Sleep Medicine 32 (2017) 143–149

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

Assessing sleepiness and cataplexy in children and adolescents with narcolepsy: a review of current patient-reported measures

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ARTICLE INFO

Article history:
Received 27 May 2016
Received in revised form
23 December 2016
Accepted 26 December 2016
Available online 20 January 2017

Keywords:
Narcolepsy
Cataplexy
Sleepiness
Assessment
Children
Adolescents

ABSTRACT

Objective: The objective of this study was to review patient-reported outcome measures assessing excessive daytime sleepiness (EDS) or cataplexy in children or adolescents to determine their usefulness and limitations in pediatric narcolepsy assessment.

Methods: Searches were performed in Embase and Medline for pediatric measures of EDS and cataplexy that are either patient- or proxy-reported, and searches of http://www.clinicaltrials.gov/ were conducted for studies in narcolepsy that included at least one patient-reported measure. Further review was performed if sleepiness questionnaires (child or proxy-reported), sleep questionnaires that may contain sleepiness questions, proxy-reported child behavior questionnaires, or information on cataplexy measures were mentioned.

Results: All self-reported cataplexy questionnaires from among 27 citations were study-specific diaries and were not identifiable as a recognized validated questionnaire. For EDS, 118 of 401 abstracts were further reviewed and the names of 21 questionnaires identified, of which eight questionnaires did not return additional citations of their validation. The Epworth Sleepiness Scale (ESS) or a modified version was the most frequently used measure of EDS. Although all measures were associated with limitations for use in the pediatric population, the ESS has been successfully used in adolescents and was deemed readily amenable to further modification for children.

Conclusions: There remains a dearth of validated measures for assessing EDS and cataplexy in children and adolescents with narcolepsy. The need for these measures may be filled by modification or adaptation of existing adult measures; a daily cataplexy diary and the ESS may be readily modified to make them child-friendly with regard to wording and settings, but should still undergo psychometric validation.

1. Introduction

Narcolepsy, a chronic neurological disorder, has a prevalence of 0.05% in the United States [1] and is considered an 'orphan' disease. Despite its low prevalence, it is a clinically important condition because there is no cure and disease management is required over the lifetime of the patient. This disease management often begins in childhood or adolescence since narcolepsy has an early onset, generally during the second decade of life, although symptoms can be present in children <10 years of age [2–5]. In addition to specific pediatric issues of obesity and precocious puberty [6], narcolepsy in the pediatric population is associated with impaired academic performance and reduction in social and participatory activities [4], suggesting the need for early recognition and initiation of treatment.

Clinically, narcolepsy is characterized by excessive daytime sleepiness (EDS), cataplexy, hallucinations during onset of sleep or waking, sleep paralysis, and disrupted nighttime sleep, although not all symptoms may be present. Cataplexy and EDS are commonly the primary symptoms targeted for treatment [7]. EDS is present in

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http://dx.doi.org/10.1016/j.sleep.2016.12.020

all narcolepsy patients, is required for diagnosis [8], and is generally the first symptom to occur, often preceding cataplexy by weeks or months [7]. In contrast, although cataplexy is considered pathognomonic for narcolepsy, it is present in approximately 70% of patients [7,8].

Current approaches to the management of narcolepsy are symptomatically driven, with EDS and cataplexy being the main therapeutic targets [9,10]. Published guidelines and best-practice recommendations suggest several pharmacological agents with the choice of therapy dependent not only on the presence of symptoms but also on a variety of patient- and therapy-related factors [9–11]. An important limitation is that these guidelines reflect an adult narcolepsy population [9,10]; thus far, no guidelines specific to the pediatric population have been developed. Nevertheless, management of pediatric patients with narcolepsy has been discussed in several publications [12–14]. However, such management primarily relies on choice of medication and dosing based on empirical data derived from adults because there has also been a lack of published clinical trials evaluating treatments in children and adolescents.

Appropriate long-term management also requires meaningful and regular assessment of treatment effects on frequency and severity of symptoms from the patient's perspective. For assessment of EDS and cataplexy, the Epworth Sleepiness Scale (ESS) [15] and a daily patient cataplexy frequency diary are generally used for these outcomes, respectively, in clinical trials and the clinical setting. However, these measures were designed for the adult population, and may not necessarily be appropriate for a pediatric population. Therefore, the purpose of this review is to identify and review patient-reported outcome (PRO) measures assessing EDS or cataplexy in children or adolescents with the goal of determining the usefulness and limitations of these instruments in pediatric narcolepsy assessment.

2. Methods

This review consisted of two parts, of which the first part was a search of the literature for pediatric measures of EDS and cataplexy that were either patient-reported or proxy-reported, ie, parents or caregivers. The second part was a search of PROs used in ongoing clinical trials of narcolepsy based on searches of http://www.clinicaltrials.gov/.

The literature searches were performed in March 2013 in Embase and Medline. For narcolepsy/cataplexy, the terms used were: "(questionnaire MeSH OR questionnaire OR diary OR diaries OR scale) AND (carer OR caregiver OR parent OR proxy OR teacher) AND narcolepsy MeSH" with no limits. The search terms for sleepiness were: "(questionnaire MeSH OR questionnaire OR diary OR diaries OR scale) AND sleepiness" with limits of humans 6–18 years old, abstract, English, and last eight years.

Duplicate abstracts were removed and all abstracts were reviewed and excluded if the population was not pediatric or if there were no relevant questionnaires used in the study as described in the abstract (eg, sleep questionnaires that included only one or two items on sleepiness, study-specific questionnaires that were not documented or validated, name of questionnaire not provided). Articles thought to contain further information on cataplexy measures, or that mentioned a measure that seemed to be a validated questionnaire but did not give its name were ordered and reviewed in detail in order to identify the relevant questionnaires.

For the search of PROs in narcolepsy trials, phase 2, 3, or 4 trials in narcolepsy were identified from http://www.clinicaltrials.gov/ if they included at least one PRO instrument. The search was performed in December 2016. The available information from each trial was reviewed for determination of which PRO measures were included and their appropriateness for use in assessment of sleepiness or cataplexy in pediatric narcolepsy.

3. Results and discussion

3.1. Literature searches

3.1.1. Cataplexy questionnaires

The literature searches returned 27 abstracts that were evaluated. All self-reported cataplexy questionnaires mentioned were study-specific diaries and were not identifiable as a recognized validated questionnaire. Only one study reported the wording of their specific question, intended for use in adolescents [16]: "how frequently have you experienced episodes of sudden muscle weakness (eg, knee buckling, jaw opening, neck flopping or postural collapse) when you are having fun, excited, angry or laughing?" However, this question was translated in the article from Korean, and the study itself was not specific to narcolepsy.

Most studies that assessed cataplexy measured frequency of attacks, and this was done exclusively through use of the study-specific diaries. Although a few studies measured severity, such assessments were based on an arbitrary scale; for example, "grade 3 is complete loss of posture with fall to the ground, grade 2 is weakness with upright posture being maintained using an external support, such as holding on to a table, grade 1 is momentary weakness without the need to hold on to an object for support, such as head drop or the jaw falling open" [17]. One study described a clinician evaluation of cataplexy changes on a four-point scale (1 = none, 2 = slightly improved, 3 = unchanged, 4 = clearly worsened) [18], and even though it was not clearly stated in the study, this clinician evaluation could be plausibly based on a reading of the daily diary entries.

3.1.2. Sleepiness questionnaires

The search for EDS scales returned 401 abstracts. After excluding non-pediatric articles ($N = 190$), duplicates ($N = 7$), and articles in which there were no relevant questionnaires ($N = 86$), a total of 118 relevant abstracts were kept as reporting the use of a questionnaire assessing sleepiness in pediatric population.

As shown in Table 1, the names of 21 questionnaires that included assessment of sleepiness in the pediatric population were extracted from the relevant articles. Of these questionnaires, the ESS or a modified version of this scale was by far the most frequently used measure of EDS, followed by the Children's Sleep Habits Questionnaire. Further searches on eight of the questionnaires did not return any additional citations of their validation. The measures that were not further identifiable and thus were not considered for subsequent review included the Sleep Disorder Scale for Children [19–21], Children's Report of Sleep Patterns [22], Chronic Sleep Reduction Questionnaire [23], General Sleep Disturbance Scale [24], NIMHANS (National Institute of Mental Health and Neurosciences) Sleep Disorders Questionnaire [25], Sleepiness Scale adapted to Children and Adolescents [26], Sleepiness Scale [27], and the Sleep–Wake Habit Questionnaire [28]. It is possible that for at least some of these measures, mislabeling of the name may account for the inability to identify it.

Of the other 13 measures (Table 2), three were designed primarily for screening: Sleep Disturbance Scale for Children [29], Pediatric Sleep Questionnaire [30], and the BEARS (Bedtime problems, Excessive sleepiness, Awakenings during the night, Regularity of sleep, Snoring) questionnaire [31]. All are parent- or proxy-reported questionnaires and are generally used, respectively, to categorize sleep disorders in children, screen for sleep-related breathing disorders and symptom-complexes, and identify major sleep disorders in children during parent interviews. Additionally,