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REVIEW

Pharmacological management of narcolepsy with and without cataplexy

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ABSTRACT

Introduction: Narcolepsy is an orphan neurological disease and presents with sleep-wake, motoric, neuropsychiatric and metabolic symptoms. Narcolepsy with cataplexy is most commonly caused by an immune-mediated process including genetic and environmental factors, resulting in the selective loss of hypocretin-producing neurons. Narcolepsy has a major impact on workableness and quality of life.

Areas covered: This review provides an overview of the temporal available treatment options for narcolepsy (type 1 and 2) in adults, including authorization status by regulatory agencies. First- and second-line options are discussed as well as combination therapies. In addition, treatment options for frequent coexisting co-morbidities and different phenotypes of narcolepsy are presented. Finally, this review considers potential future management strategies. Non-pharmacological approaches are important in the management of narcolepsy but will not be covered in this review.

Expert opinion: Concise evaluation of symptoms and type of narcolepsy, coexisting co-morbidities and patients´ distinct needs is mandatory in order to identify a suitable, individual pharmacological treatment. First-line options include Modafinil/Armodafinil (for excessive daytime sleepiness, EDS), Sodium Oxybate (for EDS and/with cataplexy), Pitolisant (for EDS and cataplexy) and Venlafaxine (for cataplexy (off-label) and co-morbid depression). New symptomatic and causal treatment most probably will be completed by hypocretin-replacement and immune-modifying strategies.

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Narcolepsy; cataplexy; excessive daytime sleepiness; hypocretin; management; pharmacological treatment; co-morbidities

1. Introduction

Narcolepsy is a rare neurological disorder and affects approx. 0.026–0.05% of the population [1]. Incidence rate is about 0.5–1/100,000 person-years [2,3]. First symptoms often (>50%) occur in adolescents or young adulthood [2,4].

Narcolepsy with cataplexy is most commonly caused by the selective and irreversible loss of neurons of the posterior hypothalamus that produce the neuropeptide hypocretin (HCRT). HCRT neuronal loss is probably caused by an immune-mediated process, including genetic (HLA-DQB1*06:02, T-cell receptor α locus) and environmental (infections, e.g. H1N1, streptococcus; vaccination with Pandemrix®) factors [5,6].

Core symptoms of narcolepsy are excessive daytime sleepiness (EDS) and cataplexy. Cataplexy is a pathognomonic symptom for narcolepsy and is defined as sudden, short-lasting, usually bilateral loss of muscle tone triggered by emotions and accompanied by a preserved state of consciousness [6,7].

Further, narcolepsy presents with additional sleep–wake (disturbed sleep), motor (sleep paralysis, rapid eye movement [REM] sleep behavior disorder), neuropsychiatric (hallucinations, depression), and metabolic (obesity) disturbances [6,7].

The last revision of the International Classification of Sleep Disorders, differentiates two types of narcolepsy, type 1 (NT1) and type 2 (NT2) [8]. NT1 refers to narcolepsy with cataplexy and NT2 to narcolepsy without cataplexy.

Diagnostic criteria for NT1 require

(A) chronic EDS (>3 months),
(B) cataplexy (more than once),
(C) sleep onset REM periods (SOREMP, at least two SOREMP in Multiple Sleep Latency Test [MSLT] and/or polysomnography) and a mean sleep latency <8 min identified during MSLT, and/or
(D) Cerebrospinal fluid HCRT deficiency (<110 pg/ml).

NT2 remains a controversial entity. Criterion A and C are required for the diagnosis of NT2. In addition, NT2 can only be diagnosed in the absence of cataplexy and with normal HCRT levels, if available.

The clinical course of narcolepsy, in particular NT1, is variable. Acute, chronic-progressive, and worsening in bouts can be observed. New symptoms or coexisting disorders can appear over time. In some cases, a general improvement of EDS and/or cataplexy with increasing age is seen, whereas nighttime sleep more often becomes worse [1,7].

Narcolepsy is a limiting disorder and severely affects ability to work and quality of life [9].

In narcolepsy, a regular daily life structure is commonly lacking and therefore, adherence to the medication regimen is often difficult.

Hence, regularly evaluation of patients' symptoms, personal and professional needs, and coexisting disorders is necessary.

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Article highlights

- First-line medications for EDS include Modafinil/Armodafinil, Pitolisant and Sodium Oxybate.
- For cataplexy, Sodium Oxybate, Venlafaxine and Pitolisant are treatments of first choice.
- Evaluation of individual management strategies also depend on additional symptoms (e.g. obesity), coexisting morbidities such as depression and patients´ needs.
- Future treatments most probably will contain hypocretin replacement compounds and immune-modifying medications.

This box summarizes key points contained in the article.

Table 1. First- and second-line treatments approved for treatment of narcolepsy, divided into NT1 and 2 and into FDA and EMA.

	FDA		EMA	
Drug	NT1	NT2	NT1	NT2
MOD	X+	X+	X+	X+
ARMOD	X+	X+		
PTL			X	X
SXB	X	X+	X	
MPH	X+	X+	X+	X+

X: Approved.
+: For EDS.

Treatment is usually needed lifelong. Available proven treatments are solely symptomatic and mainly focus on core symptoms of narcolepsy: (1) EDS and (2) cataplexy (see Table 1).

Several of the frequently used medicines for the treatment of narcolepsy are not approved by the EMA or FDA and usage of these drugs is based upon expert association recommendations, in an off-label use.

In our review, we present first- and second-line pharmacological treatments for narcolepsy (EDS, cataplexy, sleep paralysis, hallucinations, and other sleep disturbances), and for frequent comorbidities (e.g. obesity, depression). Additionally, we provide an outlook on future therapies.

2. Methods

A PubMed research was conducted for topical literature published until 31 January 2017. Search terms included but were not limited to narcolepsy, narcolepsy with and w/o cataplexy, NT1, NT2, narcolepsy-like, management, treatment, therapy, pharmacotherapy, prescription, EDS, cataplexy, hallucinations, sleep paralysis, disturbed nocturnal sleep; narcolepsy and weight gain, obesity, sleep disordered breathing, REM-sleep behavior disorder (RBD), RLS, and period limb movements in sleep (PLMS). Search was limited to adult narcolepsy.

In addition, review of published articles on the treatment of narcolepsy and guidelines was used as primary resources. Among those, EFNS (European Federation of Neurological Societies) guidelines on management of narcolepsy, 2006 [10]; AASM – Treatment of narcolepsy and other hypersomnias of central origin, 2007 [11]; and Quality measures for the care of patients with narcolepsy, 2015 [12], have been used. Currently, the two authors coordinate the updated, joint European (European Academy of Neurology, European Sleep Research Society, European Narcolepsy Network) guideline on management of narcolepsy.

Table 2. Therapy recommendations (first- and second-line medications).

	Symptom		
	EDS	Cataplexy (+hallucinations/sleep paralysis)	Disturbed nocturnal sleep
First line	• Modafinil/ Armodafinil • Pitolisant • Sodium oxybate[a]	• Sodium oxybate • Venlafaxine[b] • Pitolisant	• Sodium oxybate[a] • Benzodiazepine receptor agonists[b] • Benzodiazepines[b]
Second line	• Methylphenidate	• Fluoxetine[b] • Citalopram[b] • Clomipramine[b]	

[a]EMA: only for NT1 patients.
[b]Off-label (exception: Clomipramine approved in Germany).

3. Results

3.1. Pharmacological treatment – individual symptoms

In this chapter, first-line (and second-line) treatments for *individual* symptoms of narcolepsy will be presented. An overview is provided in Table 2. This review refers to treatment for adults.

3.1.1. Excessive daytime sleepiness (EDS)

3.1.1.1. First-line treatments.

(1) **Modafinil/Armodafinil**

Background

Modafinil (MOD) promotes wakefulness, probably by involving the dopamine system: MOD increases the extracellular concentration of dopamine [13,14]. However, the exact mechanism of action still remains unclear [15].

The maximum concentration is reached after 2–4 h and elimination half-life is 10–14 h.

Several class I evidence studies have demonstrated efficacy on EDS in doses 200, 300, and 400 mg/day by a reduction of EDS on subjective estimates (clinical global impression), Epworth Sleepiness Scale (ESS) values, Maintenance of Wakefulness Test (MWT), and MSLT [16–18]. The alerting effect is observed typically already within days. In some open-label extension trial, efficacy over 40 weeks was reported [19,20]. Some improvement of mild cataplexy (due to improved EDS) can be observed.

MOD is generally well tolerated. Common side effects include headache (often disappearing after few weeks), nausea, nervousness/anxiety, and insomnia [16–20]. MOD decreases the efficacy of oral contraceptives. Hence, a product containing 50 µg/day or higher ethinyloestradiol or another contraceptive method should be prescribed [21].

EMA and FDA-approved MOD for the treatment of EDS in narcolepsy (NT1 and 2).

Armodafinil is the R-enantiomer of MOD and has been found to act as a D2 receptor partial agonist. It has a more extended effect than MOD [22,23].

FDA has approved armodafinil for the treatment of EDS in narcolepsy (NT1 and 2).

Practical issues

MOD intake usually starts with 100 mg in the morning (fasting) solely or with additional 100 mg at lunch. MOD dosage can be gradually increased over several weeks to up to 400 mg/day, often distributed as 200 mg in the morning and 200 mg at lunch (or 300/100 mg).

The maximum approved dosage is 400 mg/day, but in clinical practice, some patients experience additional efficacy of MOD in higher dosages, up to 600 mg/day. Higher doses than 400 mg/day should be applied only after a careful individual case evaluation, and when drug-resistance to other compounds is reviewed.

Armodafinil is taken in a single dose in the morning, starting with 100 mg up to a maximum of 250 mg per day.

(2) **Pitolisant**

Background

Pitolisant (PTL) is a new compound enhancing wakefulness. PTL is a selective histamine H3 receptor inverse agonist, resulting in an increase of brain histamine. The maximum plasma concentration is reached after 3 h. Elimination half-life is 10–12 h [24].

In two class I evidence studies, PTL has been shown to be effective in the reduction of EDS [25,26]. Reduction on ESS was significantly higher compared to placebo and comparable to MOD. Also on MWT, a favorable effect compared to placebo was seen [26]. Efficacy is mainly described in a dose of 36 mg/day and is usually reached within few weeks. Clinical long-term efficacy experience is still lacking.

The comparable effect of PTL compared to MOD on EDS still needs to be confirmed in real-life clinical practice.

Treatment with PTL is well tolerated. Side effects include headache, insomnia, and nausea. Headache and nausea are often found especially in the beginning of the treatment [25,26]. Due to a potential interaction with oral contraceptives, another contraceptive method should be prescribed.

EMA has approved PTL for the treatment of narcolepsy (NT1 and 2).

Practical issues

Oral PTL is taken in the morning with breakfast, in a single dose. Treatment starts with 9 mg and is usually increased up to 36 mg/day over 3–4 weeks.

(3) **Sodium oxybate**

Background

Sodium oxybate (SXB) probably acts via stimulation of GABA-B receptors, but the precise mechanism of action still remains incompletely understood. SXB elimination half-life time is 1.5–2 h.

SXB improves cataplexy, EDS, and other narcolepsy symptoms, in particular and usually first disrupted nighttime sleep. Improvement of EDS may be observed only after several weeks/months. Different class I evidence studies could demonstrate reduced EDS and increased level of alertness [27–29]. One study has shown SXB and MOD to be equally efficacious for the treatment of EDS [30]. Clinical experience speaks however for a less strong alerting effect of SXB as compared to MOD. Effectiveness is supported by meta-analysis [31,32].

Most common side effects include nausea, dizziness/confusion, weight loss, enuresis, anxiety, and depressive symptoms [27–32].

FDA approved SXB for the treatment of cataplexy and of EDS in narcolepsy (NT1 and 2). EMA approved SXB for the treatment of narcolepsy with cataplexy (NT1).

Practical issues

SXB is only available in liquid form and must be taken twice a night. SXB should be taken in bed. Patients wake up or use a clock to wake up and take the second dose. The recommended starting dose is usually 4.5 g/night (clinically however as low as 2–3 g), divided into two equal doses of 2.25 g at bedtime before sleeping and 2.5–3 h later. A slow up-titration of additional 1.5 g/night doses (in total) per week is recommended. Full therapeutic benefit generally occurs at the 6–9 g/night doses and/or after 4–8 weeks of treatment.

3.1.1.2. Second-line treatments.

(1) **Methylphenidate**

Background

Methylphenidate (MPH) induces dopamine release, in partial similar to amphetamines. MPH has been used for a long time as first-line therapy [33] and is still used when other compounds, such as MOD, are ineffective. MPH has a short elimination half-life of 2–7 h. In only one class II evidence study, MPH could demonstrate improvement of EDS compared to baseline [34]. This effect is usually rapidly observed (typically within days) and found in all tested dosages (10, 30, and 60 mg/day). In additional class IV evidence studies, reduction of EDS (on ESS and MWT) was described [35,36].

Tachycardia, hypertension, sweating, palpitations, irritability, hyperactivity, mood changes, weight loss, anorexia, and insomnia are common side effects. Tolerance often develops [33–36].

FDA and EMA approved MPH for the treatment of EDS in narcolepsy (NT1 and 2).

Practical issues

Oral MPH, also available (but not approved) as sustained-release formulation, intake usually starts with 10–20 mg in the morning (fasting or during breakfast) and additional 10–20 mg at lunch. Doses range from 10 to 60 mg/day and are usually spread in 2–4 portions over the day.

3.1.1.3. Third-line treatments.

Amphetamines [37], mazindol [37,38] (which was removed from the market because of hepatoxocity), selegiline [39], reboxetine [40], ephedrine, pemoline, L-carnitine [41], and other stimulants are third-line treatments. Although often effective, amphetamines have a high risk for cardiovascular events and abuse. Dextroamphetamine is approved in some countries (including Germany and Switzerland) for the treatment of EDS in narcolepsy [42,43]. Recently, FDA has approved two compounds for the treatment of EDS in narcolepsy. One drug is a combination of amphetamine and dextroamphetamine (Adderall™) and the other contains amphetamine sulfate (Evekeo™).

3.1.2. Cataplexy

3.1.2.1. First-line treatments.

(1) **SXB**

Background

Several class I evidence studies, supported by a meta-analysis, have shown a significant, dose-dependent (3–9 g/night) reduction of the number of cataplectic attacks and of cataplexy intensity (as assessed by questionnaire/interview) by SXB. Effect is usually observed only after weeks to months. Long-term efficacy (over >44 months) could be demonstrated [31,32,44–48]. Abrupt discontinuation does not lead to status cataplecticus.

For additional information on side effects, please see Section 3.1.1.1. (3)

Practical issues: As described in Section 3.1.1.1 (3)

(2) **Venlafaxine**

Background

Venlafaxine (VLX) is widely used to treat cataplexy. However, no study evidence is provided for VLX being efficacious in the reduction of cataplexy [49]. VLX is a serotonin and norepinephrine reuptake inhibitor (SNRI) and approved as antidepressant. The use in narcolepsy is derives from expert association recommendations [10]. In clinical practice, VLX reduces cataplexy, often in low dosages compared to the use in depression. The anticataplectic effect arrives within few days.

Elimination half-life is 5 h, for active metabolites 12 h. Short-acting and sustained release formulations are available.

VLX is usually well tolerated. Side effects include increased blood pressure, headache, dry mouth, nausea, and dizziness.

VLX is not approved as treatment for narcolepsy.

Practical issues

The starting dose of VLX is 37.5 mg/day, taken in the morning. VLX can be increased slowly over 4–8 weeks up to 300 mg/day. In higher dosages, often sustained release formulations are used. Short-acting VLX can also be split into 2–4 portions over day.

(3) **PTL**

Background

In a *post-hoc* analysis of a class I evidence study and in another, very recent class I evidence study, reduction of cataplexy frequency against placebo could be confirmed. Short-term (7 weeks) results still require long-term confirmation [25,26]. First clinical experience suggests that the anticataplectic effect of PTL is weaker than that of SXB.

For additional information on side effects, please see Section 3.1.1.1. (2)

Practical issues: As described in Section 3.1.1.1 (2)

3.1.2.2. Second-line treatments.

(1) **Fluoxetine, citalopram, and clomipramine**

Background

Fluoxetine and citalopram are both selective serotonin reuptake inhibitors (SSRIs) and are frequently used in the treatment of cataplexy in narcolepsy. Limited data give evidence for their use. Two class III evidence studies for fluoxetine [50,51] and one class IV evidence study for citalopram reported minor improvements of cataplexy [52]. Both compounds are well tolerated. Excitation, gastrointestinal problems, insomnia, and sexual difficulties are common side effects. Abrupt discontinuation can lead, as with other antidepressant drugs, to status cataplecticus [53].

Clomipramine is a tricyclic antidepressant and has been used to treat cataplexy since the 1960s. One class III evidence study and several class IV studies have shown a strong impact on the reduction of cataplexy [54–56]. Reported side effects are dry mouth, sweating, constipation, diarrhea tachycardia, weight gain, hypotension, difficulty in urinating, and impotence. Side effects are more frequent than with SSRIs or SNRIs.

Fluoxetine, citalopram, and clomipramine are not approved as treatment for narcolepsy (exception: clomipramine for cataplexy in narcolepsy, in Germany).

Practical issues

Fluoxetine and citalopram intake is suggested in the morning. Fluoxetine treatment starts with 10–20 mg/day and can be titrated up to 60 mg/day. For citalopram, 10–20 mg/day, up to 40 mg/day, is recommended. Daily 10 mg clomipramine is the initial dosage and can be gradually increased up to 75 mg/day. Often dosages between 10 and 25 mg/day are already sufficiently effective.

3.1.2.3. Third-line treatments.

Several other tricyclic antidepressants [57], SSRIs, or novel SNRIs such as duloxetine or norepinephrine dopamine reuptake inhibitors (e.g. bupropion), might improve cataplexy. Other compounds include mazindol, selegiline, baclofen, and sibutramine. Clinical evidence for the effectiveness is completely lacking, and no compound is approved for the treatment in narcolepsy with cataplexy.

3.1.3. Disturbed nighttime sleep

Frequent awakenings, stage shifts, and a general fragmentation of sleep are frequent in narcolepsy. In several class I evidence studies, SXB could improve nighttime sleep and reduce fragmentation and awakenings [45,46,58–60]. Clinical experience confirms these results and suggests that sleep may be the first symptom to be improved by SXB [61].

Other treatment options include benzodiazepines and non-benzodiazepine agonists. In one class III evidence study, triazolam improved sleep efficiency [62] and in one class IV evidence study, temazepam was reported to improve sleep [63]. No study with non-benzodiazepine agonists has been performed. Benzodiazepines and non-benzodiazepine agonists might cause additional sedation/EDS.

3.1.4. Hallucinations, sleep paralysis, and nightmares

The appearance of hallucinations and sleep paralysis varies in frequency and impact in narcolepsy patients. Often treatment that improves the symptoms, in particular cataplexy, also leads to a reduction of hallucinations and sleep paralysis.

In one class I evidence study, a reduction of the daily number of hallucinations by SXB was reported [46]. Clinical experience confirms positive effects on hallucinations, sleep paralysis, and nightmares [61]. Antidepressants (e.g. VLX) also seem to improve hallucinations and sleep paralysis.

3.1.5. Obesity

In narcolepsy, weight gain and obesity are common. No specific pharmacological therapy is recommended for this purpose; however, side effects of several approved therapies are weight loss or lack of appetite: SXB, MOD, MPH. For SXB treatment in particular, some data indicate for a significant weight loss [64].

In contrast, most antidepressants may cause in an increase of appetite and weight gain.

3.1.6. RBD

RBD is a frequent (30–60%) symptom in narcolepsy. There is no report of any clinical study of any drug specific for RBD in narcoleptic subjects. In few case reports, conventional RBD treatment with clonazepam or melatonin has been described to be effective [65,66]. SXB might also lead to some improvement [67].

3.1.7. Comorbidities

Common comorbidities include neuropsychiatric disorders such as depression, anxiety, and possibly eating disorders. PLMS, restless legs syndrome (RLS), sleep apnea, and NREM parasomnias are more frequently found in narcolepsy than in the general population.

3.1.7.1. Depression. Depression is the most frequent neuropsychiatric comorbidity found in narcolepsy. Antidepressant therapy and psychotherapy are indicated in many cases. Hence, pharmacological treatment with an antidepressant can be helpful in the management of both, depression and cataplexy. In contrast, most stimulants and SXB might worsen depression or cause it '*de novo*' rapidly after start of treatment [68]. No clinical evidence studies yet have been performed.

3.1.7.2. RLS/PLMS. Commonly found PLMS and RLS can be effectively treated with L-Dopa or dopamine agonists [69,70]. Most antidepressants can deteriorate RLS/PLMS. Studies on the impact of SXB on PLMS are not conclusive [71–73].

3.1.7.3. Sleep disordered breathing. Sleep disordered breathing (SDB) is more prevalent in narcolepsy, possibly due to the higher prevalence of obesity, and should be treated conventionally by CPAP. There are no studies on the effect of CPAP in narcolepsy in particular. Clinical experience suggests that CPAP is less effective/well tolerated in narcoleptic than in the general population with SDB.

SXB can deteriorate (occasionally however also improve) SDB, therefore, respiratory function, and if necessary evaluation and therapy before initiation of SXB therapy is important [74].

3.2. Treatment options: the whole patient in mind

NT1 patients per definition are suffering from at least two leading symptoms: EDS and cataplexy. Usually, additional symptoms, e.g. disturbed nocturnal sleep, are also present. In NT2, EDS is the leading symptom. Selection of treatment depends on symptoms and hence, a medication regimen that improves several symptoms at once is preferable, in cases where different symptoms are present. Further, comorbid conditions might have an impact on the determination of which treatment to apply. Combinations of medications can be useful. Most narcolepsy treatments can be combined, e.g. stimulants with SXB or with antidepressants. Even a combination of MOD and PTL seems to be feasible. In some studies, coadministration of SXB and MOD has shown additional effects on improvement of EDS [30]. Some combinations should normally not be utilized: the combination of MOD and MPH should be avoided because of the potential increased risk for cardiovascular adverse events, or combinations of different antidepressant agents (SSRIs with SNRIs).

In the following, we suggest appropriate treatment regimens and modifications, if the patient is clinically depressed, obese, or suffering from disturbed nocturnal sleep. Further, therapy for patients with certain occupations should be as simple and prolonged as possible, in order to avoid fluctuations and the need to take medications several times during the day.

3.2.1. The mainly sleepy patient (NT2 or NT1 with clear focus on EDS)

In this phenotype of narcolepsy, different stimulants (MOD, Armodafinil, PTL, or [second-line] MPH) are recommended. In one class I, evidence study directly comparing MOD and PTL similar results on the reduction of ESS has been shown [25].

SXB therapy can also be considered but is usually used when additional narcolepsy symptoms are present (see Section 3.2.3).

3.2.1.1. The mainly sleepy patient….

…with depression

For all stimulants (and SXB), depression is described as possible side effect [20,25,30,36]. The risk seems to be prominent for MPH and SXB; hence, only MOD, ARMOD, and PTL seem to be reasonable first-line option in this case. Coadministration of an antidepressant needs to be evaluated.

…with obesity

Lack of appetite and weight loss is described for most stimulants (MOD, ARMOD, MPH) and for SXB [20,30,36,64]. In this phenotype of patients, all previously mentioned drugs are appropriate options. PTL is also a possible therapy; however, in few patients, an increase of weight has been described [25].

…with disturbed sleep

SXB is effective in the reduction of nocturnal sleep fragmentation [59,60]. SXB as monotherapy or even a combination therapy SXB together with MOD, ARMOD, or PTL can be considered.

…with safety sensitive work

MOD, ARMOD, and PTL are drugs with a simple, once a day (often twice for MOD) intake and prolonged efficacy. SXB is also useful for EDS and only to be taken at night.

3.2.2. The narcolepsy patient with both EDS and cataplexy (NT1)

For patients with both core symptoms, first-line options are SXB or PTL. Both drugs, SXB and PTL, have an impact on the

two symptoms EDS and cataplexy [25,26,29,46,47]. They can be used as monotherapy in this narcolepsy phenotype.

Other first-line treatments include a combination therapy of a stimulant (MOD, ARMOD, PTL) together with an antidepressant (VLX, others) or SXB in combination with a stimulant (MOD, ARMOD, PTL).

3.2.2.1. The narcolepsy patient with both EDS and cataplexy (NT1)….

…with depression

In this case, a combination therapy including an antidepressant (e.g. VLX) and a stimulant (MOD, ARMOD, PTL) is suggested. The dose of the antidepressant should focus on effects for depression.

…with obesity

The recommended first-line therapy is SXB. SXB is effective for both symptoms and in some patients causes weight loss [29,46,64]. In this subgroup of patients, particular attention to sleep apnea should be paid before starting SXB therapy [74].

Most antidepressants increase weight; accordingly, a combination therapy including an antidepressant should not be started as first-line option.

…with disturbed sleep

SXB improves EDS, cataplexy, and disturbed nocturnal sleep [29,46,47,59,60].

…with safety sensitive work

PTL is effective for EDS and cataplexy and has a simple, once a day intake and prolonged efficacy. SXB is also useful for both symptoms and only to be taken at night. SXB might be combined with a stimulant (MOD, ARMOD, PTL) in the morning.

3.2.3. The patient mainly bothered by cataplexy

SXB, PTL, and antidepressants (VLX) are first-line options for this subgroup of narcolepsy. All are effective in the reduction of cataplexy, but only clinical evidence is provided for SXB and PTL [25,26,46,47].

3.2.3.1. The patient mainly bothered by cataplexy…

…with depression

An antidepressant therapy (VLX) is the first option of choice.

…with obesity

SXB is most appropriate to improve cataplexy and to maintain or lose weight.

…with disturbed nighttime sleep

First-line option is SXB for the improvement of cataplexy and disturbed nocturnal sleep [59,60].

…with safety sensitive work

PTL and SXB are effective for cataplexy and intake is once a day (PTL) or only at night (SXB). VLX, in particular as sustained release formulation, taken once or twice a day can also be an option.

4. Future treatments

4.1. Symptomatic treatments

PTL is a recently approved (EMA) agent for narcolepsy type 1 and 2. Additional new symptomatic treatments include JZP-110 and delayed release SXB. JZP-110 is a compound with dopaminergic and noradrenergic activity. In a phase II b study, JZP-110 has shown an improvement of EDS on ESS and MWT [75]. Recently, a phase III trial is ongoing.

Long-acting SXB using a Micropump® system is currently evaluated in a phase III clinical trial. Micropump is a microparticulate system that allows controlled and delayed release of formulations of drugs [76].

4.2. HCRT replacement strategies

Symptoms of NT1 are thought to be caused by HCRT deficiency. In animal studies, only intraventricular infusion of HCRT could improve symptoms of narcolepsy, as HCRT cannot cross the blood–brain barrier (BBB) [77]. In a clinical trial, replacement therapy with HCRT via intranasal application (thereby trying to bypass the BBB) was mainly unsuccessful [78]. Replacement with HCRT receptor agonists is one option for the future [79]; another, more difficult option might be replacement by HCRT-1 pluripotent stem cells. In an experimental animal study, this has been demonstrated as possible and successful [80].

4.3. Causal treatments: immune-modulating approaches

Selective HCRT neuron loss in NT1 is most probably result of an immune-mediated attack. Interval of time from the beginning of the immune reaction to the final destruction of HCRT neurons is short, probably weeks to few months. Due to this concept, some attempts to modulate the immune system have been made.

Several case series of patients treated with intravenous immunoglobulins are published but mostly showing negative results [81–83].

More recent articles describe cases where a – sometimes only temporary – improvement of narcolepsy symptoms due to steroids or immunomodulating treatments such as alemtuzumab could be found [84–86]. Further immune-suppressing or -modulating therapies will be evaluated for efficacy in narcolepsy in the future.

5. Conclusion

Narcolepsy is a limiting neurological disorder and usually requires life-long pharmacological treatment. An increasing number of efficacious symptomatic medications can improve narcolepsy. Consideration of described individual disturbances, looking at the patient as a whole as well as patients' needs, is important for the evaluation of an appropriate therapeutic strategy.

In the future, outcome measure and quality of life should be addressed more/better in symptomatic studies. Additional conclusive outcome measures are needed. Furthermore, the use of immune-modulating and HCRT-replacement treatments should be tested more systematically particularly in patients with recent-onset narcolepsy.

6. Expert opinion

Narcolepsy is a chronic disorder often starting in adolescents or young adulthood. It has a negative impact on school, vocational education and training, occupation, quality of life, and personal and familiar relationship [9].

Precise clinical evaluation and ancillary testing is mandatory in order to classify narcolepsy appropriately. NT2 remains in fact a diagnosis of exclusion.

Currently, improvement relies on symptomatic treatment. Drugs improving multiple symptoms (such as SXB and PTL) improve adherence may on occasions be preferable.

Ongoing research on the etio-pathophysiology of narcolepsy is expected to provide a better understanding of the underlying immune mechanisms (e.g. impact of T and/or B cell, antibodies) and by this offers new biomarkers for diagnosis and targets for treatment [87].

This will enhance the importance of a correct and early diagnosis. On the other end, disease-modifying therapies when applied early could have a favorable effect on the course of the disease.

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