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GUIDELINES

European guideline and expert statements on the management of narcolepsy in adults and children

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Summary

Background and aim: Narcolepsy is an uncommon hypothalamic disorder of presumed autoimmune origin that usually requires lifelong treatment. This paper aims to provide evidence-based guidelines for the management of narcolepsy in both adults and children.
Methods: The European Academy of Neurology (EAN), European Sleep Research Society (ESRS) and European Narcolepsy Network (EU-NN) nominated a task force of 18 narcolepsy specialists. According to the EAN recommendations, 10 relevant clinical questions were formulated in PICO format. Following a systematic review of the literature (performed in Fall 2018 and updated in July 2020) recommendations were developed according to the GRADE approach.
Results: A total of 10,247 references were evaluated, 308 studies were assessed and 155 finally included. The main recommendations can be summarized as follows: (i) excessive daytime sleepiness in adults—scheduled naps, modafinil, pitolisant, sodium oxybate (SXB), solriamfetol (all strong), methylphenidate, amphetamine derivates (both weak); (ii) cataplexy in adults—SXB, venlafaxine, clomipramine (all strong) and pitolisant (weak); (iii) excessive daytime sleepiness in children—scheduled naps, SXB (both strong), modafinil, methylphenidate, pitolisant, amphetamine derivates (all weak); (iv) cataplexy in children—SXB (strong), antidepressants (weak). Treatment choices should be tailored to each patient's symptoms, comorbidities, tolerance and risk of potential drug interactions.
Conclusion: The management of narcolepsy involves non-pharmacological and pharmacological approaches with an increasing number of symptomatic treatment options for adults and children that have been studied in some detail.

KEYWORDS
cataplexy, European, guideline, management, narcolepsy

INTRODUCTION: BACKGROUND AND SCOPE

Clinical need for a guideline

Narcolepsy is a disabling hypothalamic disorder that presents with a variety of sleep–wake and other symptoms. Excessive daytime sleepiness (EDS) is usually the most troublesome feature although significantly fragmented and disturbed nighttime sleep (DNS) is common with phenomena including sleep paralysis and hallucinatory experiences around sleep–wake transitions (hypnagogic and hypnopompic hallucinations) [1,2]. Whereas narcolepsy with typical cataplexy (type 1 narcolepsy, NT1) is considered a distinct entity, associated with hypocretin deficiency, narcolepsy without cataplexy (type 2 narcolepsy, NT2) is less clearly defined and when diagnosed following the current diagnostic criteria is a heterogeneous disorder [1]. Although the precise aetiology of narcolepsy is unknown, most evidence suggests it is usually a sporadic acquired immune-mediated condition that develops in people who are genetically predisposed [2-5].

Worldwide prevalence estimates suggest that approximately 25–50 persons out of 100,000 are affected [6,7]. Some recent studies indicate that narcolepsy may be less frequent [8]. Narcolepsy potentially affects every aspect of daily life with considerable personal, social and economic consequences. As a result, quality of life measures of both patients and their families are significantly reduced [9,10]. Current treatments include non-pharmacological and pharmacological approaches [1,11,12].

Treatment guidelines for narcolepsy were first published in Europe in 2006 [13] and in the United States in 2007 [14]. Criteria for diagnosing narcolepsy into types 1 and 2 (NT1 and NT2) were revised in 2014 by the American Academy of Sleep Medicine. A recent paper addressed the limitations of the current International Classification of Sleep Disorders 3 (ISCD-3) diagnostic criteria and made suggestions for future improvements [15].

Since 2006, there have been considerable developments in our understanding of both the aetiopathology and clinical characteristics in narcolepsy. Furthermore, several new drugs have become available. This has prompted the European Academy of Neurology (EAN), European Sleep Research Society (ESRS) and European Narcolepsy Network (EU-NN) to join forces to provide up-to-date, evidence-based recommendations for narcolepsy treatments. Patient representatives have been included in the task force, expanding its perspective.

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Scope

This guideline focuses on people of any age with a specific diagnosis of narcolepsy (NT1 and NT2). It does not address disorders in the narcoleptic 'borderland' such as idiopathic hypersomnia or any other condition causing EDS. Symptomatic treatments of EDS, cataplexy and the predominantly nocturnal symptoms of narcolepsy (DNS, sleep paralysis, sleep-related hallucinations) are assessed, including first-line, second-line and combination therapies. It also evaluates pharmacological treatments that are potentially disease modifying as well as therapies for a variety of comorbid conditions. The latter include psychiatric symptoms and fatigue [16], obesity, sleep-disordered breathing, rapid eye movement sleep behaviour disorder (RBD), restless legs syndrome and periodic limb movements (RLS/PLMS). Where appropriate, evaluations for adults and children are described separately. For some clinical situations, expert statements are included. Patients' view on the management of narcolepsy is also included in a special section.

METHODS

The EAN, the ESRS and the EU-NN nominated 18 experts in narcolepsy from 11 European countries to form a task force. Four patient representatives were elected by a patient assembly during the European Narcolepsy Day 2018 and were subsequently added to the task force to provide an opinion statement around key areas of clinical management and research outcomes. Within the task force, 10 working sub-groups were appointed, each consisting of two experts responsible for one clinical question.

This guideline was developed in accordance with the recommendations of the GRADE Working Group (https://www.gradeworkinggroup.org/) and in line with the 2015 practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces [17]. For the procedures in detail see the Supporting Information Appendix S1 online.

Following preparatory talks in 2016, the task force was established after a signed agreement between the three societies in 2017. The guideline production was finalized in September 2020.

Guideline questions

As an initial step, key questions and potential outcomes essential for the clinical management of patients with narcolepsy were identified. An explicit list of outcomes for each question was proposed by the co-chairs and circulated to the rest of the task force working group, prior to rating their relative importance for clinical decision making. Outcome prioritization was undertaken using a 9-point Likert scale and grouped into three categories (1–3, outcome of low importance; 4–6, outcome important but not critical for decision making; and 7–9, outcome critical for decision making). Only outcomes graded as critical or important according to expert opinion were subsequently analysed. Finally, 10 key questions were formulated and organized into five sections (see below). The Patients–Intervention–Comparator–Outcome (PICO) framework was then used to formulate sub-questions, integral to the search strategies and draft recommendations. For the exact wording of the PICO questions and additional information see the Supporting Information and also see below.

PICOs classified into groups and as individual questions

Group/topic

1. Are there disease-modifying pharmacological treatments for narcolepsy that can restore hypocretin transmission or reverse the disease process?
2. Can non-pharmacological treatments improve symptoms of narcolepsy?
3. Can pharmacological treatments improve the symptoms of narcolepsy in adults?
4. Can any non-pharmacological or pharmacological treatments improve comorbidities and/or quality of life measures in patients with narcolepsy?
5. Can pharmacological treatments improve the symptoms of narcolepsy in children?

Search strategy

Published studies were identified from the National Library of Medicine's MEDLINE database, Elsevier's Embase database and the Cochrane Central Register of Controlled Trials by means of specific search strategies using a combination of exploded terms and free text, focusing on narcolepsy and treatments for narcolepsy. The strategy used for MEDLINE was translated to other databases. No language or date of publication restrictions were applied. Rarely, if studies had distinguished between the differing types of narcolepsy, notably NT1 and NT2, this is mentioned in the text. The literature search was performed between July and October 2018 and finally updated in July 2020. For pharmacological treatments, another update was performed in October 2020.

Data synthesis

A descriptive summary of the included studies with details of study design, number and characteristics of enrolled patients, intervention(s) and comparator(s), outcome measures and results

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was first provided in tables and then presented in Summary of Findings tables by individual outcome and intervention.

Grading the quality of the evidence and developing recommendations

The guideline was developed following the GRADE approach. Overall quality of evidence for each outcome was assessed by the methodology sub-group (EB, LV). For further details see the Method chapters found in the Supporting Information Appendix S1 online.

RESULTS

A total of 10,241 references were evaluated for possible inclusion. Full texts of 308 studies were assessed with 155 meeting the inclusion criteria. A descriptive summary of the whole process and findings is provided in the Supporting Information Appendix S1. Results of the literature search and overall quality of evidence for individual PICOs are also provided in the Supporting Information Appendix S1. References 35–173 refer to the Supporting Information.

Search Questions

Group 1 Question(s)—Disease modification

PICO 1

What is the clinical evidence for the efficacy of disease-modifying treatments for the remission or improvement of narcolepsy?

Introduction

Preventing total hypocretin neuron loss by an immunomodulatory treatment close to disease onset or in highly selected patients or hypocretin replacement therapy (hypocretin, hypocretin analogues, hypocretin receptor agonists) may be considered as a potential treatment strategy.

Recommendations – Among the disease modifying treatments evaluated none is recommended.

See Table S1.

Future directions/outlook

Specific monoclonal antibody therapies might represent a therapeutic option in the future to prevent or slow hypocretin neuron loss. The potential for severe side effects of such immune-modulatory treatments and uncertainties when to start therapy will require well-designed studies in carefully selected narcolepsy populations.

Selective hypocretin receptor agonists are a promising new class of drugs. Recently pilot trials on the hypocretin receptor agonist TAK-994 (animal data) and TAK-925 (adults with NT1) indicated a significant improvement of EDS (with normalization of the maintenance of wakefulness test in a few cases of NT1) and cataplexy (in animals) [18].

Group 2 Question(s)—Non-pharmacological management

PICO 2

What is the clinical evidence of non-pharmacological treatments in the management of narcolepsy?

Introduction

Non-pharmacological management of symptom control in narcolepsy should always be considered first. Non-pharmacological approaches increase patient involvement and enhance self-empowerment. Factors such as age, gender, profession, specific life situations and comorbidities will influence the potential for using non-pharmacological strategies. In some situations where medication is considered inappropriate such as pregnancy or potentially in early childhood, non-pharmacological management approaches are mandatory.

Recommendations – We recommend planned daytime naps to improve immediate subjective and objective sleepiness both in drug naïve narcolepsy patients and in those taking stimulant medication, at any age.

See Table S2.

Although available evidence on non-pharmacological treatment other than scheduled napping is low, the concept of such approaches is strongly supported as they promote better acceptance of the disease and compliance. Informed scientific knowledge of narcolepsy in any patient group is mandatory, including disease mechanisms and treatment options. Attempts to implement a fixed schedule for nocturnal sleep and daytime activities with short scheduled naps during the day are considered important. A general healthy lifestyle including regular physical activity and weight control are also considered important and might be expected to result not only in an improvement of symptom control but also enhanced patient empowerment. For many patients, joining a patients' organization turns out to be of great help as a source of information, exchange and support.

Future directions/outlook

Non-pharmacological treatment is considered important and forms an initial foundation for managing narcolepsy. Patients often have a special interest in non-pharmacological approaches (see below) although available scientific evidence for efficacy is very limited. Studies evaluating the potentially positive impact of special diet, light therapy or exercise programmes are needed.

Group 3 Question(s)—Symptomatic pharmacological treatments in adults

General comment: The overall goal of most symptomatic treatments should focus on improving the sleep–wake cycle of narcoleptic patients with particular attention on daytime performance. Improving EDS and reducing cataplexy are typically most important. Treatment goals and choice of treatments should take into consideration an individual's pattern of symptoms, preferences and existing comorbidities.

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PICO 3

What is the clinical evidence for the efficacy of pharmacological treatment of EDS and associated features? Is there a difference in efficacy between different wake-promoting drugs? What is the benefit-to-risk ratio of treatments?

Introduction

Excessive daytime sleepiness is usually the most prominent disabling symptom in patients with narcolepsy [1]. EDS can present with different phenotypes including sleep attacks, involuntary napping, automatic behaviours, an excessive need for sleep (hypersomnia sensu strictu), difficulty sustaining attention, and cognitive dysfunction. An improvement in EDS is usually assessed by clinical history or questionnaires. Objective testing such as the multiple sleep latency test (often used for diagnosis) and the maintenance of wakefulness test (often used to document treatment response) may provide useful information.

Based on several randomized controlled trials (RCTs) and clinical experience, there is clear evidence that a number of wake-promoting agents and sodium oxybate improve EDS. Treatment choices may change over time and be affected by factors such as age, lifestyle, severity, tolerance and comorbidities. Clinicians should therefore regularly reassess treatment efficacy and safety during follow-up visits. Data on long-term efficacy and safety are limited. A recent 1-year open label single arm pragmatic study supports the long-term safety and efficacy of pitolisant for treatment of EDS in patients with NT1 and NT2 [19]. However, one-third of patients stopped the medication due to lack of efficacy or side effects.

A recent trial performed over 24 months [20] reported a reduction in body mass index in NT1 patients treated with sodium oxybate, confirming previous clinical observations.

Stimulants (methylphenidate, modafinil, amphetamines and solriamfetol) may increase heart rate and blood pressure with risk of hypertension. These potential side effects require careful monitoring and may lead to specific management strategies [21].

Recommendations

See Figure 1 and Table S3.

The lack of head-to-head studies makes comparisons of efficacy between different stimulants/wake-promoting drugs difficult. The alerting effects of stimulating antidepressants were not evaluated as clinical experience suggests any impact on EDS in narcolepsy is at best minor. Antidepressants should not be considered as treatments for EDS.

Future directions/outlook

New compounds including novel histamine 3 receptor inverse agonists and hypocretin receptor agonists may soon become available for treatment of EDS in NT1 and NT2.

PICO 4

What is the clinical evidence for efficacy of pharmacological treatment of moderate to severe cataplexy? Is there a difference in efficacy between different drugs? What is the benefit-to-risk ratio of treatments?

Introduction

Cataplexy is a pathognomonic symptom of narcolepsy, which is reported by 60%–70% of all narcolepsy patients [1]. In moderate to severe cataplexy, pharmacological treatment is usually warranted.

Recommendations

See Figure 1 and Table S4.

Due to a lack of data, comparison of the efficacy of different drugs is not possible.

Future directions/outlook

Randomized clinical trials (RCTs) comparing serotonin–norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine against sodium oxybate to assess the specific benefit-to-risk ratio

	Drug	EDS		Cataplexy		DNS		SP/HH	
		Rec	QoE	Rec	QoE	Rec	QoE	Rec	QoE
1	Modafinil	↑↑	⊕⊕⊕⊖	↓↓	⊕⊕⊖⊖		no data		no data
	Pitolisant	↑↑	⊕⊕⊕⊖	↑-	⊕⊕⊕⊖		no data	↑-	⊕⊕⊖⊖
	Sodium Oxybate	↑↑	⊕⊕⊕⊖	↑↑	⊕⊕⊕⊖	↑↑	⊕⊕⊕⊖	↑-	⊕⊕⊖⊖
	Solriamfetol	↑↑*	⊕⊕⊕⊖	↓↓	⊕⊕⊕⊖		no data		no data
2	Antidepressants			↑↑	⊕⊕⊖⊖		no data	↑-	⊕⊕⊖⊖
	Amphetamine derivates	↑-	⊕⊕⊖⊖	↓↓	⊕⊖⊖⊖		no data		no data
	Methylphenidate	↑-	⊕⊕⊖⊖	↓↓	no data		no data		no data
	Zolpidem/Zopiclone					↓- #	⊕⊕⊖⊖		no data

Recommendations	
For Strong	↑↑
For Weak	↑-
Against Weak	↓-
Against Strong	↓↓

Quality of Evidence	
High	⊕⊕⊕⊕
Moderate	⊕⊕⊕⊖
Low	⊕⊕⊖⊖
Very Low	⊕⊖⊖⊖

Order: 1. EU-approved medications (in alphabetic order); 2. EU-frequently used medications for narcolepsy; * needs further evaluation from clinical practice; # chronic use not recommended

FIGURE 1 Overview of recommendations and of quality of evidence (adults) (SP, sleep paralysis; HH, hypnagogic/hypnopompic hallucinations)

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should be considered. New drugs such as hypocretin receptor agonists may represent a valid option for future treatment of cataplexy.

PICO 5

What is the clinical evidence for efficacy of pharmacological treatment for moderate to severe DNS? Is there a difference in efficacy between different drugs? What is the benefit-to-risk ratio of treatments?

Introduction

Nocturnal sleep is significantly disturbed in at least 65% of patients with narcolepsy. Disruption of sleep maintenance is the most common problem with recurring short and long wake periods. Sleep onset is usually unaffected. Over 24 h, the total sleep time of a narcoleptic person is often within normal limits. The extent of sleep fragmentation potentially in association with vivid dreaming and/or nightmares, RBD but also RLS/PLMS and sleep-disordered breathing can adversely influence daytime functioning and EDS prompting many patients to seek treatment for improving DNS.

Recommendations

See Figure 1 and Table S5.

Future directions/outlook

Different compositions of sodium oxybate e.g., low-salt, and long acting formulations may have an additional impact on improvement of DNS and are studied in RCTs. There is a need for more RCTs assessing DNS in narcolepsy both for existing drugs and newer compounds.

PICO 6

What is the clinical evidence for efficacy of the pharmacological treatment of moderate to severe sleep paralysis and hypnagogic/hypnopompic hallucinations? What is the benefit-to-risk ratio of treatments? Is there a difference in efficacy between different drugs?

Introduction

Sleep paralysis and hypnagogic/hypnopompic hallucinations are reported by approximately 50% of patients with narcolepsy [1]. No RCTs focused primarily on these symptoms and none were appropriately powered to detect efficacy of treatments.

Recommendations

See Figure 1 and Table S6.

Future directions/outlook

There is a need for specific trials on the impact of compounds including antidepressants and sodium oxybate on sleep paralysis and hypnagogic/hypnopompic hallucinations.

Group 4 Question(s)—Comorbidities

PICO 7

What is the clinical evidence of treatment for psychiatric comorbid symptoms?

Introduction

Psychiatric disturbances are frequently present (20%–30%) in narcolepsy, particularly depression and anxiety, potentially as a secondary phenomenon reflecting the psychosocial burden of the disease [1]. Either near diagnosis or during the course of the illness, psychiatric symptoms may require management.

Recommendations

It is suggested that psychiatric disorders in narcolepsy should be treated in accordance with general principles for a general population. Shared compounds for the symptoms of narcolepsy and depression should be considered where appropriate such as antidepressants for cataplexy and comorbid mood disorder (Weak recommendation). Depressive symptoms need regular re-evaluation [22].

The lack of specific studies does not provide support for any particular treatments for depression in narcolepsy. There is no reason, however, to consider well-established treatments for major depression in the general population to be less effective in narcolepsy.

Future directions/outlook

Specific non-pharmacological approaches including cognitive behavioural therapy and pharmacological approaches for psychiatric comorbidities in narcolepsy are implicitly needed.

PICO 8

What is the clinical evidence of efficacy and safety for treatment of other sleep disorders in narcolepsy such as RBD, sleep-disordered breathing, parasomnias, RLS/PLMS? Is there a difference in efficacy between different drugs or approaches?

Introduction

A variety of sleep disorders such as RLS (prevalence 10%–20%), sleep apnoea (20%–40%) or RBD (25%–70%) are more frequent in narcolepsy than in the general population [1]. The underlying aetiology of other sleep disorders and their clinical impact on narcolepsy remain unclear although specific treatments are often warranted.

Recommendations – Other sleep disorders in narcolepsy should be treated in accordance to the general recommendations for their specific treatment in non-narcoleptic patients.

See Table S7.

Future directions/outlook

Studies evaluating effects of treatments for other sleep disorders in narcolepsy are needed.

PICO 9

What is the clinical evidence of efficacy for treatments on measures of quality of life, global improvement or psychosocial factors? Is there a difference in efficacy between different drugs?

Introduction

Improving daily performance, quality of life measures and increasing the ability to work are key aims of the management of narcolepsy given their severe impact.

Special condition: driving

The ability to drive safely and the adverse effects of EDS are often extremely important issues for patients and their families. Driving regulations for people suffering from narcolepsy vary between European countries although successful treatment often allows patients to drive. However, any risk in driving crucially depends

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on patients recognizing or monitoring their levels of EDS and refraining from driving if appropriate.

Recommendations

No specific recommendations were provided. Clinical global impression, quality of life and prevention of everyday life risks were considered to substantiate the recommendations on symptomatic treatments. Single drugs in Table S8 report the synthesis of effect on these outcomes.

Future directions/outlook

In future trials, more attention should be given to quality of life measures together with other patient reported outcome measures.

Group 5 Question(s)—Symptomatic pharmacological treatment in children

PICO 10

What is the clinical evidence for efficacy of pharmacological treatment of any symptom of narcolepsy (including metabolic problems such as obesity and precocious puberty) in children? Is there a difference in efficacy between different treatments?

Introduction

Initial symptoms of narcolepsy occur before the age of 18 in over 50% of patients [1] and may start at a very young age also before puberty onset [23]. The nature of narcoleptic symptoms in childhood and adolescence such as cataplexy and EDS differs from the adult picture and may change over time [24]. Treatment strategies including a non-pharmacological approach are different from adult strategies and require taking into account the developmental aspects. Particular attention is needed when evaluating safety and the risk-to-benefit ratio of any treatment. Potential treatment side effects such as mood disorder and metabolic upset leading to weight gain or loss should be proactively assessed.

To date there are no established recommendations for the use of narcoleptic drugs when considering pubertal development. Endocrinologists who may prescribe adapted treatments in the case of advanced puberty should carefully monitor pubertal development.

Recommendations

See Figure 2 and Table S9.

Future directions/outlook

Compounds for the treatment of narcolepsy in children were approved only recently, following appropriate trials. The clinical efficacy of sodium oxybate for the treatment of EDS and cataplexy in children was first reported in 2018. Trials on the safety and efficacy of pitolisant in children are yet to be published and will start soon for solriamfetol. More studies and approved treatments are needed for the management of children and adolescents with narcolepsy.

Overview of quality of evidence and recommendations

See Figures 1 and 2.

PATHWAY, STATEMENTS AND EXPERT RECOMMENDATIONS

This guideline provides recommendations that are primarily evidence-based together with opinions from experts. Several clinical questions cannot be satisfactorily addressed because of limited evidence and lack of RCTs. Furthermore, firm conclusions are hampered by a limited systematic approach to formal assessment of symptoms and outcomes using a variety of non-validated and validated measures. Almost no head-to-head trials between drugs have been performed.

Drug	EDS		Cataplexy		DNS		SP/HH	
	Rec	QoE	Rec	QoE	Rec	QoE	Rec	QoE
Sodium Oxybate	↑↑	⊕⊕⊖⊖	↑↑	⊕⊕⊖⊖	↑-	no data	↑-	no data
Methylphenidate	↑-	⊕⊖⊖⊖		no data		no data		no data
Modafinil	↑-	⊕⊖⊖⊖	↓↓	no data		no data		no data
Pitolisant	↑-*	⊕⊖⊖⊖		⊕⊖⊖⊖		⊕⊖⊖⊖		no data
Antidepressants		no data	↑-	⊕⊖⊖⊖		no data	↑-	⊕⊖⊖⊖
Solriamfetol		no data		no data		no data		no data
Amphetamine derivates	↑-	no data		no data		no data		no data

Recommendations	
For Strong	↑↑
For Weak	↑-
Against Weak	↓-
Against Strong	↓↓

Quality of Evidence	
High	⊕⊕⊕⊕
Moderate	⊕⊕⊕⊖
Low	⊕⊕⊖⊖
Very Low	⊕⊖⊖⊖

Order: EU-frequently used medications for narcolepsy (strong, weak recommendation, no recommendation). Only Sodium Oxybate EU- approved. All other medications are not approved for the use in children (off-label); * Very limited data, in particular on safety, further evaluation needed.

FIGURE 2 Overview of recommendations and of quality of evidence (children) (SP, sleep paralysis; HH, hypnagogic/hypnopompic hallucinations)

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This part was completed applying an informal method of consensus, based on an extensive literature review, expert opinion and discussion. The task force reached consensus and agreed on the following recommendations.

Table S10 provides additional information on the medication.

Pathway for the management of narcolepsy

See Figures 3 and 4.

Overview of the impact on symptoms of frequently used drugs (adults)

See Figure 5.

Particular situations

Experts discussed several particular situations in narcolepsy in the absence of any published evidence from formal studies, leading to recommendations that are exclusively based upon expert knowledge and experience. The task force reached full consensus for these recommendations.

Pregnancy, breastfeeding, and contraception

In the majority of patients, the symptoms of NT1, particularly cataplexy, appear to become milder during pregnancy. However, there are no prospective studies and only few published retrospective studies on this topic [25,26]. Because of the teratogenic potential of all drugs used in the treatment of narcolepsy and other risks of complications during pregnancy, it is strongly advised to discontinue all drugs before any planned pregnancy [1]. This discontinuation will nearly always have an adverse effect on symptom control which can be particularly challenging prior to successful conception. If total discontinuation of drug therapy is thought not practicable, it is advised to limit treatment to monotherapy.

Of the drugs generally used in narcolepsy, low doses of antidepressants seem relatively safe. However, a recent publication has raised doubts on the previously assumed safety of modafinil, reporting a high prevalence of congenital defects [27]. There are some data indicating a positive effect of L-carnitine in a reduction of total nap time during the day [28].

The use of medication during breast-feeding in narcolepsy is not generally advised.

If a patient has a young child, initiating or restarting sodium oxybate should only be considered if there is a partner or family member who can reliably oversee the care of the child at night.

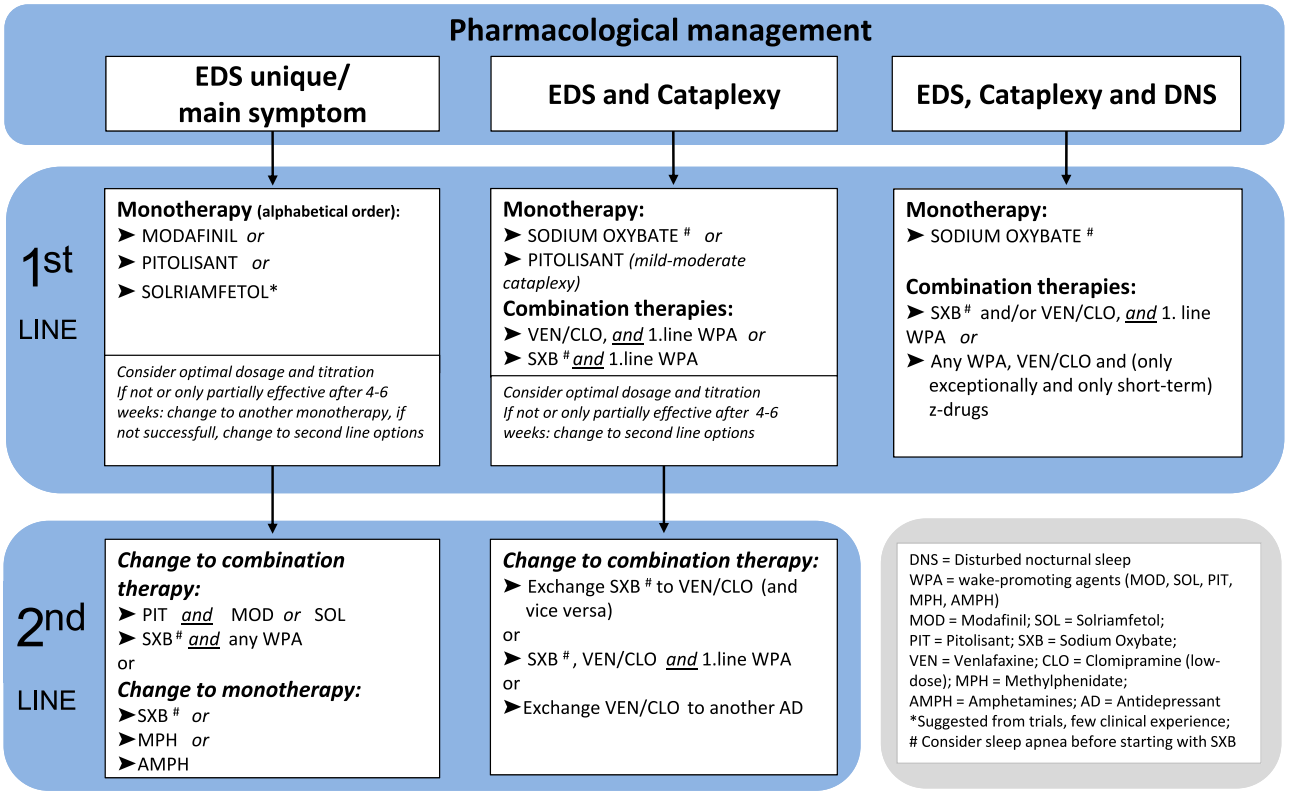

FIGURE 3 Clinical pathway for the management of narcolepsy (adults) [Colour figure can be viewed at wileyonlinelibrary.com]

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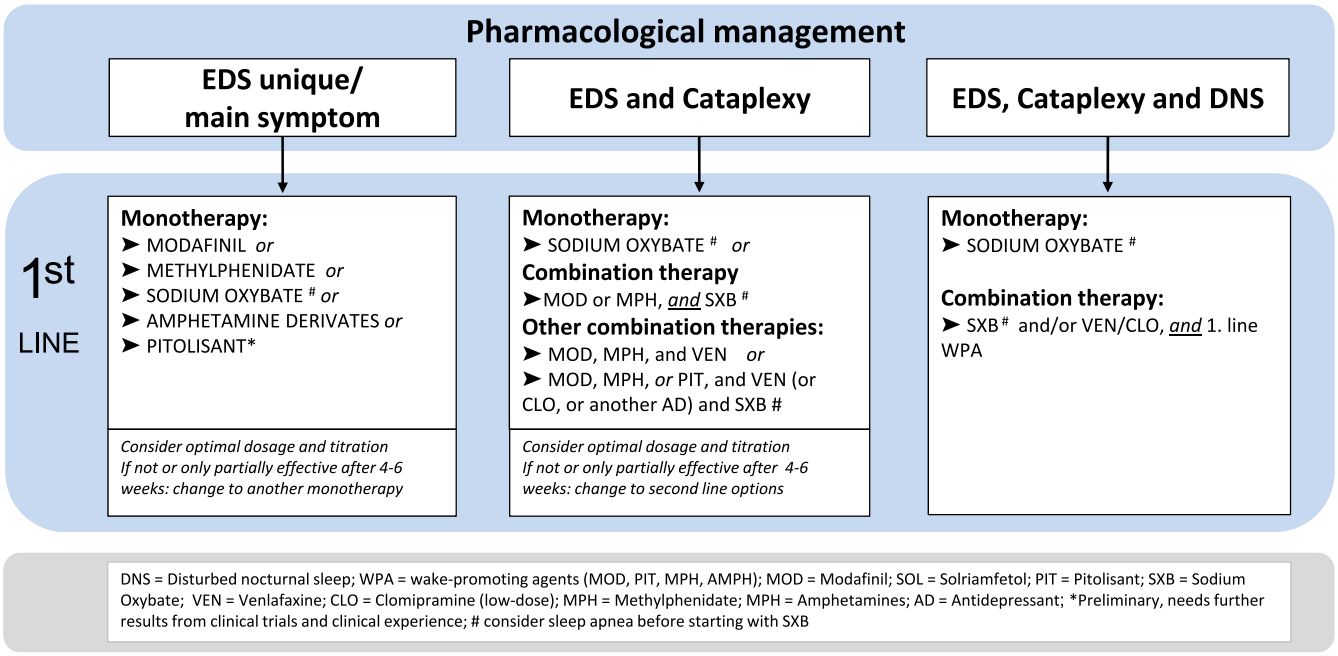

FIGURE 4 Clinical pathway for the management of narcolepsy (children) [Colour figure can be viewed at wileyonlinelibrary.com]

Drug	EDS	Cataplexy	DNS
Modafinil	↑↑	↓↓	
Pitolisant	↑↑	↑-	
Sodium Oxybate	↑↑	↑↑	↑↑
Solriamfetol	↑↑*	↓↓	
Venlafaxine / Clomipramine		↑↑#	
Methylphenidate / Amphetamines	↑-	↓↓	

Recommendations
For Strong ↑↑ For Weak ↑- Against Weak ↓- Against Strong ↓↓

* needs further evaluation from clinical practice # based on expert opinion exclusively

FIGURE 5 Overview of recommendations of key pharmacological treatments (adults)

Another issue related to pregnancy is the potential pharmacokinetic interaction of prescribed medications with oral contraceptives. Most of the recommended drugs in the treatment of narcolepsy seem to have no relevant interaction. An exception is modafinil, and there is debate about pitolisant. The European Medicines Agency advises dose adjustment and/or additional measures to prevent pregnancy when initiating modafinil or pitolisant treatment in women using low dose oral contraceptives.

Narcolepsy in the elderly

Clinical experience suggests an improvement of symptoms of narcolepsy such as cataplexy and EDS with age. However, DNS often worsens, potentially due to age-related accrual of additional sleep disorders. The available evidence on such issues is very limited. It is difficult to establish whether the disorder becomes milder or if patients simply improve their coping mechanisms over the years. Potentially, there may be a less demanding lifestyle after retirement with more planned naps, for example. If there are no significant or relevant comorbidities, pharmacological treatment of narcolepsy is not age dependent. The potential risk of worsening pre-existing cardiovascular disease in the elderly age group, particularly with stimulants, may influence treatment options, as may the presence of hypertension [29,30].

In general, reduced levels of activity in old age, with or without comorbidities, may affect the impact of EDS and significantly increase its burden. When EDS is adversely affected by inevitable behavioural changes associated with age, manipulation of currently available drug treatment is rarely successful.

Anaesthesia

There are very few data assessing perioperative risk in NT1 as recently concluded by an expert panel [31]. In general, there are no indications to suggest that narcolepsy itself is an independent risk factor for surgery although, depending on the type of anaesthesia, existing comorbidities and medication use may be of concern. Also, sudden discontinuation of narcolepsy medication may cause problems but is not necessary for most surgical procedures. Some narcolepsy patients can have a longer recovery time to wake up from anaesthesia.

Patients refractory to treatment

With an increasing pharmacological arsenal, it is becoming increasingly rare that patients with narcolepsy are truly refractory

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to therapy. However, there are large inter-individual differences in treatment effect sizes and occurrence of side effects. If a patient exhibits no response whatsoever to a variety of treatments, it is advisable to reconsider the diagnosis and clarify precise drug dosing and compliance. Also, it should be verified that they have adjusted their lifestyle appropriately and are not attempting to use medication to compensate for any lack of adjustment. A variety of combination therapies are possible in narcolepsy although there is little published evidence to guide precise choices.

It should be noted that complete symptom control in narcolepsy is relatively rare and medication often serves simply to limit the burden of symptoms such as EDS. In published studies, it is common for less than 50% of treated patients to be normalized on subjective measures of EDS (Epworth sleepiness scale <11).

Emergencies

In the context of narcolepsy, emergencies are rare, usually relating to medication-induced intoxication or acute withdrawal effects. Regarding the former, the clinical presentation clearly depends on the specific medication that has been overused. The latter typically occurs in NT1 when long-term treatment of cataplexy with antidepressant therapy is suddenly discontinued, causing status cataplecticus, characterized by long sequences of cataplectic attacks without full recovery between episodes [32]. Very rarely, particularly in children, the phenomenon can occur spontaneously in the absence of treatment changes. The anti-hypertensive drug prazosin is an alpha 1 adrenoreceptor antagonist which may also aggravate cataplexy and even induce status cataplecticus [33]. Managing status cataplecticus focuses on environmental adjustments to avoid potential injuries after falls and restarting cataplexy treatment or avoiding precipitating drugs.

PATIENT SECTION—OPINION STATEMENT

Leontien Sickenga, Madeleine Wallenius, Connie Landstedt and Marleny Macario Argueta

Understanding patients' views and needs is central to developing good clinical practice and patient-oriented guidelines. Narcolepsy patients' representatives identified key areas of interest and made the following recommendations and suggestions.

1. When enquiring about the various symptoms of narcolepsy, physicians should be aware that expressions used by patients may diverge from those used by the medical establishment and lead to potential inaccuracy. Loose terms such as fatigue and tiredness used to describe EDS may cause confusion and prompt more detailed interrogation of those symptoms relating to excessive sleepiness. Physicians should formulate questions openly without leading the patient. For example, when enquiring about cataplexy, a general question such as 'how do you react when you laugh?' is appropriate. Further, they should be able to probe other aspects of narcolepsy outside the core symptoms of EDS and cataplexy that may necessitate a fuller understanding of sleep–wake disorders and more specialized medical training.
2. There is an unmet need for specialized ancillary health workers including nurses and psychologists working in sleep centres specializing in narcolepsy. A nurse, in particular, could focus more on practical issues and help manage the daily life of patients as well as addressing practical concerns.
3. Measures of treatment success used in clinical trials, for example, should be reconsidered. Patient reported outcome measures should be incorporated in the individualized management of patients.
4. Physicians and specialized nurses should address non-pharmacological treatments more fully. Discussion of strategies such as regular naps, exercise, good sleeping habits and regular schedules are likely to help and additional input from a psychologist/therapist or dietician may be needed. Patients should also be directed to patient organizations and be given advice about benefits and social support when appropriate.

COMMENTS ON RECOMMENDATIONS AND FUTURE DIRECTIONS

Narcolepsy typically has a pleomorphic clinical presentation and produces a considerable variety of different symptoms with a variable clinical course. Prospective and long-term clinical observational studies would help define the natural course of narcolepsy and its variants, improving the development of disease-modifying drugs and allowing a better long-term evaluation of symptomatic medications.

Although the last 20 years have seen well-designed studies analysing the effectiveness and safety of several symptomatic drugs in narcolepsy, some methodological flaws make results difficult to transfer to clinical practice or to compare results between studies. One issue of concern is that RCTs have had short periods of follow-up, usually limited to around 2 months. In some instances, the so-called 'withdrawal design' has been applied, exposing the study to a high risk of bias. Additionally, older drugs used in narcolepsy such as antidepressants and traditional psychostimulants have been poorly investigated before the era of controlled studies and evidence-based medicine.

Our recommendations for the management of narcolepsy refer to the best available evidence and expert experience. Nevertheless, amongst patients there is considerable inter-individual variation in the efficacy and side effect profile of all commonly used medications. This necessitates a precise individual treatment plan for each patient, contingent on their pattern of symptoms, disease severity and comorbid conditions. This may lead to (co-)treatment with substances that have traditionally been used in the treatment of narcolepsy but have not been studied properly in trials.

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It is important to acknowledge that EDS, the usually dominant symptom in narcolepsy, has multifaceted expressions including impaired attention, poor vigilance and cognitive impairment which may be more difficult to treat than unwanted daytime sleep. These important expressions may not be adequately assessed if the main focus is on sleep. Associated problems such as fatigue may be even more refractory to treatment. See the suggested pharmacological management algorithm in Figures 3 and 4.

Further information is required on the current armamentarium of effective drugs with more head-to-head comparison trials along with studies that use drug combinations and a sufficiently long period of follow-up. There is also limited information on levels of compliance with current treatments.

Narcolepsy-relevant outcome measures are generally poorly correlated with measurements of treatment efficacy used in clinical trials. For example, sleep latency is a common outcome measure whereas performance measures on attention tasks requiring prolonged vigilance may be more informative for activities of daily living. Furthermore, by focusing on individual symptoms, the overall impact of therapeutic interventions on narcolepsy is not properly addressed. There is therefore a need for validated disease severity scales along with global measures of how the disease impacts on quality of life that incorporate patient-reported outcomes. Patient involvement in the development of these measures is recommended. The Narcolepsy Severity Scale is a recently described first attempt to assess narcolepsy symptoms in one single scale [34]. This may have utility in the quantification of narcoleptic symptoms when monitoring or optimizing management strategies.

There is a significant lack of clinical trials investigating the whole spectrum of pharmacological treatments for narcolepsy in children and other groups potentially meriting special consideration such as pregnant women and the elderly. This also applies to non-pharmacological approaches including special diets, regular exercise and scheduled naps, for example.

Finally, preliminary clinical and pre-clinical data from studies investigating hypocretin receptor agonists appear promising and could potentially herald a new approach to treatment in narcolepsy. Other potential techniques to restore hypocretin levels such as stem cell replacement or gene therapy remain experimental. Following on from recent studies that have expanded our knowledge of the immune basis of narcolepsy, more specific immunomodulatory treatments close to disease onset are likely to be fruitful in the development of much needed disease-modifying therapy.

ADDITIONAL INFORMATION

Table S10 given an overview of medication (titration schedule, mechanism of action, dosage, half-life, European Medicines Agency approval, possible treatment combinations) for narcolepsy in adults.

GUIDELINE UPDATE

The present guideline will be updated in 5 years. In the case of major changes in the evidence on the existing benefits and harms of included interventions or if new interventions become available, this update could be approached earlier.

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CONFLICT OF INTEREST

Claudio Bassetti organized teaching events and conferences that were supported by Jazz, UCB Pharma and Bioprojet. One of his IIT studies is supported by UCB Pharma and Jazz. He has also participated in advisory boards of UCB, Bioprojet, Takeda, Idorsia and Jazz Pharmaceuticals. Ulf Kallweit has participated in advisory boards of AOP Orphan Pharmaceuticals, Bioprojet, Harmony Biosciences, Jazz, Takeda and UCB. Giuseppe Plazzi has participated in advisory boards of UCB, Bioprojet, Idorsia and Jazz Pharmaceuticals. Michel Lecendreux has received consultancy and lecture fees from UCB, Jazz Pharma, Bioprojet and participated in clinical trials for Flamel-Avadel, Bioprojet and Jazz Pharmaceuticals. Poul Jennum reports advisory board fees from UCB and Jazz, Ramin Khatami advisory board and lecture fees from UCB, Geert Mayer advisory boards for UCB Belgium, UCB Pharma Germany, Jazz Pharma UK; speakers bureau for UCB Germany and Belgium, Jazz Pharma UK. Markku Partinen reports grants from Academy of Finland, Bioprojet, Jazz Pharmaceuticals, personal fees from UCB-Pharma, GSK, Takeda, MSD, Orion and Umecrine, outside the submitted work. Paul Reading has received speaker and consultancy fees from UCB Pharma and Bioprojet. Karel Šonka has received consultancy and lecture fees from UCB and Sanofi and participated in clinical trials for Flamel-Avadel, Jazz and Luitpold Pharmaceutical. Yves Dauvilliers has participated in advisory boards of UCB, Bioprojet, Theranexus, Takeda, Avadel, Idorsia and Jazz Pharmaceuticals. Gert Jan Lammers has participated in advisory boards of UCB, Bioprojet and Jazz Pharmaceuticals; one of his studies is supported by Bioprojet and he served as consultant for Jazz. Leja Dolenc-Groselj, Joan Santamaria, Luca Vignatelli, Elisa Baldin, Mauro Manconi and Thomas Pollmächer described no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting Information.

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REFERENCES

1. Bassetti CLA, Adamantidis A, Burdakov D, et al. Narcolepsy—clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Nat Rev Neurol*. 2019;15:519-539.
2. Yoss RE, Daly DD. Criteria for the diagnosis of the narcoleptic syndrome. *Proc Staff Meet Mayo Clin*. 1957;32:320-328.
3. Liblau RS, Vassalli A, Seifinejad A, Tafti M. Hypocretin (orexin) biology and the pathophysiology of narcolepsy with cataplexy. *Lancet Neurol*. 2015;14:318-328.
4. Latorre D, Kallweit U, Armentani E, et al. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature*. 2018;562:63-68.
5. Partinen M, Kornum BR, Plazzi G, et al. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. *Lancet Neurol*. 2014;13(6):600-613.
6. Partinen M, Kronholm E. Epidemiology: principles and application in sleep medicine. In: Chokroverty S, ed. *Sleep Disorders Medicine: Basic Science, Technical Considerations and Clinical Aspects*, 4th edn. New York, NY: Springer; 2017:485-521.
7. Ohayon MM, Priest RG, Zulley J, Smirne S, Paiva T. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. *Neurology*. 2002;58:1826-1833.
8. Tió E, Gaig C, Giner-Soriano M, et al. The prevalence of narcolepsy in Catalunya (Spain). *J Sleep Res*. 2018;27:1-9.
9. Dodel R, Peter H, Spottke A, et al. Health-related quality of life in patients with narcolepsy. *Sleep Med*. 2007;8:733-741.
10. Jennum P, Ibsen R, Petersen ER, Knudsen S, Kjellberg J. Health, social, and economic consequences of narcolepsy: a controlled national study evaluating the societal effect on patients and their partners. *Sleep Med*. 2012;13:1086-1093.
11. Dauvilliers Y, Roth T, Guinta D, Alvarez-Horine S, Dynin E, Black J. Effect of sodium oxybate, modafinil, and their combination on disrupted nighttime sleep in narcolepsy. *Sleep Med*. 2017;40:53-57.
12. Kallweit U, Bassetti CL. Pharmacological management of narcolepsy with and without cataplexy. *Expert Opin Pharmacother*. 2017;18:809-817.
13. Billiard M, Bassetti C, Dauvilliers Y, et al. EFNS guidelines on management of narcolepsy. *Eur J Neurol*. 2006;13(10):1035-1048.

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14. Morgenthaler TI, Kapur VK, Brown TM, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30:1705-1711.
15. Lammers GJ, Bassetti CLA, Dolenc-Groselj L, et al. Diagnosis of central disorders of hypersomnolence: a reappraisal. *Sleep Med Rev*. 2020;52:101306.
16. Droogleever Fortuyn HA, Fronczek R, Smitshoek M, et al. Severe fatigue in narcolepsy with cataplexy. *J Sleep Res*. 2012;21:163-169.
17. Leone MA, Keindl M, Schapira AH, Deuschl G, Federico A. Practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces. *Eur J Neurol*. 2015;22:1505-1510.
18. Yukitake H, Fujimoto T, Ishikawa T, et al. TAK-925, an orexin 2 receptor-selective agonist, shows robust wake-promoting effects in mice. *Pharmacol Biochem Behav*. 2019;187:172794.
19. Dauvilliers Y, Arnulf I, Szakacs Z, et al. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. *Sleep*. 2019;42(11):zsz174.
20. Schinkelshoek MS, Smolders IM, Donjacour CE, et al. Decreased body mass index during treatment with sodium oxybate in narcolepsy type 1. *J Sleep Res*. 2019;28:e12684.
21. Bosco A, Lopez R, Barateau L, et al. Effect of psychostimulants on blood pressure profile and endothelial function in narcolepsy. *Neurology*. 2018;90:e479–e491.
22. Barateau L, Lopez R, Chenini S, et al. Depression and suicidal thoughts in untreated and treated narcolepsy. *Neurology*. 2020;95(20):e2755-e2768. https://doi.org/10.1212/WNL.0000000000010737
23. Postiglione E, Antelmi E, Pizza F, Lecendreux M, Dauvilliers Y, Plazzi G. The clinical spectrum of childhood narcolepsy. *Sleep Med Rev*. 2018;38:70-85.
24. Pizza F, Franceschini C, Peltola H, et al. Clinical and polysomnographic course of childhood narcolepsy with cataplexy. *Brain*. 2013;136:3787-3795.
25. Maurovich-Horvat E, Tormášiová M, Slonková J, et al. Assessment of pregnancy outcomes in Czech and Slovak women with narcolepsy. *Med Sci Monit*. 2010;16:SR35–SR40.
26. Thorpy M, Zhao CG, Dauvilliers Y. Management of narcolepsy during pregnancy. *Sleep Med*. 2013;14:367–376.
27. Damkier P, Broe A. First-trimester pregnancy exposure to modafinil and risk of congenital malformations. *JAMA*. 2020;323:374-376.
28. Miyagawa T, Kawamura H, Obuchi M, et al. Effects of oral L-carnitine administration in narcolepsy patients: a randomized, double-blind, cross-over and placebo-controlled trial. *PLoS One*. 2013;8:e53707.
29. Jennum P, Ibsen R, Knudsen S, Kjellberg J. Comorbidity and mortality of narcolepsy: a controlled retro- and prospective national study. *Sleep*. 2013;36:835-840.
30. Kovalská P, Kemlink D, Nevšímalová S, et al. Narcolepsy with cataplexy in patients aged over 60 years: a case–control study. *Sleep Med*. 2016;26:79-84.
31. Hershner S, Kakkar R, Chung F, Singh M, Wong J, Auckley D. Narcolepsy, anesthesia, and sedation: a survey of the perioperative experience of patients with narcolepsy. *Anesth Analg*. 2019;129:1374–1380.
32. Poryazova R, Siccoli M, Werth E, Bassetti CL. Unusually prolonged rebound cataplexy after withdrawal of fluoxetine. *Neurology*. 2005;65:967–968.
33. Aldrich MS, Rogers AE. Exacerbation of human cataplexy by prazosin. *Sleep*. 1989;12:254-256.
34. Dauvilliers Y, Barateau L, Lopez R, et al. Narcolepsy Severity Scale: a reliable tool assessing symptom severity and consequences. *Sleep*. 2020;43:zsaa009.
35. Aran A, Lin L, Nevsimalova S, et al. Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. *Sleep*. 2009;32:979-983.
36. Barateau L, Liblau R, Peyron C, Dauvilliers Y. Narcolepsy type 1 as an autoimmune disorder: evidence, and implications for pharmacological treatment. *CNS Drugs*. 2017;31:821-834.
37. Cvetkovic-Lopes V, Bayer L, Dorsaz S, et al. Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. *J Clin Invest*. 2010;120:713-719.
38. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet Neurol*. 2013;12:1068-1075.
39. Hallmayer J, Faraco J, Lin L, et al. Narcolepsy is strongly associated with the T-cell receptor alpha locus. *Nat Genet*. 2009;41:708-711.
40. Han F, Lin L, Warby SC, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann. Neurol*. 2011;70:410-417.
41. Huang YS, Guilleminault C. Narcolepsy: action of two gamma-aminobutyric acid type B agonists, baclofen and sodium oxybate. *Pediatr Neurol*. 2009;41:9-16.
42. Kallweit U, Bassetti CLA, Oberholzer M, et al. Coexisting narcolepsy (with and without cataplexy) and multiple sclerosis: six new cases and a literature review. *J Neurol*. 2018;265:2071-2078.
43. Lecendreux M, Churlaud G, Pitoiset F, et al. Narcolepsy type 1 is associated with a systemic increase and activation of regulatory T cells and with a systemic activation of global T cells. *PLoS One*. 2017;12:e0169836.
44. Lippert J, Young P, Gross C, et al. Specific T-cell activation in peripheral blood and cerebrospinal fluid in central disorders of hypersomnolence. *Sleep*. 2019;1:42.
45. Luo G, Ambati A, Lin L, et al. Autoimmunity to hypocretin and molecular mimicry to flu antigens in type 1 narcolepsy. *PNAS*. 2018;115:12323-12332.
46. Overeem S, Dalmau J, Bataller L, et al. Hypocretin-1 CSF levels in anti-Ma2 associated encephalitis. *Neurology*. 2004;62:138-140.
47. Tafti M, Hor H, Dauvilliers Y, et al. DQB1 locus alone explains most of the risk and protection in narcolepsy with cataplexy in Europe. *Sleep*. 2014;37:19-25.
48. Ahmed M, Bassetti C, Becker P, et al. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Med*. 2005;6:415-421.
49. Akins BE, Miranda E, Lacy JM, Logan BK. A multi-drug intoxication fatality involving Xyrem (GHB). *J Forensic Sci*. 2009;54:495-496.
50. Alshaikh MK, Tricco AC, Tashkandi M, Mamdani M, Straus SE, BaHammam AS. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. *J Clin Sleep Med*. 2012;8:451-458.
51. Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E. Clinical and therapeutic aspects of childhood narcolepsy–cataplexy: a retrospective study of 51 children. *Sleep*. 2010;33:1457-1464.
52. Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL. Risks of high-dose stimulants in the treatment of disorders of excessive somnolence: a case–control study. *Sleep*. 2005;28:667-672.
53. Baier PC, Hallschmid M, Seeck-Hirschner M, et al. Effects of intranasal hypocretin-1 (orexin A) on sleep in narcolepsy with cataplexy. *Sleep Med*. 2011;12:941-946.
54. Becker PM, Schwartz JR, Feldman NT, Hughes RJ. Effect of modafinil on fatigue, mood, and health-related quality of life in patients with narcolepsy. *Psychopharmacology*. 2004;171:133-139.
55. Bedard MA, Montplaisir J, Godbout R, Lapierre O. Nocturnal gamma-hydroxybutyrate. Effect on periodic leg movements and sleep organization of narcoleptic patients. *Clin Neuropharmacol*. 1989;12:29-36.
56. Bedard MA, Montplaisir J, Godbout R. Effect of Ldopa on periodic movements in sleep in narcolepsy. *Eur Neurol*. 1987;27:35-38.

14681331, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ene.14888 by University Of California, Los, Wiley Online Library on [23/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

57. Besset A, Tafti M, Villemin E, Billiard M. The effects of modafinil (300 mg) on sleep, sleepiness and arousal in narcoleptic patients. *Neurophysiol Clin*. 1993;23:47-60.
58. Beusterien KM, Rogers AE, Walsleben JA, et al. Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep*. 1999;22:757-765.
59. Billiard M, Besset A, Montplaisir J, et al. Modafinil: a double-blind multicentric study. *Sleep*. 1994;17:S107-S112.
60. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006;29:939-946.
61. Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy. *Sleep Med*. 2009;10:829-835.
62. Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. *J Clin Sleep Med*. 2010;6:596-602.
63. Black JE, Hull SG, Tiller J, Yang R, Harsh JR. The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. *J Clin Sleep Med*. 2010;6:458-466.
64. Bogan RK, Feldman N, Emsellem HA, et al. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. *Sleep Med*. 2015;16:1102-1108.
65. Bogan RK, Roth T, Schwartz J, Miloslavsky M. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. *J Clin Sleep Med*. 2015;11:427-432.
66. Boivin DB, Lorrain D, Montplaisir M. Effects of bromocriptine on periodic limb movements in human narcolepsy. *Neurology*. 1993;43:2134-2136.
67. Boivin DB, Montplaisir J, Lambert C. Effects of bromocriptine in human narcolepsy. *Clin Neuropharmacol*. 1993;16:120-126.
68. Boivin DB, Montplaisir J, Petit D, Lambert C, Lubin S. Effects of modafinil on symptomatology of human narcolepsy. *Clin Neuropharmacol*. 1993;16:46-53.
69. Boivin DB, Montplaisir J, Poirier G. The effects of L-dopa on periodic leg movements and sleep organization in narcolepsy. *Clin Neuropharmacol*. 1989;12:339-345.
70. Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev*. 2012;16:431-443.
71. Broughton RJ, Fleming JA, George CF, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology*. 1997;49:444-451.
72. Buckley PJ, Wolf CT. Psychosis in a 22-year-old woman with narcolepsy after restarting sodium oxybate. *Psychosomatics*. 2018;59:298-301.
73. Chen SY, Clift SJ, Dahlitz MJ, Dunn G, Parkes JD. Treatment in the narcoleptic syndrome: self assessment of the action of dexamphetamine and clomipramine. *J Sleep Res*. 1995;4:113-118.
74. Chen W, Black J, Call P, Mignot E. Late-onset narcolepsy presenting as rapidly progressing muscle weakness: response to plasmapheresis. *Ann Neurol*. 2005;58:489-490.
75. Coelho FM, Pradella-Hallinan M, Alves GR, Bittencourt LR, Tufik S. Report of two narcoleptic patients with remission of hypersomnolence following use of prednisone. *Arq Neuropsiquiatr*. 2007;65:336-337.
76. Dauvilliers Y, Abril B, Mas E, Michel F, Tafti M. Normalization of hypocretin-1 in narcolepsy after intravenous immunoglobulin treatment. *Neurology*. 2009;73:1333-1334.
77. Dauvilliers Y, Carlander B, Rivier F, Touchon J, Tafti M. Successful management of cataplexy with intravenous immunoglobulins at narcolepsy onset. *Ann Neurol*. 2004;56:905-908.
78. Dauvilliers Y. Follow-up of four narcolepsy patients treated with intravenous immunoglobulins. *Ann Neurol*. 2006;60:153.
79. Donjacour CE, Lammers GJ. A remarkable effect of alemtuzumab in a patient suffering from narcolepsy with cataplexy. *J Sleep Res*. 2012;21:479-480.
80. Drakatos P, Lykouras D, D'Ancona G, et al. Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice. *Sleep Med*. 2017;35:80-84.
81. Ferri R, Zucconi M, Marelli S, Plazzi P, Schenck CH, Ferini-Strambi L. Effects of long-term use of clonazepam on nonrapid eye movement sleep patterns in rapid eye movement sleep behavior disorder. *Sleep Med*. 2013;14:399-406.
82. Filardi M, Pizza F, Antelmi E, Ferri R, Natale V, Plazzi G. In-field assessment of sodium oxybate effect in pediatric type 1 narcolepsy: an actigraphic study. *Sleep*. 2018;41(6).
83. Fronczek R, Verschuuren J, Lammers GJ. Response to intravenous immunoglobulins and placebo in a patient with narcolepsy with cataplexy. *J Neurol*. 2007;254:1607-1608.
84. Golicki D, Bala MM, Niewada M, Wierzbicka A. Modafinil for narcolepsy: systematic review and meta-analysis. *Med Sci Monit*. 2010;16:Ra177-Ra186.
85. Guilleminault C, Mancuso J, Salva MA, et al. Viloxazine hydrochloride in narcolepsy: a preliminary report. *Sleep*. 1986;9:275-279.
86. Guilleminault C, Raynal D, Takahashi S, Carskadon M, Dement W. Evaluation of short-term and long-term treatment of the narcolepsy syndrome with clomipramine hydrochloride. *Acta Neurol Scand*. 1976;54:71-87.
87. Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin*. 2006;22:761-774.
88. Hecht M, Lin L, Kushida CA, et al. Report of a case of immunosuppression with prednisone in an 8-year-old boy with an acute onset of hypocretin-deficiency narcolepsy. *Sleep*. 2003;26:809-810.
89. Helmus T, Rosenthal L, Bishop C, Roehrs T, Syron ML, Roth T. The alerting effects of short and long naps in narcoleptic, sleep deprived, and alert individuals. *Sleep*. 1997;20:251-257.
90. Hishikawa Y, Ida H, Nakai K, Kaneko Z. Treatment of narcolepsy with imipramine (tofranil) and desmethylimipramine (pertofran). *J Neurol Sci*. 1966;
91. Holfinger S, Roy A, Schmidt M. Stevens–Johnson syndrome after armodafinil use. *J Clin Sleep Med*. 2018;14:885-887.
92. Hublin C, Partinen M, Heinonen EH, Puukka P, Salmi T. Selegiline in the treatment of narcolepsy. *Neurology*. 1994;44:2095-2101.
93. Husain AM, Yancy WS, Carwile ST, Miller PP, Westman EC. Diet therapy for narcolepsy. *Neurology*. 2004;62:2300-2302.
94. Inocente C, Arnulf I, Bastuji H, et al. Pitolisant, an inverse agonist of the histamine H3 receptor: an alternative stimulant for narcolepsy–cataplexy in teenagers with refractory sleepiness. *Clin Neuropharmacol*. 2012;35:55-60.
95. Inoue Y, Nanba K, Higami S, Honda Y, Takahashi Y, Arai H. Clinical significance of sleep-related breathing disorder in narcolepsy. *Psychiatry Clin Neurosci*. 2002;56:269-270.
96. Ivanenko A, Tauman R, Gozal D. Modafinil in the treatment of excessive daytime sleepiness in children. *Sleep Med*. 2003;4:579-582.
97. Jin L, Shi L, Zhang Y, Chen BB, Wang XL, Liu YH. Antidepressants for the treatment of narcolepsy: a prospective study of 148 patients in northern China. *J Clin Neurosci*. 2019;63:27-31.
98. Knudsen S, Biering-Sorensen B, Kornum BR, et al. Early IVIg treatment has no effect on post-H1N1 narcolepsy phenotype or hypocretin deficiency. *Neurology*. 2012;79:102-103.
99. Knudsen S, Mikkelsen JD, Bang B, Gammeltoft S, Jennum PJ. Intravenous immunoglobulin treatment and screening for

14681331, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ene.14888 by University Of California, Los, Wiley Online Library on [23/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

hypocretin neuron-specific autoantibodies in recent onset childhood narcolepsy with cataplexy. *Neuropediatrics*. 2010;41:217-222.
100. Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res*. 2010;19:591-596.
101. Lammers GJ, Arends J, Declerck AC, Ferrari MD, Schouwink G, Troost J. Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. *Sleep*. 1993;16:216-220.
102. Langford J, Gross WL. Psychosis in the context of sodium oxybate therapy. *J Clin Sleep Med*. 2011;7:665-666.
103. Larrosa O, de la Llave Y, Bario S, Granizo JJ, Garcia-Borreguero D. Stimulant and anticataplectic effects of reboxetine in patients with narcolepsy: a pilot study. *Sleep*. 2001;24:282-285.
104. Lecendreux M, Berthier J, Corny J, Bourdon O, Dossier C, Delclaux C. Intravenous immunoglobulin therapy in pediatric narcolepsy: a nonrandomized, open-label, controlled, longitudinal observational study. *J Clin Sleep Med*. 2017;13:441-453.
105. Lecendreux M, Maret S, Bassetti C, Mouren MC, Tafti M. Clinical efficacy of high-dose intravenous immunoglobulins near the onset of narcolepsy in a 10-year-old boy. *J Sleep Res*. 2003;12:347-348.
106. Lecendreux M, Poli F, Oudiette D, et al. Tolerance and efficacy of sodium oxybate in childhood narcolepsy with cataplexy: a retrospective study. *Sleep*. 2012;35:709-711.
107. Lee EK, Douglass AB. Baclofen for narcolepsy with cataplexy: two cases. *Nat Sci Sleep*. 2015;7:81-83.
108. Liakoni E, Dempsey DA, Meyers M, et al. Effect of gamma-hydroxybutyrate (GHB) on driving as measured by a driving simulator. *Psychopharmacology*. 2018;235:3223-3232.
109. Malhotra A, Shapiro C, Pepin JL, et al. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. *Sleep*. 2020;43(2):zsz220.
110. Mamelak M, Swick T, Emsellem H, Montplaisir J, Lai C, Black J. A 12-week open-label, multicenter study evaluating the safety and patient-reported efficacy of sodium oxybate in patients with narcolepsy and cataplexy. *Sleep Med*. 2015;16:52-58.
111. Mansukhani MP, Kotagal S. Sodium oxybate in the treatment of childhood narcolepsy–cataplexy: a retrospective study. *Sleep Med*. 2012;13:606-610.
112. Mayer G, Ewert Meier K, Hephata K. Selegeline hydrochloride treatment in narcolepsy. A double-blind, placebo-controlled study. *Clin Neuropharmacol*. 1995;18:306-319.
113. Mayer G, Plazzi G, Iranzo A, et al. Long-term compliance, safety, and tolerability of sodium oxybate treatment in patients with narcolepsy type 1: a post-authorization, non-interventional surveillance study. *Sleep*. 2018;41(9):zsy128.
114. Mayer G. Efficacy of sodium oxybate on REM sleep behavior disorder in a patient with narcolepsy type 1. *Neurology*. 2016;87:2594-2595.
115. Mitler MM, Hajdukovic R, Erman M, Koziol JA. Narcolepsy. *J Clin Neurophysiol*. 1990;7:93-118.
116. Mitler MM, Hajdukovic R, Erman MK. Treatment of narcolepsy with methamphetamine. *Sleep*. 1993;16:306-317.
117. Mitler MM, Shafor S, Hajdukovich R, Timms RM, Browman CP. Treatment of narcolepsy: objective studies on methylphenidate, pemoline, and protriptyline. *Sleep*. 1986;9:260-264.
118. Miyata R, Hayashi M, Kohyama J, Honda M. Steroid therapy ameliorated cataplexy in three children with recent-onset of narcolepsy. *Sleep Med*. 2017;29:86-87.
119. Moldofsky H, Broughton RJ, Hill JD. A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. *Sleep Med*. 2000;1:109-116.
120. Moller LR, Ostergaard JR. Treatment with venlafaxine in six cases of children with narcolepsy and with cataplexy and hypnagogic hallucinations. *J Child Adolesc Psychopharmacol*. 2009;19:197-201.
121. Morse AM, Kelly-Pieper K, Kothare SV. Management of excessive daytime sleepiness in narcolepsy with baclofen. *Pediatr Neurol*. 2019;93:39-42.
122. Mullington J, Broughton R. Scheduled naps in the management of daytime sleepiness in narcolepsy–cataplexy. *Sleep*. 1993;16:444-456.
123. Murali H, Kotagal S. Off-label treatment of severe childhood narcolepsy–cataplexy with sodium oxybate. *Sleep*. 2006;29:1025-1029.
124. Nordstrand SH, Hansen BH, Kamaleri Y, et al. Changes in quality of life in individuals with narcolepsy type 1 after the H1N1-influenza epidemic and vaccination campaign in Norway: a two-year prospective cohort study. *Sleep Med*. 2018;50:175-180.
125. Noujaim MG, Mourad A, Clough JD. Sodium oxybate: a cause of extreme involuntary weight loss in a young lady. *Case Rep Med*. 2019;2019:6537815.
126. Ortega-Albas JJ, Lopez-Bernabe R, Garcia AL, Gomez JR. Suicidal ideation secondary to sodium oxybate. *J Neuropsychiatry Clin Neurosci*. 2010;22(3):352.
127. Parkes JD, Fenton GW. Levo(–)amphetamine and dextro(+)amphetamine in the treatment of narcolepsy. *J Neurol Neurosurg Psychiatry*. 1973;36:1076-1081.
128. Parkes JD, Schachter M. Clomipramine and clonazepam in cataplexy. *Lancet*. 1979;2:1085-1086.
129. Parkes JD. Clomipramine (Anafranil) in the treatment of cataplexy. *J Int Med Res*. 1973;1:427-431.
130. Pataka AD, Frangulyan RR, Mackay TW, Douglas NJ, Riha RL. Narcolepsy and sleep-disordered breathing. *Eur J Neurol*. 2012;19:696-702.
131. Plazzi G, Poli F, Franceschini C, et al. Intravenous high-dose immunoglobulin treatment in recent onset childhood narcolepsy with cataplexy. *J Neurol*. 2008;255:1549-1554.
132. Plazzi G, Ruoff C, Lecendreux M, et al. Treatment of paediatric narcolepsy with sodium oxybate: a double-blind, placebo-controlled, randomised-withdrawal multicentre study and open-label investigation. *Lancet Child Adolesc Health*. 2018;2:483-494.
133. Poli F, Ricotta L, Vandi S, et al. Catathrenia under sodium oxybate in narcolepsy with cataplexy. *Sleep Breath*. 2012;16:427-434.
134. Poryazova R, Tartarotti S, Khatami R, et al. Sodium oxybate in narcolepsy with cataplexy: Zurich sleep center experience. *Eur Neurol*. 2011;65:175-182.
135. Prince V, Philippidou M, Walsh S, Creamer D. Stevens–Johnson syndrome induced by modafinil. *Clin Exp Dermatol*. 2018;43:191-192.
136. Ratkiewicz M, Splaingard M. Treatment of cataplexy in a three-year-old using venlafaxine. *J Clin Sleep Med*. 2013;9:1341-1342.
137. Reinish LW, MacFarlane JG, Sandor P, Shapiro CM. REM changes in narcolepsy with selegiline. *Sleep*. 1995;18:362-367.
138. Ristanovic RK, Liang H, Hornfeldt CS, Lai C. Exacerbation of cataplexy following gradual withdrawal of antidepressants: manifestation of probable protracted rebound cataplexy. *Sleep Med*. 2009;10:416-421.
139. Roehrs T, Zorick F, Wittig R, Paxton C, Sicklesteel J, Roth T. Alerting effects of naps in patients with narcolepsy. *Sleep*. 1986;9:194-199.
140. Rogers AE, Aldrich MS, Lin X. A comparison of three different sleep schedules for reducing daytime sleepiness in narcolepsy. *Sleep*. 2001;24:385-391.
141. Rogers AE, Aldrich MS. The effect of regularly scheduled naps on sleep attacks and excessive daytime sleepiness associated with narcolepsy. *Nurs Res*. 1993;42:111-117.
142. Roth T, Dauvilliers Y, Guinta D, Alvarez-Horine S, Dynin E, Black J. Effect of sodium oxybate on disrupted nighttime sleep in patients with narcolepsy. *J Sleep Res*. 2017;26:407-414.
143. Ruoff C, Swick TJ, Doekel D, et al. Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study. *Sleep*. 2016;39:1379-1387.

14681331, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ene.14888 by University Of California, Los, Wiley Online Library on [23/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

144. Ruppert E, Zagala H, Chambe J, et al. Intravenous immunoglobulin therapy administered early after narcolepsy type 1 onset in three patients evaluated by clinical and polysomnographic follow-up. *Behav Neurol*. 2018;2018:1671072.
145. Rye DB, Dihenia B, Bliwise DL. Reversal of atypical depression, sleepiness, and REM-sleep propensity in narcolepsy with bupropion. *Depress Anxiety*. 1998;7:92-95.
146. Saletu M, Anderer P, Saletu-Zyhlarz GM, et al. EEG-mapping differences between narcolepsy patients and controls and subsequent double-blind, placebo-controlled studies with modafinil. *Eur Arch Psychiatry Clin Neurosci*. 2005;255:20-32.
147. Salin-Pascual RJ. Improvement in cataplexy and daytime somnolence in narcoleptic patients with venlafaxine XR administration. *Sleep Hypnosis*. 2002;4:22-25.
148. Sanyal D, Ghosh M. A case of modafinil induced mania in a child suffering from narcolepsy. *Bengal J Private Psychiatry*. 2017;8:14-15.
149. Sarkanen T, Alén R, Partinen M. Transient impact of rituximab in H1N1 vaccination-associated narcolepsy with severe psychiatric symptoms. *Neurologist*. 2016;21:85-86.
150. Sarkanen T, Niemelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. *Front Neurol*. 2014;5:136.
151. Schachter M, Parkes JD. Fluvoxamine and clomipramine in the treatment of cataplexy. *J Neurol Neurosurg Psychiatry*. 1980;43:171-174.
152. Schrader H, Kayed K, Bendixen Markset AC, Treidene HE. The treatment of accessory symptoms in narcolepsy: a double-blind cross-over study of a selective serotonin re-uptake inhibitor (femoxetine) versus placebo. *Acta Neurol Scand*. 1986;74:297-303.
153. Scrima L, Hartman PG, Johnson FH, Hiller FC. Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy–cataplexy: double-blind subjective measures. *Biol Psychiatry*. 1989;26:331-343.
154. Scrima L, Hartman PG, Johnson FH, Thomas EE, Hiller FC. The effects of gamma-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. *Sleep*. 1990;13:479-490.
155. Shindler J, Schachter M, Brincat S, Parkes JD. Amphetamine, mazindol, and fencamfamin in narcolepsy. *Br Med J (Clin Res Ed)*. 1985;290:1167-1170.
156. Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16:200-207.
157. Thakrar C, Patel K, D'Ancona G, et al. Effectiveness and side-effect profile of stimulant therapy as monotherapy and in combination in the central hypersomnias in clinical practice. *J Sleep Res*. 2018;27:e12627.
158. The U.S. Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep*. 2002;25:42-49.
159. The Xyrem® International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med*. 2005;1:391-397.
160. Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Ann Neurol*. 2019;85:359-370.
161. Thorpy MJ, Snyder M, Aloe FS, Ledereich PS, Starz KE. Short-term triazolam use improves nocturnal sleep of narcoleptics. *Sleep*. 1992;15:212-216.
162. US Xyrem Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep*. 2003;26:31-35.
163. Uchiyama M, Mayer G, Meier-Ewert K. Differential effects of extended sleep in narcoleptic patients. *Electroencephalogr Clin Neurophysiol*. 1994;91:212-218.
164. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol*. 1998;43:88-97.
165. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology*. 2000;54:1166-1175.
166. Valko PO, Khatami R, Baumann CR, et al. No persistent effect of intravenous immunoglobulins in patients with narcolepsy with cataplexy. *J Neurol*. 2008;255:1900-1903.
167. Viste R, Soosai J, Vikin T, Thorsby PM, Nilsen KB, Knudsen S. Long-term improvement after combined immunomodulation in early post-H1N1 vaccination narcolepsy. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e389.
168. Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a boy treated with modafinil for narcolepsy. *Am J Psychiatry*. 2005;162:813-814.
169. Wang J, Greenberg H. Status cataplecticus precipitated by abrupt withdrawal of venlafaxine. *J Clin Sleep Med*. 2013;9:715-716.
170. Weinhold SL, Seeck-Hirschner M, Nowak A, Hallschmid M, Goder R, Baier PC. The effect of intranasal orexin-A (hypocretin-1) on sleep, wakefulness and attention in narcolepsy with cataplexy. *Behav Brain Res*. 2014;262:8-13.
171. Wu P, Jones S, Ryan CJ, Michail D, Robinson TD. Modafinil-induced psychosis. *Intern Med J*. 2008;38:677-678.
172. Yasui-Furukori N, Kusunoki M, Kaneko S. Hallucinations associated with modafinil treatment for narcolepsy. *J Clin Psychopharmacol*. 2009;29:408.
173. Zvosec DL, Smith SW, Hall BJ. Three deaths associated with use of Xyrem. *Sleep Med*. 2009;10:490-493.

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