoms subsequently thought to be associated with the narcolepsy. Given this foundation for exploration of an association between depression and narcolepsy, an identification that 12 other studies had explored this area since that time is heartening.

Two studies conducted by Inocente et al.[22,34] explored the association between depression and narcolepsy using relatively large groups of children (n = 88 and n = 117). Depression was positively correlated with sleepiness, and when comparison with a control group was established the children with narcolepsy were significantly more depressed than their healthy colleagues. Both studies utilized the CDI as well as other assessment instruments. Lecendreux et al.[32] focused on the incidence of ADHD symptoms in children with narcolepsy, including groups with (n = 86) and without cataplexy (n = 22), and in comparison with a control group (n = 67). In addition to identifying clinically significant levels of ADHD symptoms in the two narcolepsy groups (30% and 15% respectively compared to an incidence of 5% to 6% in the control

group) Lecendreux et al. also posited that those children with the clinically significant levels of ADHD symptoms also had higher levels of depressive symptoms. It appears, therefore, that a number of comorbid conditions develop with the onset of narcolepsy.

Other sizeable studies had similar findings: 20% of the 40 screened (n = 51) in the study by Aran et al.[23] were identified as having clinically significant depression or anxiety after the onset of narcolepsy symptoms. Stores et al.[21] explored emotional and psychosocial problems among three groups: narcolepsy (n = 42), EDS (n = 18), and healthy controls (n = 23), using the CDI. Both the narcolepsy and EDS group means were significantly higher than the control group mean. The narcolepsy and EDS group means were statistically similar, suggesting that the association with depressive symptoms may be EDS. The Rocca et al.[24] study used the Child Behavior Checklist (CBCL) and the Pediatric Quality of Life Inventory to screen for anxiety and depression. They found both the narcolepsy type 1 group (n = 29) and the idiopathic epilepsies group (n = 39) had significantly higher mean scores than the healthy control group (n = 39) for anxiety/depression, whereas the narcolepsy group's mean scores were in the pathological range. Both the Szakács et al.[16] (post-H1N1 vaccination narcolepsy group; n = 31) and the Szakács[17] (n = 37) studies identified a high incidence of children with major depression: 20% and 16% respectively. This study also identified 3 of the 37 children as having generalized anxiety disorder. Many of these larger studies also found comorbidities with a number of other psychiatric disorders. Jennum et al.[36] investigated all diagnosed cases of narcolepsy from 1998 through to 2012 using the Danish National Patient Registry (n = 243). These cases were compared with 970 matched controls, 4 for each narcolepsy patient and randomly chosen from the Danish Civil Registration System Statistics. In Denmark, each person is placed on a national patient database and, because all Danes are registered with their Social Security codes, the two databases can be linked. Jennum et al. investigated 21 World Health Organization areas, using several classification systems including the International Classification of Disorders, Tenth Edition. They found that in the year prior to their official diagnosis of narcolepsy, 10.8% of the patients also had diagnoses of mental and psychiatric disorders compared to only 2.4% of the controls having these diagnoses. In the third year following their diagnosis of narcolepsy, 11.4% of patients also had diagnoses of mental and psychiatric disorders compared to only 2.1% of the controls having these diagnoses.[15,16,17,18,36] They concluded that narcolepsy in children and adolescents is associated with a range of comorbidities, and in this case, with a significant number of mental and psychiatric disorders.

Four studies conducted a deeper investigation into smaller groups of children using a case-study approach: Dias Costa et al.[27] (n = 8), Dorris et al.[14] (n = 12), Karjalainen et al.[26] (n = 6), and Posar et al.[15] (n = 13). All had similar findings regarding the risk for emotional problems, internalizing problems, and depressive symptomatology. The psychological morbidity associated with narcolepsy appears to be significant, and affects most aspects of these children's lives. Indeed, interviews conducted by Karjalainen et al. with the children, their parents, teachers, and community support workers reported that the children felt their "lives had lost joy and childhood unconcern" (p. 876).

An association between hypersomnolence and emotional problems was found in all 14 studies. Although no studies in this section included a population of children with idiopathic hypersomnia, it could reasonably be assumed that these children and adolescents are also at risk of the development of emotional problems due to the EDS associated with that condition. Table 2 includes a summary of findings of associations explored between emotion and hypersomnolence.

DISCUSSION

A review of the association between central disorders of hypersomnolence in children and adolescents and the effect of hypersomnolence on intellectual functioning, academic functioning, executive functioning, behavior, and emotion was conducted. Twenty studies, published between 1960 and June 2017 were included in this review.

Given there were only four studies that explored the relationship between hypersomnolence and intellectual functioning, no clear association between the two aspects was identified. Many participants did have a significant difference between their nonverbal IQ and verbal IQ; however, this difference was also inconsistent, with some individuals having a significantly stronger nonverbal IQ and others having a significantly stronger verbal IQ. Significant differences between factor indices are not unusual in the regular population. Therefore, it could not be clearly established that hypersomnolence is associated with specific inconsistencies within a cognitive profile.[18]

School difficulties, however, were frequently identified as being significantly associated with the EDS of central disorders of hypersomnolence. These difficulties were often reported through use of qualitative methods such as interviews with parents and teachers. The interviews yielded descriptions of the effect such as: "deterioration in school performance," or "decrease in academic performance," or "school functioning is identified as significantly lower" following the onset of narcolepsy. Because only one study had included a population of children with idiopathic hypersomnolence (n = 15), no generalizations can be drawn for that population; however, this study did identify that all children with central hypersomnia had lower academic grades, and were significantly sleepier than healthy children.[28] The proportion of children and adolescents with narcolepsy who had repeated a year in school was also significantly higher than that of the general population. Much of the decrease in academic achievement was identified as resulting from the strong effect of the EDS associated with narcolepsy. EDS appears to affect concentration and attention, thus inhibiting the individual from engaging fully with the classroom curriculum and being able to learn, rehearse, and consolidate concepts in the foundational academic areas of literacy and numeracy.

This academic effect through poor attention and concentration appears to be related to EF. As reported earlier, because of inconsistencies in the definition of EF, the variety of EF aspects assessed, and the various assessment instruments used, a robust association between narcolepsy and EF cannot be clearly

articulated. Further exploration of the association between EF and central disorders of hypersomnolence using standardized assessment instruments and an internationally recognized model of executive functioning is required, as there could be a strong relationship between them.

EF encompasses a number of higher order thinking skills that can be organized into four discrete yet interrelated domains: cognitive flexibility, goal setting, attentional control, and information processing—each with a number of integrated cognitive processes.[37] These skills are necessary for everyday living, academic development, and participation in the social arena. Any future research should also articulate the specific aspects of EF being investigated particularly as there are numerous higher-order thinking skills identified within this area. That is, the definition of EF needs to be formalized using reliable and valid assessment instruments clearly linked to the particular aspect of EF being assessed. Further, behaviors associated with EF should also be capable of undergoing objective observation using credible instruments. Finally, the sleep-wake behaviors associated with central disorders of hypersomnolence need to be objectively and reliably measured because at this point in time the possibility that central disorders of hypersomnolence affect EF is unsubstantiated.

This review also identified an association between behavior problems and narcolepsy or idiopathic hypersomnia. Across studies, significant numbers of participants gained a comorbid diagnosis of ADHD (inattentive type) following the onset of narcolepsy. In addition to this diagnosis, heightened hyperactivity, ODD, and increased aggression were identified in significant numbers of participants. The influence on family life, the individual's social life, and their schooling present research challenges, but this review suggests the effects are significant. Behavior is reportedly so significantly affected by a central disorder of hypersomnolence such as narcolepsy that it warrants further investigation, particularly into efficacious treatment strategies.

These individuals with narcolepsy or idiopathic hypersomnia experience emotional difficulties. This review identified the strong association between depression and narcolepsy across many studies incorporating large numbers of participants. Participants were also frequently identified with other emotional disorders, particularly anxiety. The most in-depth study found a significant number of children and adolescents with narcolepsy also had comorbid diagnoses of mental and psychiatric disorders.[36]

The current review further highlights both the thrust of research into central disorders of hypersomnolence, and the significant association that EDS has with the academic, behavioral, and social aspects of these individual's lives. These contribute to a poorer quality of life and loss of self-esteem. The current state of research findings requires further in-depth investigations into the effects of EDS associated with these disorders, and especially identifies the need to explore populations with idiopathic hypersomnia.

Limitations

This review highlights a number of limitations of the current literature available on this topic. Of particular concern is the low number of studies utilizing larger groups of participants and the lack of studies including a control group. The apparent inconsistency in use of standardized assessment instruments is also a limitation, due to the lack of opportunity for comparisons between studies. This was particularly evident for the EF and academic functioning effect areas. In addition, the inclusion of an objective measure of sleepiness would have enabled clearer associations to be identified, as would identification of whether the participants were medicated, and to what extent.

There appears to be overlap between certain studies, with three publications possibly reporting on the same population of patients, despite a difference in n values.[22,32,34] This also appears to have been the case in a separate two publication analysis.[16,17] Duplication of participants would render the final participant count much lower, further reducing any generalizability of findings.

A major limitation of this review was the inability to apply a meta-analysis as the data were too diverse to be integrated and analyzed. Although much of the research included quantitative data, there was an insufficient body of primary research studies to enable generation of a wide variety of research questions.

Practice Points

- There appears to be an effect of EDS associated with central disorders of hypersomnolence, on academic achievement, behavior, and emotion.
- EF appears to be affected; however, the data are inconsistent.
- The effects of narcolepsy and idiopathic hypersomnolence are life changing, and close monitoring by parents, teachers, community workers, and physicians is required to ensure each individual is able to reach his or her potential.

Research Agenda

- Further exploration of the effect of the EDS associated with central disorders of hypersomnolence in children and adolescents in a wider range of areas is required. This includes a focus on intellectual functioning, academic development, behavior, and emotional well-being, using standardized instruments, clearer definitions of the affected area, and larger cohorts.
- Research into the EF of children needs to more clearly define the model of EF and its integral components prior to conducting the research. Standardized, normed, and validated instruments need to be used, with the specific area of EF clearly identified.
- Inclusion of measurements of sleepiness at time of testing to more clearly identify any association between each affected area and EDS is required.
- Identification of the effect of medication on EDS and assessment findings also needs to be included in future research.

CONCLUSIONS

This review of 20 studies, some with large groups using standardized assessment instruments and a variety of interviews

or questionnaires, and others with small groups using a case-study approach has identified probable associations between central disorders of hypersomnolence and a number of areas including academic functioning, behavior, and emotion. The effect of EDS associated with central disorders of hypersomnolence is not well known and indicates the need for parents, teachers, community support workers, and physicians to closely monitor each individual's progress. Further research using objective and standardized assessment instruments, particularly with those individuals who have a diagnosis of idiopathic hypersomnia, may allow causality and treatment options to be identified.

ABBREVIATIONS

ADD, attention deficit disorder
ADHD, attention deficit hyperactivity disorder
AHI, apnea-hypopnea index
CBCL, Child Behavior Checklist
CPRS, Conners' Parent Rating Scales
EDS, excessive daytime sleepiness
EF, executive functioning
FSIQ, full scale intelligence quotient
ODD, oppositional defiant disorder
OSA, obstructive sleep apnea
PIQ, performance intelligence quotient
PRI, Perceptual Reasoning Index
PSG, polysomnography
RCT, randomized controlled trial
SDQ, Strengths and Difficulties Questionnaire
SORT, Strength of Recommendation Taxonomy
VCI, Verbal Comprehension Index
WMI, Working Memory Index

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