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CLINICAL REVIEW

A systematic review of cognitive function and psychosocial well-being in school-age children with narcolepsy

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Shortened version of the title for use in running heads: Cognitive function and psychosocial well-being in children with narcolepsy.

Conflicts of interest

The authors have no conflicts of interest to declare pertaining to this review.

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SUMMARY

In August 2010, concerns were raised about an increase in the incidence rate of narcolepsy diagnosis in children and adolescents. Narcolepsy is a chronic neurological sleep disorder characterised by excessive daytime sleepiness and attacks of muscle weakness which are often precipitated by strong emotions, known as cataplexy. We systematically examined and updated the scientific literature on the consequences of narcolepsy on cognitive function and psychosocial well-being in school-age children. Eight studies published between 2005 and 2015 were eligible for inclusion in this review. Collectively the results provide evidence to suggest that children who develop narcolepsy are at significant risk of cognitive impairment in at least one domain and emotional problems including depression, anxiety and low self-esteem. Children with narcolepsy should be monitored carefully in order to manage and reduce the impact of any impairments present. The existing literature is limited by small sample sizes, lack of appropriate controls and lack of longitudinal data. Future research should aim to address the limitations of the current work and aim to determine the underlying cause of cognitive and psychological impairments. This will enable the design of effective interventions to support children with narcolepsy so that they are able to achieve their full potential.

Keywords:

Narcolepsy
Cataplexy
Children and adolescents
Cognition
Psychosocial well-being
Sleep

Glossary of terms

Abbreviation	Definition
ADHD-RS	attention deficit hyperactivity disorder-rating scale
AS03	adjuvant system 03
CBCL	Achenbach child behavior checklist
CDI	children’s depression inventory
CPRS-R	Conners parent rating scale-revised
EDS	excessive daytime sleepiness
H1N1	H1N1 is a virus
ICSD-3	international classification of sleep disorders-third edition
I.Q	intelligence quotient
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROSPERO	international database of prospectively registered systematic reviews in health and social care
PSG	polysomnography
QATSDD	quality assessment tool for reviewing studies with diverse design
SDQ	strength and difficulties questionnaire
WIAT-II	Wechsler individual achievement test - second edition

Introduction

Narcolepsy is a chronic and disabling neurological sleep disorder characterised by excessive daytime sleepiness (EDS) and attacks of muscle weakness which are often precipitated by strong emotions (cataplexy). The estimated prevalence of narcolepsy with cataplexy in western countries is 25 to 50 per 100,000 [1]. The International classification of sleep disorders-third edition (ICSD-3, 2014) [2] distinguishes between two types of narcolepsy; narcolepsy type 1 and narcolepsy type 2. Individuals with type 1 narcolepsy experience cataplexy or have a deficiency of the neuropeptide hypocretin, whereas individuals with type 2 narcolepsy do not experience cataplexy and the relationship to cerebrospinal levels of hypocretin is less definite.

Narcolepsy is a condition that has traditionally been thought of as a disease of adulthood [3] however, contrary to this assumption, more than 50% of individuals with narcolepsy report experiencing the onset of symptoms before the age of 18 years [4], typically during adolescence. Children and adolescents with narcolepsy are at increased risk of their condition being unrecognised, misinterpreted and misdiagnosed due to the disorder's wide range of clinical manifestations [5]. EDS is the most commonly reported first symptom of narcolepsy and therefore it can be difficult for the clinician to distinguish between the normal requirement for daytime naps during childhood and excessive need for sleep. Cataplexy, which is a unique and characteristic feature of narcolepsy, may only appear many years after the development of EDS. It has been estimated that delays between the onset of symptoms and the diagnosis of narcolepsy can range from 10-15 years [6]. Individuals with narcolepsy display a great deal of variation in their presentation and this can lead to misinterpretations of symptoms and misdiagnosis.

In August 2010, alarms were raised in Scandinavian countries about an increase in the incidence rate of narcolepsy diagnosis in children and adolescents after September 2009. The

pharmacovigilance authorities in Sweden and Finland were concerned that this increase in the number of narcolepsy cases may be associated with the use of the ASO3 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix) during the H1N1 (swine flu) Pandemic in 2009 and 2010 [7,8]. Following these concerns, a cohort study was conducted in Finland and the results showed that there was a 13-fold increased risk of narcolepsy in children aged 4-19 years old who received the vaccination compared to unvaccinated children [9]. These concerns led to further investigations about the incidence of narcolepsy in Europe before, during and after the swine flu pandemic and vaccination campaigns [4, 10, 11]. Supporting the association, Miller et al. [10] found a significantly increased risk of narcolepsy in children who received the vaccine in England, consistent with the findings of the cohort study conducted in Finland. It has been estimated that globally more than 1000 children have developed narcolepsy following the vaccination [12]. Unfortunately official data on the incidence and prevalence of childhood narcolepsy (both for vaccine related and unrelated cases) are currently unavailable [13].

It is important to consider the effect narcolepsy may have on school-age children who are in a critical period for their physical, emotional and social development and their academic attainment. Given the recent increase in the number of children and adolescents diagnosed with narcolepsy, it is timely to systematically review, critically appraise and summarise the current quantitative and qualitative research that has investigated the consequences of this serious disorder in childhood. The review aims to update understanding of how cognitive function and psychosocial well-being in school-age children with narcolepsy compares with that of school-age children without narcolepsy and to assess what study designs and methods have been used to investigate this. The review also aims to assess the quality of the included studies and to provide recommendations for future research by highlighting gaps in the current evidence base.

Methods

A systematic review was conducted to assess whether cognitive function and psychosocial well-being is impaired in school-age children with narcolepsy. This review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 checklist and is registered in PROSPERO. The registration number is CRD42015018949 [14].

Literature search

Electronic databases were searched on 28th August 2015. The databases searched included; The Cochrane Library, EMBASE, Ovid MEDLINE and PsycINFO (See Table 1). Records were downloaded and added to EndNote bibliography software. The records were de-duplicated.

The search was structured to combine the following concepts:

(Narcolepsy OR Cataplexy) AND (Children OR Adolescents) AND Cognition OR Psychosocial Well-Being.

Inclusion criteria

For this review one reviewer (JB) screened titles and abstracts. Another reviewer (HA) independently screened 5% of these articles in order to establish agreement about the inclusion and exclusion of studies. The website random.org was used to randomly select 5% of the articles and the inter-rater agreement was 98%. Any disagreements during this process were resolved by discussion and a consensus decision was reached.

Quantitative and qualitative research studies primarily concerned with narcolepsy (and cataplexy) in school-aged children (5-18 years old) and cognitive function or psychosocial well-being were eligible for inclusion in the review. Research studies written in English

language and published in peer-reviewed journals between 2005 and 2015 were included in the review. Single case studies were excluded from this review. This inclusion criteria was selected so that only the most current research (published in the last decade), relevant research and high quality research was included within this review.

Full papers that were identified as potentially relevant were retrieved and screened in the same way as previously described based on the inclusion criteria and authors were contacted to clarify any missing information. Inter-rater agreement was 100%.

Data extraction

The Cochrane data extraction form was modified for the purposes of this review. Data were extracted into the standardised form by one researcher (JB) and authors were contacted when insufficient information was provided. 50% of these articles were then double data extracted by another researcher (HA). Any disagreements were resolved by discussion and a consensus decision was reached.

Quality assessment

Individual study quality was assessed with the 'quality assessment tool for reviewing studies with diverse design' (QATSDD) [15], a 16-item, validated quality assessment tool applicable to research with heterogeneous study designs (qualitative, quantitative and mixed methods). This tool was particularly suitable for assessing the quality of the papers included in this review as it encompasses an evaluation of both quantitative and qualitative aspects of research. Two reviewer's (JB and HA) independently awarded each research paper a quality score on a 4-point scale from 0 to 3 for each of the QATSDD criteria (0=the criterion is totally undescribed, 1= described to some extent, 2= moderately described and 3= described in full). An example criterion from the QATSDD is "description of procedure for data collection". As none of the studies included in this review employed mixed methods, only 14

out of the possible 16 quality assessment criteria were evaluated for each paper (as the remaining two criteria only address mixed-method research). For each paper, the sum of the 14 quality assessment scores indicated the overall quality of the paper (expressed as a percentage of the maximum possible score of 42). Additionally, an overall quality score was assigned for all studies using the same design (e.g. quantitative or qualitative studies) in order to assess the full body of evidence. To do this, an average of the quality scores was calculated for each group (quantitative and qualitative papers) and was expressed as a percentage of maximum quality score. It was therefore possible to compare the qualities of the quantitative and qualitative studies included in the review. Papers were not excluded based on quality due to the very limited number of studies eligible for inclusion in this review.

Table 2 displays the quality assessment scores awarded for each paper next to each study reference. There was substantial inter-rater agreement (89.3%) between the two independent reviewers (JB and HA). Discussion following the independent scoring of papers resolved the remaining differences in agreement. Overall study quality for the seven quantitative studies included in the review was rated as 72.4% and the study quality of the one remaining qualitative study was rated as 43.0%, suggesting that the quantitative work was of a higher standard.

The quantitative papers ranged in quality ratings from 61.9 % to 71 % with the highest quality papers scoring particularly highly in criteria relating to: the aims and objectives of the study, description of procedure for data collection, the rationale for the choice of data collection tools and detailed recruitment data. The lowest rated quantitative papers scored especially low on the following criteria: statistical assessment of reliability and validity of measurement tools, explicit theoretical framework, and evidence of user involvement in design. The qualitative paper was of relatively poor quality and scored particularly low in the following areas: clear description of research setting, detailed recruitment data, assessment of

reliability of analytic process. The quality assessment revealed that the quantitative research to date on this topic has overall been of fairly good quality, however it could be improved further by future researcher's using reliable and valid measurement tools, larger more representative samples and including a matched control group in the design. More well-designed qualitative research is required with this population in order to extend the findings reported in the one included qualitative paper.

Results

Study selection

Following a systematic search, 710 articles were found from the electronic databases and an additional 3 articles were found from other sources. After exporting the articles to EndNote, 168 duplicates were removed. 545 articles were screened for relevance and 488 records were excluded after reading the title and abstract. 57 publications were retrieved for more detailed full text screening. 49 studies were excluded at full text screening. Eight studies met the inclusion criteria for the present review (See Figure 1).

Summary of papers included within the review

Table 2 was produced to summarise the main characteristics of each of the eight studies eligible for inclusion in this review. The table includes all the information provided by each study in regard to: the number of participants, their sex, age, type of narcolepsy, how diagnosis was confirmed, whether or not a control group was included, the cognitive and psychosocial measures used and the dependent variables. The comments provided in the table consider the individual strengths and weaknesses of each study in terms of design, analysis and conclusions drawn.

Summary of results

Eight articles published between 2005 – 2015 were included in this review.

Sampling

Seven of the studies included in this review were conducted in Europe, with only one of these study recruiting participants from the USA and Australia [5]. The remaining study was conducted in the USA [16]. The age range of the children varied slightly between studies (range 5-18 years) (See Table 2) and, with the exception of one study that did not report full diagnosis information [17], the majority of participants had narcolepsy with cataplexy. The studies included both treated and untreated children with narcolepsy. The type of medication and the time since starting treatment varied between participants. Two studies reported that all the children were unmedicated at the time of the study [16, 18], five studies reported that some of the participating children were treated at the time of the study [5, 19, 20, 21, 22] and one study did not report whether or not the children were medicated [17]. Sample sizes varied dramatically between studies, with the smallest sample being six participants [17] and the largest being 117 participants [20, 21]. All studies included approximately equal numbers of male and female participants.

Design

A cross sectional-design was employed by all the studies included in this review (seven quantitative studies and one qualitative study). Of the seven quantitative studies, only four included a control group and/or a comparison group [5, 16, 21, 22]. When evaluating whether or not cognitive function and psychosocial well-being in school-age children are affected by having narcolepsy the absence of a control group is a key limitation. This is because it is not possible to compare the cognitive and psychosocial profiles of children with

narcolepsy to that of healthy matched controls. In the absence of any better quality empirical research, details of the four quantitative studies that lack a control/comparison group are included in this review as they have produced interesting and relevant findings.

Of the eight studies, two studies were primarily concerned with cognitive outcomes [16, 18], three studies were primarily concerned with psychosocial outcomes [17, 20, 21] and the remaining three studies reported on both cognitive and psychosocial outcomes in school-age children with narcolepsy [5, 19, 22]

Cognitive outcomes

The five studies that examined cognitive function in school age-children with narcolepsy used a variety of different measures to assess participants' functioning. This makes it difficult to draw conclusions about the overall cognitive profile of children with narcolepsy. Two studies examined cognitive function [18, 19] using a standardised measure of intelligence (I.Q) (the Wechsler intelligence scale for children) alongside one or more additional measures of working memory, non-verbal reasoning, attention, alertness or problem solving. Overall, the results of these studies showed that the children with narcolepsy had an I.Q within the average range (with the exception of one child [19]), however clinically significant discrepancies between verbal IQ and performance IQ were reported in both studies [18, 19]. Posar et al. [18] found that verbal IQ was similar to performance IQ in eight out of their 13 cases. However, in three cases verbal IQ was higher than performance IQ and in two cases verbal IQ was lower than performance IQ. Posar et al. [18] also reported that each child had impairments in at least one of the other cognitive domains assessed (verbal working memory, non-verbal working memory, alertness, problem solving). Similarly, Dorris et al. [19] found a significant difference between verbal and performance IQ in five out of their 12 participants. For three of the participants verbal IQ was higher than performance IQ, whilst for the other two participants performance IQ was higher than verbal IQ. These results highlight that

although participants obtain an IQ within the average range, uneven cognitive profiles are frequently observed across studies.

Academic performance (reading, writing and maths) was also assessed according to teacher and family reports in two studies [5, 18]. It was found that seven out of 13 children with narcolepsy had failed academically [18] and that teachers rated children with narcolepsy as having significantly more educational difficulties than children without narcolepsy (problems with learning, not reaching academic potential, not working hard enough and being difficult to teach) [5].

The additional two studies that assessed cognitive function in school-age children with narcolepsy [16, 22] did not include a standardised measure of I.Q. Avis et al. [15]. assessed decision making and attention in unmedicated children with narcolepsy using a virtual reality pedestrian environment. Children were immersed in a virtual environment, watching vehicles pass bi-directionally. Children were asked to decide when it was safe to cross a virtual road by stepping off a simulated curb and walking along a pressure plate without getting hit. Attention to traffic was monitored using head tracking equipment, decision making was assessed by the average latency to start crossing the road and the sum of the car hits and close calls assessed pedestrian injury risk. Avis et al. [16] found that children with narcolepsy and children with idiopathic hypersomnia were twice as likely to be struck by a virtual vehicle in the virtual pedestrian environment than healthy controls. They found that although attention to traffic was not impaired, decision making was significantly impaired. However, Lecendreux et al. [22] found that inattention and impulsivity (as measured using the attention deficit hyperactivity disorder rating scale (ADHD-RS)) were significantly higher in children with narcolepsy than healthy controls. Additionally, although not statistically significant, Lecendreux et al. [22] found that the children with clinically significant ADHD symptoms were more likely to have needed to repeat a school year. It is important to note that the

ADHD-RS is completed by parents and therefore ADHD symptoms were scored by parents alone. No clinical assessment or formal diagnosis of ADHD was undertaken by a clinician and therefore the results may have been affected by response bias.

Psychological outcomes

Six studies examined psychosocial well-being in school age children with narcolepsy [5, 17, 19, 20, 21, 22]. One study used qualitative methods [17] (semi-structured interviews only) and the remaining studies employed quantitative methodology (standardised assessment tools and psychological assessment). Within the studies using quantitative methodology, the range of standardised assessments used to assess psychosocial well-being varied (Achenbach child behaviour checklist (CBCL), child depression inventory (CDI), health related quality of life questionnaires (HRQL), Conner's parent rating scale-revised (CPRS-R), strengths and difficulties questionnaire (SDQ)) making it difficult to directly compare results across studies.

Karjalainen et al. [17] published a qualitative study that collected information about how children's lives have changed after receiving the diagnosis of narcolepsy. Content analysis revealed that all parents reported that their child displayed changes in behaviour and mood around the time they developed narcolepsy and reported that these symptoms were the most difficult to manage. One parent claimed that their child's ability to function is "limited" and that their child is "tinged with aggression and disappointment several times a day" (Parent no.4) [17, p 874]. Five out of the six children in the sample had behavioural, emotional and social problems.

Three of the quantitative studies concerned with psychosocial outcomes included a control group or groups [5, 21, 22]. Stores et al. [5] included 42 children with narcolepsy, 18 children

with EDS of uncertain origin and 23 healthy control children. Inocente et al. [21] included 117 children with narcolepsy and 69 healthy control children. Lecendreux et al. [22] included 108 children with narcolepsy and 67 healthy controls. All three studies included the child depression inventory and a health related quality of life questionnaire suitable for children. The studies showed that compared to control children, children with narcolepsy had significantly poorer quality of life and significantly higher rates of depression. Stores et al. [5] found that children with narcolepsy and EDS had similar profiles of difficulties (significantly higher rates of behavioural problems and depression, which were above the population norms), suggesting that EDS may be the underlying cause of psychosocial impairment.

Similarly, Dorris et al. [19] reported that nine out of twelve children with narcolepsy scored highly on internalizing behaviour measures (withdrawal, depressive behaviour and anxiety) of the Achenbach child behaviour checklist (CBCL) and that ten out of twelve children scored in the significant range on the total score index of the child behaviour. Together these findings support the hypothesis that narcolepsy puts children at significant psychological risk.

Discussion

A systematic review of cognitive function and psychosocial-well-being in school aged children with narcolepsy was conducted. Seven quantitative studies and one qualitative study published between 2005-2015 were eligible for inclusion in this review.

Summary of findings

Collectively the results of the qualitative and quantitative research reviewed above provide evidence to suggest that children who develop narcolepsy are at significant cognitive and psychological risk. The findings suggest that narcolepsy puts children and adolescents at

particular risk of cognitive impairment in at least one domain (e.g. decision making, verbal IQ, performance IQ). The discrepant profiles of impairment described above do not reflect a consistent pattern and therefore a 'narcolepsy-specific' cognitive profile has not been established. Across the studies, the most commonly reported problems by the children were persistent sleepiness, lack of alertness and lack of concentration which are likely to impact on cognitive function and may be the underlying cause of the high levels of academic failure reported in the children with narcolepsy included in these studies. The consequences of having impaired areas of cognitive function (e.g. decision making and attention) in children with narcolepsy can be serious, as demonstrated by performance in the virtual reality environment. The reviewed research suggests that narcolepsy in school-age children is a risk factor for the development of heterogeneous cognitive problems that can impact on academic attainment, daytime functioning and safety.

Children with narcolepsy are also at risk of emotional problems including depression, anxiety and low self-esteem which may consequently lead to poorer quality of life. Despite the limited research into the cognitive and psychological consequences of childhood narcolepsy, the current findings have provided insight into the daily struggles experienced by children with narcolepsy and the consequences of this chronic disorder. These findings are particularly useful for parents, doctors and teachers so that they can work together to carefully monitor school-age children with narcolepsy and effectively manage any impairments present.

Limitations of existing evidence

The current studies suffer limitations that need to be considered when interpreting the results. Of the eight studies reviewed, only four studies recruited more than 40 children and adolescents with narcolepsy. Small sample sizes limit the generalisability of the results to the wider population of young individuals with narcolepsy. The use of different assessments and

standardised tests in the existing studies makes comparison and the determination of a narcoleptic profile difficult. Ideally, agreement needs to be reached about which standardized assessments are appropriate for adequately exploring the cognitive and psychological consequences of developing narcolepsy in childhood and this would allow for direct comparisons of results between studies. Academic attainment was investigated by asking parents or teachers to provide a description of the children's academic strengths and weaknesses and their general performance at school (e.g. the need to repeat a school year). The use of a standardised test of academic attainment (for example the Wechsler individual achievement test - second edition (WIAT-II) at the time of the study would have provided a more accurate and reliable assessment of ability and allowed for direct comparison between the participating children and between studies. The reviewed studies lacked objective and subjective measures of sleep quality and duration (polysomnography, actigraphy or sleep diaries) immediately before and during cognitive and psychological assessment, making it difficult to assess how the participants' overnight sleep and day time naps may be affecting cognitive and psychosocial outcomes. The reviewed studies also did not include any objective or subjective measures of alertness and sleepiness during testing so it is not clear whether participants were performing at an optimal level during the assessments. Some of the studies included both treated and untreated children with narcolepsy, however, due to the small sample sizes it was not possible to compare performance between these groups. It is therefore unclear how medication may have affected individual profiles. This information would be useful for doctors to know when prescribing medication to children with narcolepsy so that they are aware of any positive or negative side effects on cognitive function and psychosocial well-being. If medication was shown to have any negative effect on cognitive function, teachers should be aware that the academic performance of medicated children with narcolepsy may be adversely effected.

Future research and recommendations

In order to gain further understanding about the cognitive and psychological consequences of childhood narcolepsy, future research must address the following key issues. Ideally, future studies should aim to recruit large, representative samples of children and adolescents with narcolepsy. Controls matched on age, gender, race, SES and I.Q should be recruited and included in the studies. Children's and adolescents progress should be monitored using age-appropriate standardised assessment tools so that changes in cognitive and psychological difficulties can be measured objectively. Mixed-method research would be useful for investigating this population so that qualitative data (for examples interviews with children and parents) can be used to support quantitative results (objective sleep measurement and standardised cognitive and psychological assessment).

Research should aim to clarify whether any particular symptom or consequence of narcolepsy (for example EDS, disturbed night time sleep, reduced daytime activity) is the root cause of cognitive and psychological difficulties. If support is found for a particular symptom being the cause of cognitive and psychological difficulties in children and adolescents with narcolepsy, treatment and interventions must focus on alleviating this symptom in order to prevent or reduce its consequences. Longitudinal research is needed to follow up children and adolescents with narcolepsy and provide insights into how cognitive and psychological difficulties change over the lifespan. Longitudinal data is critical to understanding the causal relationship between the symptoms of narcolepsy and cognitive and psychological outcomes and will help establish a cognitive and psychological profile of children with narcolepsy. Understanding how sleep quality and duration and daytime activity levels affect cognitive and psychosocial outcomes in this population may inform the design of effective interventions to improve daytime functioning.

Conclusion

The reviewed literature has highlighted that school-age children with narcolepsy are at significant risk of cognitive and psychosocial impairment. These impairments are hypothesized to impact on academic performance, quality of life, daytime functioning and safety and therefore these children should be carefully monitored by doctors, parents and teachers. This review has highlighted that the current literature is limited by small sample sizes, lack of longitudinal data and lack of standardised measures. Future research should aim to determine the underlying cause of cognitive and psychosocial impairments as this will enable the most effective treatment and interventions to be put in place for these children so that they can achieve their full potential.

Practice points

1. Children and adolescents with narcolepsy are at risk of cognitive impairment in at least one domain. A consistent pattern of impairment has not been identified across the reviewed studies.
2. Children and adolescents with narcolepsy are also at risk of emotional problems including depression, anxiety and low self-esteem.
3. Children with narcolepsy should be monitored carefully by doctors, parents and teachers in order to manage and reduce the impact of any impairments present.

Research agenda

1. Future research should aim to recruit large, representative samples of children and adolescents with narcolepsy. Controls matched on age, gender, race, SES and I.Q should also be included in the studies.
2. Research should aim to clarify whether any particular symptom or consequence of narcolepsy (for example excessive daytime sleepiness, disturbed night time sleep, and reduced daytime activity) is the root cause of cognitive and psychological difficulties.
3. Longitudinal research is needed to follow up children and adolescents with narcolepsy and provide insights into how cognitive and psychological difficulties change over the lifespan.

Conflicts of interest

The authors have no conflicts of interest to declare pertaining to this review.

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Figure legends and captions

Figure 1

Flow diagram for identification of relevant studies (from January 2005 to August 2015)

Table 1

Databases searched

Table 2

Summary of papers included within the review. Abbreviations: attention deficit hyperactivity disorder (ADHD), attention deficit hyperactivity disorder-rating scale (ADHD-RS), Achenbach child behaviour checklist (CBCL), body mass index (BMI), child behaviour checklist (CBCL), child depression inventory (CDI), Chalders fatigue scale (CFS), Conners parent rating scale-revised (CPRS-R), excessive daytime sleepiness (EDS), Epworth Sleepiness Scale (ESS), health related quality of life (HRQL), international classification of sleep disorders-second edition (ICSD-2), idiopathic hypersomnia (IHS), insomnia severity index (ISI), paediatric daytime sleepiness scale (PDSS), quality assessment score (QAS), strength and difficulties questionnaire (SDQ).

Table 1

Database	Interface	Date searched
MEDLINE	Ovid MEDLINE(R), 1996 to August week 3 2015	28th August 2015
Embase	OvidSP, 1996 to 2015 week 34	28th August 2015
PsycINFO	OvidSP, 2002 to August week 4 2015	28th August 2015
The Cochrane Library	The Cochrane Database of Systematic Reviews, Issue 9 of 12, September 2015	28th August 2015

Table 2

	Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
1	Avis, K. T., Gamble, K. L. et al. (2014)[15]	66.7 %	33 children with EDS (18 narcolepsy, 15 IHS). 16 males, 17 females, mean age 12.93 years, range 8.03-16.84 years. Children met (ICSD-2) criteria for a hypersomnia of central origin (narcolepsy with or without cataplexy, or IHS). The diagnosis was made within three years of study date. 33 control children, 16 males, 17 females, mean age 12.74 years, range 8.83-17.81 years. Matched by age, sex, race and average income in the	USA	Cross sectional -design Case-control study	Simulated injury Attention to traffic Decision making ESS-modified for children.		Children with EDS were clinically sleepy (M= 12.33) The control sample were adequately alert with a mean ESS score of 6.94. Children with EDS experienced collisions and near-collisions on over 10% of crossings in the virtual street environment and at a rate twice that of matched controls.	Strengths Children came off medication three days before the study-performance unaffected by medication. Matched controls Weaknesses Children with narcolepsy and children with IHS were grouped together. No standardised measure of I.Q. Limitations to the virtual reality environment-bidirectional midblock crossing. Not a perfect replica of a real life situation. Did not measure lower lever underlying cognitive processes such as reaction

			ZIP code of residence. Diagnosis and recruitment occurred at the Pediatric Sleep Disorders Center at Children's of Alabama.						time or visual perceptual skills. Small sample size
2	Dorris, L., Zuberi, S.M. et al. (2008)[18]	64.3 %	12 children with narcolepsy (11 children reported to have cataplexy), six males, six females, mean age 10.6 years (SD= 2.9), range seven years to 16 years All were diagnosed and assessed within a multidisciplinary regional paediatric neuroscience unit on the basis of clinical history. No control group	UK	Cross-sectional	I.Q: verbal, performance and full scale Wechsler intelligence scale for children-III UK (WISC-III ^{UK})	Clinical psychologist assessed the participants using a clinical interview The parent version of the Achenbach child behaviour checklist (CBCL)	11 children obtained an IQ in the average range on the WISC-III^{UK} (median =10, SD= 10.24, range= 84-116). A significant and clinically significant difference was found between verbal (median=98, range= 88-122) and performance (median= 104, range= 77-123) scales in 42% of the children, compared to WISC-III^{UK}	Strengths Used well validated and reliable measures which have normative data and clinically significant cut off points Tests were alternated in their presentation Children tested during clinical appointment where child was assumed to be at their optimal level of arousal and wakefulness Weaknesses No control group Lack of specific measures of attention, learning or neuropsychological

normative prevalence rates of 24%. These discrepant profiles did not reflect a consistent pattern of strength and weakness 10/12 children scored in the clinically significant range (64 and above) on the total score index of the CBCL (mean= 64.83, SD= 8.39, range= 49-80). 9/12 children scored in the clinically significant range on the Internalising Index of the CBCL (mean=62.25,	measures of executive function Cognitive test measurement may be confounded by medication. Seven children treated with Modafinil (300g) before assessment, five children untreated. No comparison made between treated and untreated children due to small sample size No empirical assessment of vigilance or wakefulness was employed. Arousal fluctuations may contribute to the uneven cognitive profiles No consideration of SES Used parental accounts of psychosocial problems No longitudinal data therefore it is difficult to assess the long term relationship between narcolepsy and

	SD =11.23, range=32-77).	psychosocial and intellectual functioning
	The majority of children presented with difficulties in discussing and describing distressing physical and psychological symptoms with parents and others.	Small sample size
	Over 50% of the children were rated by their parents as having significant difficulties in areas such as social integration and academic attainment, with low levels of participation in age-appropriate activity.	

3	Inocente, C. O., Gustin, M. et al. (2014) [19]	62%	88 children with narcolepsy (cataplexy was present in 80.7% of the children), 44 males, 44 females, mean age 11. 9 years, range 5 years to 17.5 years All children were diagnosed with primary narcolepsy after a complete clinical evaluation using ICSD-2 and sleep-and wake-monitoring No control group	France	Cross-sectional	children's depression inventory (CDI) adapted Epworth sleepiness score (AESS) paediatric daytime sleepiness scale (PDSS) cataplexy severity rating score insomnia severity index (ISI) Conners parent rating scale-revised (CPRS-R) Chalders fatigue scale (CFS)	High levels of depressive symptoms affected 25% of the children There were more females with abnormal CDI scores than boys (P=.04) Depressive children were older at diagnosis than non-depressive children (P=.04) The period between disease onset and diagnosis tended to be longer in patients with abnormal CDI scores (P=.051) Depressive children had	Strengths Relatively large sample Used well validated and reliable measures with normative data available and clinically significant cut off points Weaknesses No control group Lack of children with narcolepsy without cataplexy included No consideration of SES Cut off age to compare older children to younger children was arbitrarily chosen at 10 years No longitudinal data therefore it is difficult to assess the long term relationship between narcolepsy symptoms and the development of depressive feelings Severity states of the disease not identified

							higher fatigue, hyperactivity and insomnia scores but did not have more frequent school difficulties.	
4	Inocente, C. O., Gustin, M.et al. (2014) [20]	71 %	117 children with primary narcolepsy (81% of children reported to have cataplexy), 65 males, 52 females), mean age 11.6 years, range five years to 17 years All children were diagnosed with primary narcolepsy after a complete clinical evaluation using ICSD-2 and sleep-and wake-monitoring 69 control children (29 males, 40 females), mean age 13.5 years, range seven years to 17 years.	France	Cross-sectional	children's depression inventory (CDI) Conners parent rating scale-revised (CPRS-R) health related quality of life questionnaire: -Vécu et santé perçue de l'Adolescent (11-18 years) -Vécu et santé perçur par l'Enfant (8-10 years) adapted Epworth	Narcolepsy impacts HRQL in terms of vitality and physical well-being. Children with narcolepsy were more obsess than control children (60% vs 1.4 %, P < 0.001). 25% of children with narcolepsy has clinically significant depressive feelings on the CDI (CDI≥16)	Strengths Control group Relatively large sample Used well validated and reliable measures with normative data available and clinically significant cut off points Weaknesses No consideration of SES No longitudinal data therefore it is difficult to assess the long term relationship between narcolepsy symptoms and HRQL.

sleepiness score (AESS)	compared to 15.6 % of controls
paediatric daytime sleepiness scale (PDSS)	7% of children with narcolepsy had a high level of Attention Deficit/Hyperactivity Disorder symptoms (CPRS-R>75)
Chalders fatigue scale	
cataplexy severity rating score	
insomnia severity index	41% of children with narcolepsy reported school difficulties compared to 7.5% of controls (P=0.002) (reported by parents)
parent reports of school difficulties, absenteeism and grade repetition	
height, weight and body mass index (BMI)	28 % of children with narcolepsy did not pass a school year

							and repeated it prior to narcolepsy diagnosis compared to 7.5% of controls (P< 0.001) 30 % of children with narcolepsy compared with 8.9% of controls had high levels of absenteeism (P=0.002) Compared with control children, children with narcolepsy(P= 0.0001) and adolescents (P=0.008) had lower HRQL	
5	Karjalainen, S., Nyrhilä,	43%	Six children with narcolepsy (2 males, 4 females),	Finland	Cross-sectional	Questionnaire including structured and	Narcolepsy affected children’s school	Strengths

	A.M. et al. (2014)[16]	mean age 11 years, range 10 years-13 years. No control group		open-ended questions aimed for parents children and teachers (data analysed with content analysis) The structured questions followed standardised questionnaires such as the strength and difficulties questionnaire (SDQ) but the open ended questions were composed specifically for this research	work and need for support. There are no established forms of support but solutions vary. Five out of six children had behavioural, emotional and social problems Symptoms of narcolepsy affect many areas of the children's lives and decrease the general well-being of their families, too. Teachers reported that five children had general support and one child was receiving intensive support EDS and fatigue attacks are reported to have affected	Produced qualitative and quantitative data Detailed evaluation of six children and highlights that concern over well-being of children with narcolepsy is justified Weaknesses Small sample Reliance on questionnaires and interview – no objective measures

								concentration and attention Illness is reported to have affected the children's overall ability to function and learning processes considerably Skills that were learned previously were lost at the beginning of the illness	
6	Lecendreux, M., Lavault, S. et al. (2015)[21]	64.3%	108 children with narcolepsy, 86 of these children had cataplexy, 22 did not have cataplexy. The median age of children who had narcolepsy with cataplexy was 14 years, age range 6.6-17.8 years. 48 males, 38 females. The median age of children who had narcolepsy without	France	Cross-sectional	Paediatric daytime sleepiness scale (PDSS) Insomnia severity index (ISI) Chalder's fatigue Scale ADHD-RS Need to repeat a	Structured interview Physical examination Child depression inventory (CDI) Heath-related quality of life	Paediatric patients with narcolepsy had high levels of treatment-resistant ADHD symptoms. Individuals with narcolepsy were at an increased risk for ADHD symptoms	Strengths Relatively large sample Used well validated and reliable measures with normative data available and clinically significant cut off points Control group Weaknesses No longitudinal data therefore it is difficult to assess the long term relationship between

			cataplexy was 10.3 years, range 5.9-17.4 years. 10 males, 12 females. 67 healthy controls with a median age of 14.8 years, range 7 years-17.9 years.			grade in school		compared to controls (2 fold). They were also at greater risk for depressive symptoms and were reported to have a poorer quality of life	narcolepsy and ADHD symptoms. ADHD symptoms were not measured before the onset of narcolepsy and after the initiation of psychostimulants therefore the causal relationship between narcolepsy and ADHD cannot be established. No clinical assessment or formal diagnosis of ADHD was undertaken.
7	Posar,A., Pizza, F. et al. (2014)[17]	61.9%	13 children with narcolepsy with cataplexy (eight males, five females), mean age 10.3 years, range 6.8 years to 13.6 years All children underwent a series of investigations and were included if they met the criteria for narcolepsy with	Italy	Cross-sectional	Academic performance (reading, writing, mathematics) assessed according to familial and personal interview Full IQ, Verbal IQ, Performance IQ: Wechsler intelligence scale for children-	SDQ for parents	All children had normal full IQ (mean =104, range 87-115) verbal IQ (mean=105, range 91-117) and performance IQ (mean=104, range 85-118) Comparisons between verbal IQ and performance	Strengths The individual performing the neuropsychological testing was informed so that he could realize even minimal signs of sleepiness in the patient, in order to stop the evaluation if necessary Weaknesses Lack of physiological monitoring of sleepiness while testing

	cataplexy according to the ICSD-2. No control group	revised (WISC-R) Auditory verbal working memory: “Digit span” verbal subtest of WISC-R. Non verbal reasoning: Raven’s progressive matrices (1974) Fepsy (a computerized test battery, Alphers, 1987) tasks: Alertness (auditory and visual reaction times) Attention (binary choice task)	IQ showed that verbal IQ was similar to performance IQ in eight cases, whereas it was higher than performance IQ in three cases and lower than performance in two cases according the WISC-R normative values. Nonverbal reasoning was adequate in all children according to Raven’s progressive Matrices 7 out of 13 subjects reported academic failure	Academic performance was assessed via familial and personal interview rather than standardised measurement Lack of follow up evaluation Not all participants were submitted to all Fepsy tasks because of a lack of available normative values for all the ages. Lack of control group

			Visual verbal and nonverbal working memory(recognition of words and figures, respectively) Abstraction and problem solving (classification task: total and preservative errors)	An impairment of at least one of the assessed cognitive aspects was present in nine of 13 cases and in five of seven children with academic failure Attention was normal in all of the 11 children tested on the binary choice task Childhood narcolepsy with cataplexy is a risk factor for the development of heterogeneous cognitive problems. No consistent cognitive profile was

								found in the subgroup of children with academic failure	
8	Stores,G., Montgomery, P. et al. (2006)[14]	61.9 %	42 children with narcolepsy (24 male, 18 female), mean age 12.5 years, age range 7.3 years to 17.9 years The child's clinician was contacted and asked to provide as much diagnostic detail as possible about the child's condition. This information was supplemented by the Ullanlinna narcolepsy scale as a check on the original diagnosis 18 children with excessive daytime sleepiness (EDS) of uncertain origin without definite additional features of narcolepsy (14	UK Recruitment in: Europe U.S Australia	Cross-sectional	International cross-sectional questionnaire asking teachers to provide information about child's absent days from school in the previous term and their opinion on the child in relation to: -problems with learning -not reaching academic potential -not working hard enough	Behaviour: (SDQ) Quality of life: child health questionnaire Mood: child depression inventory (CDI) Ullanlianna narcolepsy scale	Children with narcolepsy and those with EDS reported significantly higher rates of behavioural problems and depression than controls. Their quality of life was significantly poorer and they had more educational problems (as reported by teachers). The similar profiles of difficulties in the narcolepsy and the EDS groups suggest that excessive sleepiness may	Strengths Relatively large sample size Precise assessment of the symptoms of children previously given the diagnosis of narcolepsy International questionnaire Weaknesses The controls are not matched on age and gender Reliant on teachers responses rather than on standardised assessment of children's abilities

male, 4 female), mean age 14.3 years, range 5.1 years to 18.8 years 23 control children (12 male, 11 female), mean age 11.30 years, age range 6.0 years-16.8 years	-being difficult to teach	be the underlying cause.