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Chapter

Narcolepsy Treatment: Present and Future

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Abstract

Narcolepsy is a chronic, disabling sleep disorder with a significant diagnostic delay. Nowadays, treatment is focused on managing symptoms that impacts patient's life, such as at workplace, social events or even at school, but not aimed cure the disease. However, we have pharmacological treatments that effectively help control the main symptoms (excessive daytime sleepiness, cataplexy, fragmentation of nocturnal sleep, sleep paralysis and hypnagogic and hypnopompic hallucinations). On the other hand, pharmacological treatment must be individualised as there are great variations in severity, order of appearance symptoms and development of the disease. We intend to expose the different symptomatic treatments recommended by clinical guidelines and the clinical management from a practical point of view. Future treatments include therapies based on the replacement of hypocretin or the administration of agonist receptors. Other techniques such as hypothalamic stem cell transplantation, gene replacement therapy or immunotherapy are also being investigated.

Keywords: narcolepsy, sleep, cataplexy, pharmacotherapy, pharmacology, sleepiness

1. Introduction

Narcolepsy is a chronic and disabling disease, which, according to the International Classification of Sleep Disorders (ICSD-3), considered to be hypersomnias of central origin [1]. Narcolepsy presents with a variable combination of sleep–wake symtoms and motor, psychiatric, emotional, cognitive, metabolic and autonomic disturbances that reflect the hypothalamic origin of the disorder.

The leading symptoms are:

1. Excessive daytime sleepiness (EDS), which can also manifest with sleep attacks, involuntary napping, automatic behaviours, difficulty sustaining attention and memory disturbances.

2. Cataplexy, briefs episodes of bilateral loss of muscle tone triggered by sudden emotions in the presence of a normal state of consciousness. Often is partial, rarely complete with falls.

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Other sleep–wake symptoms are fatigue, sleep paralysis, hypnagogic and hypnopompic hallucinations, nightmares, lucid dreams, enacted dreams, disrupted night-time sleep, restless legs syndrome or parasomnias.

The current International Classification of Sleep Disorders (ICSD-3) defines two types of narcolepsy:

a. Narcolepsy type 1 (NT1): EDS for > 3 months in association with either CSF orexin levels < 110 pg./ml or cataplexy and a mean sleep latency < 8 minutes on the multiple sleep latency test (MSLT) and at least two sleep onset REM periods (SOREMPs) during MSLT y/o night-time polysomnography.

b. Narcolepsy type 2 (NT2): EDS for > 3 months in the absence of cataplexy but with a mean sleep latency on the MSLT < 8 minutes and at least two SOREMPs on the MSLT y/o night-time polysomnography, as well as CSF orexin levels > 110 pg./ml (or not measured).

If cataplexy develops over time or CSF orexin levels decrease to < 110 pg./ml, the diagnosis of NT2 must be change to NT1.

The main symptoms of NT1 are related to hypocretin/orexin (ORX) deficiency, due to the selective destruction, likely autoimmune in origin, of ORX-producing hypothalamic neurons. Likewise, hypocretin deficiency reduces the excitatory signal of the neurons responsible for the synthesis of neurotransmitters that promote wakefulness, such as noradrenaline (NA), dopamine (DA), serotonin (5-HT) and histamine.

Genetically, approximately 98% of patients with NT1 carry the HLA class II allele DQB1*06:02; this allele is present in 50% of patients with NT2 and only 12–30% of the general population [2]. So far, no specific antibodies against ORX neurons have been detected. This could be due either to their location in a restricted area where there is a small number of damaged antibodies, or because the activation of specific T cells is negligible.

There is a clear variability in the evolution of the disease over time. On one hand, it is important to note that when a patient develops symptoms, the hypocretinergic neurons may already present irreversible damage; on the other hand, on average, there is a diagnostic delay of 10 years from the onset of symptoms. For this reason, it is still not possible to establish a concrete and extrapolable pattern. Some patients observed with severe narcolepsy and cataplexy show full symptomatology in the first days of the disease, while others develop a progressive course with excessive daytime sleepiness (EDS) as the initial symptom and followed by cataplexy after months or years of evolution.

Different hypotheses have been postulated regarding the pathophysiology of cataplexy. On one hand, there is a direct relationship between the brain areas responsible for inhibition of muscle tone in REM sleep and hypocretinergic neurons. The loss of these neurons would cause dissociated REM sleep (the atonia of the REM phase would appear during wakefulness) manifesting itself clinically as cataplexy or sleep paralysis [3]. Likewise, it has been proposed that hypocretin deficiency would facilitate sleep–wake transitions more frequently due to the instability of wake–sleep regulation mechanisms.

Pharmacotherapy in the treatment of narcolepsy is currently aimed at controlling the principal symptoms: EDS, cataplexy, sleep fragmentation, sleep paralysis and hypnagogic and hypnopompic hallucinations, but are not intended to cure the disease. However, the treatment does manage to significantly improve quality of life.

The following is a detailed breakdown of the different existing treatments and the promising future lines that are being developed for the treatment of Narcolepsy.

2. Existing lines of therapy

As we have already mentioned, current therapies are aimed at the symptomatic treatment of narcolepsy. One key point to take into account is the high degree of inter-individual variability in the clinical presentation of the disease, in terms of the different clinical evolution over the years, and the therapeutic response and possible side effects related to the different treatments.

The first approach should therefore focus on the adoption of non-pharmacological measures, with programmed short-duration daytime naps being one of the most prominent.

Establishment of rigid schedules for waking up and going to bed, attempting to avoid transgressions or sleep deprivation, should be recommended. Like other patients with sleep disorders, avoiding excessive caffeine or alcohol consumption should be recommended. Last, but not least, it is helpful to orient the patient from the point of view of work, providing suggestions as to the jobs that are most advisable and less advisable for patients with narcolepsy. In addition, they should be informed of associations or support groups at the national and international level.

Regarding pharmacological therapy, the different existing lines of therapy can be classified according to their mode of action or according to the type of symptomatology that they are intended to treat (daytime sleepiness, cataplexy, sleep fragmentation, etc.).

2.1 Recommended treatments for excessive daytime sleepiness (EDS)

1. Modafinil: inhibits the dopamine transporter, facilitating an increase in its concentration, although its mechanism of action is still unclear. Approved by the FDA and EMA. Armodafinil is also FDA approved and the usual doses for adults range from 100 to 250 mg.

   Dosage: in tablets of 100–400 mg orally. Initially, treatment is started with 100 mg, which can be divided into two intakes of 50 mg at least 2 hours apart. The dose should later be increased depending on the degree of drowsiness, considering the dose-dependent occurrence of side effects.

   Pharmacokinetics: the absorption of modafinil is fast, with a maximum plasma concentration of about 2 to 4 h. The effective elimination half-life of modafinil after multiple doses is approximately 15 h. The main route of excretion is via the liver and part of its metabolites via the kidneys. Patients with severe hepatic impairment should be treated with lower doses. Reversible inhibition of the cytochrome P450 enzyme CYP2C19, as well as CYP3A4, CYP1A2 and CYP2B633 has been observed. Coadministration of modafinil with diazepam, phenytoin and propranolol, which are eliminated via the CYP2C19 enzyme, may increase their levels. It is recommended that alternative methods of contraception be considered during treatment with modafinil and one month after the end of the treatment.

   Safety and adverse events: generally well tolerated and the most common adverse events were headache (13%), nervousness (8%) and nausea (5%). Treatment-related cardiovascular events were infrequent, including palpitations (1.5%), hypertension (1%) and tachycardia (1%). Studies with modafinil have shown a potential for dependence, so the possibility of dependence with long-term use cannot be completely ruled out. It is also recommended that an ECG be performed on all patients prior to the start of treatment.

The combination of modafinil with connexin-30 inhibitors is under development (discussed later in the chapter).

2. Methylphenidate: blocks the reuptake of noradrenaline and dopamine (inhibiting the transporters of these neurotransmitters at the presynaptic level) increasing the concentration of dopamine and noradrenaline in the synaptic cleft. Broadly speaking, this generates its stimulant effect within the central nervous system (CNS), primarily in the prefrontal cortex. It is also a weak agonist at the 5-HT1A receptor, which is an additional mechanism that contributes to increased dopamine levels. Before starting any treatment with stimulants, it is advisable to perform at least an electrocardiogram to rule out possible cardiac arrhythmias [4]. Due to the risk of serious side effects, avoiding use with patients with structural heart abnormalities is recommended.

   Dosage: doses are administered orally and range between 10 and 60 mg and should not exceed 72 mg. Immediate and extended release are available.

   Adverse effects: insomnia and nervousness are the most frequent events, although other effects related to the CNS (dizziness, headache, tics, akathisia), gastrointestinal (nausea/vomiting, dry mouth, decreased appetite, weight loss, abdominal pain) and cardiovascular system (tachycardia and palpitations) have also been reported. Methylphenidate is FDA approved for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults and as a second-line treatment for narcolepsy in adults.

3. Pitolisant: histamine H3-receptor antagonist-inverse agonist (to be developed later).

4. Amphetamines or dextroamphetamine: the main action is through increases in synaptic concentrations of monoamine neurotransmitters, thus indirectly enhancing noradrenergic and dopaminergic neurotransmission in the CNS. Catecholaminergic signalling is the primary mediator of efficacy in narcolepsy. This same pathway is also responsible for the major side effects, as well as its potential for abuse. It should be considered that it is a drug with very limited use, because there is a difficult balance between achieving correct therapeutic efficacy and an acceptable control of side effects.

   Dosage: doses between 5 and 30 mg orally, twice a day, or 20 mg in a sustained release formulation twice a day are usually used.

   Adverse effects: decreased appetite, nausea, vomiting, insomnia, headache, increased blood pressure and heart rate, etc.

   Safety: has a high potential for abuse, can cause psychosis and manic episodes.

2.2 Recommended treatments for cataplexy and symptoms resulting from dysregulation of REM sleep

1. Sodium oxybate (Xyrem®): this is the sodium salt of gamma-hydroxybutyrate (GHB). GHB is synthesised in neurons throughout the CNS and is an active metabolite of gamma-aminobutyric acid (GABA). It inhibits noradrenergic neurons in the locus coeruleus during sleep, with a rebound effect of these neurons during the day thus promoting wakefulness, although its mechanism of action remains unclear. One of the hypotheses about the mechanism of action on the control of EDS and cataplexy postulates that it could be mediated

through GABA-B agonist actions on dopaminergic, noradrenergic, as well as thalamocortical neurons. In 1998, the FDA granted permission to test oxybate as an orphan drug for narcolepsy. In 2002 it developed a distribution program through hospital pharmacies only. And in Europe, it is available under restricted prescription and special situation. It also has a risk management and pharmacovigilance program.

Dosage: it is an oral solution (500 mg/ml). The recommended initial dose is 4.5 g/night (divided into 2 doses, each of 2.25 grams) spaced at least 2.5–4 hours apart before the new dose, so that most of the drug has been eliminated when the patient wakes up. Up to a maximum of 9 g/day (7 g/day in children <12 years).

Pharmacokinetics: it is rapidly absorbed with a maximum plasma concentration (tmax) of 1.5–2 h. Less than 5% of the unaltered drug appears in the urine 6–8 h after dosing. No active metabolites. Also does not induce cytochrome P450 enzymes. In patients with cirrhosis of the liver, a lower dose should be started because a doubling of the area under the curve, reduced oral clearance and prolonged elimination half-life have been observed.

Safety: the most frequent adverse effects were: headache (11.6%), nasopharyngitis (6.4%), dizziness (5.2%), weight loss (5.2%), nausea (5.1%), urinary incontinence in (2.4%) and sleepwalking in (3.1%). Serious adverse events included depression, angina, inguinal hernia, psychosis or attempted suicide. In addition, the European Medicines Agency (EMA) recommends assessing the risk/benefit in patients with obstructive sleep apnoea syndrome (OSA), especially in doses higher than 6 g/night. On the other hand, it is important to control daily salt intake in patients with heart failure, hypertension or renal failure because the molecule has a high salt content. It also must be taken under consideration the potential for abuse, before being administered, the patient's medical history should be reviewed.

Recently, a multi-centre, randomised, placebo-controlled trial involving children and adolescents with narcolepsy with cataplexy was developed examining efficacy and safety. Based on this study, the FDA approved the use of sodium oxybate in paediatric patients with narcolepsy beginning at seven years of age.

There are now new therapeutic lines with controlled-release GHB (see below).

2. Pitolisant: histamine H3-receptor inverse antagonist–agonist (to be developed later).

3. Venlafaxine and Duloxetine: are dual serotonin and noradrenaline reuptake inhibitors. These are the most used antidepressants to control cataplexy. This recommendation lacks clinical evidence of efficacy and is based solely on expert opinions.

   Dosage: initially 37.5 mg, sometimes requiring higher doses (75–300 mg). The extended-release form is preferable.

   Safety: It can be administered to children and is not recommended for pregnant women.

4. Fluoxetine and Citalopram: are selective serotonin reuptake inhibitors (SSRIs). A crossover study comparing clomipramine and fluvoxamine showed that

SSRIs improved cataplexy, but were less active than the antidepressant. Studies have been carried out with femoxetine, zimelidine and escitalopram showing a clear anticataplectic effect and good tolerance.

5. Reboxetine: dopamine and noradrenaline reuptake inhibitor (discussed below).

6. Monoamine oxidase inhibitors (MAOIs): act by inhibiting the enzyme monoamine oxidase by increasing the availability of monoamine neurotransmitters. A suppression of REM sleep has been observed as the main effect. Phenelzine has been used successfully in seven patients with resistant narcolepsy, with persistent efficacy after 1 year of treatment. In addition, there have been two placebo-controlled studies with selegiline (MAO-B inhibitors) at doses of 20–40 mg which demonstrated a significant reduction in the frequency of cataplexy. With MAO-A inhibitors such as brofaromine, significant results were also obtained, reducing cataplexy with no significant side effects. However, they are rarely used in clinical practice due to their adverse effects (weight gain, orthostatic hypotension, irritability, sweating, dry mouth, etc.)

7. Tricyclic antidepressants (TCAs): are non-specific monoamine reuptake inhibitors that increase the availability of serotonin, noradrenaline and dopamine. Some also have anticholinergic effects that may affect the anti-cataplegic properties.

   Dosage: between 10 and 150 mg, generally lower doses than those used as an antidepressant are needed to be effective in controlling cataplexy and its effects are very fast (only a few days) compared to the effects as an antidepressant. Several antidepressants have been tried, but clomipramine has been the most commonly used TCA.

   Safety: if the antidepressant is abruptly discontinued, an elevated risk of rebound cataplexy or "status cataplecticus" has been observed.

It should be noted that the Class I evidence for Narcolepsy with cataplexy (NT1) and without cataplexy (NT2) was obtained for the previously described psychostimulant drugs and for sodium oxybate. Oxybate therefore remains the first-line treatment of choice in NT1, especially for the control of cataplexy, although as we will see below, pitolisant demonstrated efficacy similar to oxybate in patients with NT1 in a recent randomised placebo-controlled clinical trial.

2.3 Treatments currently being developed

1. Pitolisant (Wakix®): as we have explained previously, this is an inverse agonist of the histamine H3 receptor (competitive H3R antagonist) that acts at presynaptic level activating histaminergic neurons (it blocks the inhibitory effect of histamine on the release of endogenous histamine and improves the release in the entire central nervous system) favouring wakefulness and also with an additive anticataplectic effect. It was designated an Orphan Medicinal Product by the European Medicines Agency in 2007 and confirmed again in 2016 [5]. It was also granted orphan drug status by the FDA in 2010. It has been approved by the European Medicines Agency (EMA) in 2016 and by the FDA in 2019 for NT1 and NT2.

Dosage: single morning dose (9–36 mg/day) orally. 4.5 mg and 18 mg tablets. In Spain it is dispensed in hospital pharmacies. The guideline approved in Europe is as follows:

1st week: the starting dose is 9 mg divided into two 4.5 mg tablets to be administered at the same time in the morning.

2nd week: increase to one 18 mg tablet or consider decreasing the dose to 4.5 mg.

3rd week: the recommended dose is 36 mg, consisting of two 18 mg tablets.

Pharmacokinetics: it is rapidly absorbed, with a maximum plasma concentration (tmax) of 3.5 h and an elimination half-life (t1/2) of approximately 10–12 hours. It is metabolised through cytochrome p450 (CYP3A4) and (CYP2D6) and eliminated in urine as inactive metabolites and 25% of the dose is excreted through exhaled air.

Safety: it has a good tolerance profile even after one year of follow-up, as well as good control of cataplexy. It should be noted that Pitolisant would be of special interest to patients with cardiovascular comorbidities. It has very low abuse potential: a study in comparison to Phentermine and a placebo in patients with a history of recreational polydrug use indicated that Pitolisant, at therapeutic and supratherapeutic doses, has a similar abuse risk to the placebo. The maximum recommended dose in moderate–severe hepatic or renal impairment is 17.8 mg and it is contraindicated in end-stage kidney disease or severe liver disease. In women of childbearing age, it is recommended that a non-hormonal method of contraception be used during treatment and 21 days after stopping treatment. Antidepressants and antihistamines (which cross the blood–brain barrier) may reduce the efficacy of Pitolisant and special caution should be exercised because of the narrow therapeutic margin when using certain treatments such as immunosuppressants.

In a clinical trial, it was observed that pitolisant did not modify the pharmacokinetic profiles of oxybate or modafinil, and oxybate showed no relevant effect on pitolisant. However, a reduction in exposure was observed with modafinil, although no dose adjustment was necessary.

Side effects: in order of frequency were insomnia (8.4%), headache (7.7%), nausea (4.8%), anxiety (2.1%), irritability (1.8%), dizziness, etc. The most serious adverse effects: abnormal weight loss and miscarriage (only 0.09%).

In the HAROSA I and II trials in patients with Obstructive Sleep Apnoea Syndrome and cardiovascular comorbidities, no changes in systolic and diastolic blood pressure and heart rate were observed [6] compared to a placebo. Supratherapeutic doses between 108 and 216 mg produce an increase in the QTc interval (10–13 ms), so caution should be exercised with those drugs that prolong QT. No ECG is required before starting treatment.

Based on our clinical experience in the Sleep Unit of the Hospital General Universitario de Castellón, below we provide the results of patients who followed the compassionate-use program prior to commercialization, to initiate treatment with pitolisant in 14 adult patients and one patient with paediatric narcolepsy who did not respond to the treatments available at that time:

8 patients diagnosed with NT1: request made on the basis of EDS, and/or persistent cataplexy.

Resistance or intolerance to available treatments (modafinil, sodium oxybate, dimethylphenidate ...)

3 patients with NT2: two patients with secondary narcolepsy (Steinert's myotonic dystrophy, Devic's neuromyelitis optica) and one patient with intolerance to modafinil and/or dimethylphenidate.

2 patients with idiopathic hypersomnia: one patient who reported severe hypersomnia and another patient in whom Modafinil was contraindicated due to adverse effects.

1 patient with obstructive sleep apnoea syndrome (OSAHS) who presented residual hypersomnolence without improvement with modafinil.

A 14-year-old boy with narcolepsy without cataplexy, as first line treatment for excessive daytime sleepiness after having been treated with methylphenidate.

Currently, all patients with NT2, idiopathic hypersomnia and sleepiness secondary to (OSA) continue to be treated and the symptoms of EDS have been corrected.

Of the patients with NT1, 3 continue to be treated and the cataplexy, which was mild–moderate, has been controlled. The other 5 patients dropped out due to lack of response because they presented severe cataplexy since being diagnosed with the disease.

In Ref. to safety and adverse events (AE): 2 patients out of the 15 who started treatment with pitolisant had conciliation insomnia. One was a patient with NT2 secondary to neuromyelitis optica, who presented this symptomatology with a dose of 18 mg, which was resolved by lowering the dose to 13.5 mg. The second patient presented NT1, in treatment with sodium oxybate 5.5 grams/night associated with pitolisant 36 mg/day that reverted when the dose of pitolisant was reduced to 22.5 mg. There was no other type of AE.

2. Solriamfetol (JZP-110): a selective dopamine and noradrenaline reuptake inhibitor (with no effect on the release of other monoamines) intended to improve drowsiness (EDS) in patients with obstructive sleep apnoea or narcolepsy [7]. In 2019, the FDA approved it for narcolepsy-associated drowsiness and the EMA is currently reviewing the marketing authorisation application for this indication. At the moment, experience with Solriamfetol is limited.

   Dose: range 75–150 mg/day of oral administration.

   Pharmacokinetics: it is rapidly absorbed, with a maximum plasma concentration (tmax) of 2 hours and an elimination half-life (t1/2) of approximately 7 hours. It is minimally metabolised and excreted mainly in the urine as an unchanged drug. Dose adjustment is recommended in moderate and severe renal insufficiency (maximum doses 75 and 37.5 mg/day, respectively). It should not be used concomitantly with monoamine oxidase inhibitors (MAOIs), which should be discontinued 2 weeks in advance.

   Adverse events: headache (11.1%), nausea (6.6%) and decreased appetite (6.8%) and less frequently dry mouth, constipation, anxiety and palpitations.

It is important to note that it is not necessary to discontinue oral and hormonal contraception as is recommended for modafinil and pitolisant.

Safety: Abuse potential was assessed in patients with a history of recreational polydrug use compared to phentermine. In conclusion, they present a similar or lower risk of abuse than phentermine and have therefore received a Schedule IV designation in the United States.

Two studies have been conducted: a first 12-week, randomised, double-blind, placebo-controlled phase IIb trial to evaluate efficacy in adults with narcolepsy with or without cataplexy. And a similarly designed phase III trial of 12 weeks duration for the treatment of obstructive sleep apnoea and EDS in narcolepsy.

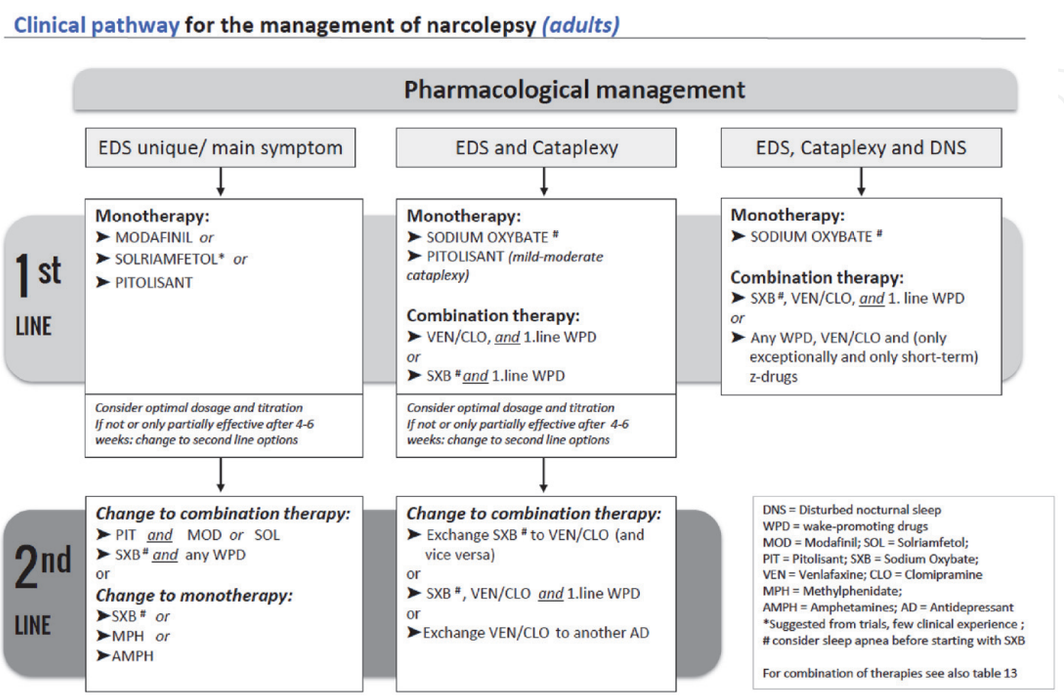
3. Summary

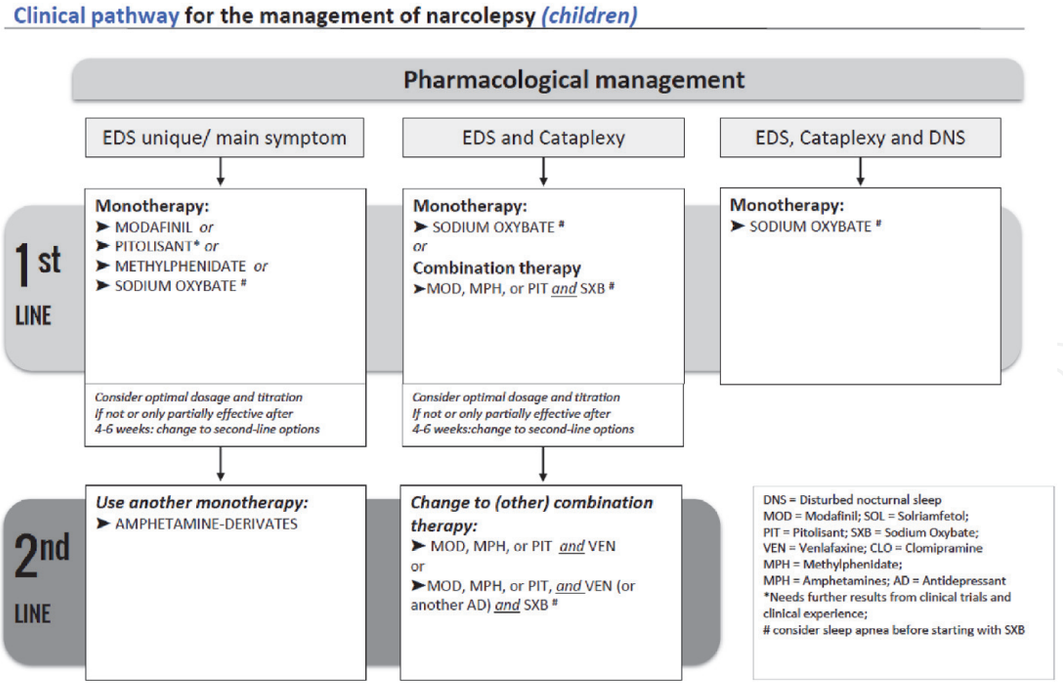
In recent years there has been a significant increase in new therapeutic options such as Pitolisant and Solriamfetol, aimed at developing better control of narcolepsy symptoms.

Pitolisant is positioned as a first-line drug of choice for the management of symptoms such as excessive daytime sleepiness and cataplexy, in addition to being able to be used in both adults and children, and is the only one of the new therapeutic lines whose use is considered in paediatric narcolepsy. With regard to the usual treatments, as we have already mentioned, a clinical trial with sodium oxybate in the paediatric population has also been published recently.

Solriamfetol would be included in the first line treatment of excessive daytime sleepiness (EDS) in adults. In addition, the use of both Pitolisant and Solriamfetol would be advisable as a first-line strategy, in combination with the other anticataplectic drugs for a better control of cataplexy. Both can be used in combination for second-line treatment of EDS.

Pharmacological strategy of the European guidelines for the treatment of narcolepsy [8]:





3.1 Therapies under development

1. AXS-12 (Reboxetine): a selective NA reuptake inhibitor with a weak effect on 5-HT reuptake and no effect on DA reuptake. It is a drug initially intended for the treatment of depression. It is currently in development for the treatment of cataplexy and EDS associated with narcolepsy. The FDA has designated it as an orphan drug. Preclinical data have shown a reduction in cataplexy and sleep attacks in narcoleptic mice (attributed to an effect on NA reuptake inhibition). Since noradrenaline reuptake inhibitors are very effective for the treatment of cataplexy, it will probably be used to control cataplexy and become an alternative for patients who cannot take oxybate and pitolisant. One of the possible indications could be the treatment of patients with major depressive disorder and narcolepsy [8].

   Pharmacokinetics: Rapidly absorbed after oral administration (tmax) approximately 2–4 h and eliminated mainly through metabolism by CYP3A4.

   Safety: A Phase II, randomised, double-blind, placebo-controlled, crossover study is underway in participants with narcolepsy with cataplexy and EDS.

   Adverse events: dry mouth, hyperhidrosis, constipation and restlessness were reported in a 2-week pilot study. Post-marketing experience (with indication for depression) has reported other AEs such as: insomnia, dizziness, dry mouth, constipation, nausea and hyperhidrosis.

2. THN102 (modafinil/flecainide): this is the association of the inhibitory effect of astroglial connexins associated with a dopamine reuptake inhibitor, improving the coupling of astroglial cells, since it is believed that astrocytes and astroglial connexins are involved in the regulation of sleep and wakefulness. In the cortex, modafinil would act by increasing the expression of messenger RNA (mRNA) and the connexin 30 protein, one of the main astroglial connections. On the other hand, flecainide has an inhibitory effect on astroglial connexins. In preclinical studies, flecainide enhanced the

procognitive and wakefulness-promoting effects of modafinil in mice and modafinil/flecainide coadministration decreased the number and duration of direct transitions to REM sleep in orexin-inactivated mice.

Pharmacokinetics: not specifically reported. Data from mouse models indicate that flecainide did not affect the pharmacokinetic parameters and bioavailability of modafinil.

Efficacy: evaluated in a three-way, phase II, double-blind, randomised, placebo-controlled, crossover trial in 48 adults with narcolepsy with or without cataplexy for 2 weeks. Participants received modafinil/flecainide 300/3 mg, modafinil/flecainide 300/27 mg and modafinil 300 mg/placebo in each of the three periods. Preliminary results indicated no difference in efficacy between THN102 and modafinil alone. This could be due to an over-representation of participants with severe narcolepsy who presented a low response to modafinil.

Safety: no safety data currently available.

The potential role of THN102 in narcolepsy is unclear. The narcolepsy study was stopped due to lack of efficacy in the phase II study.

3. Divalproex sodium: increases exposure to sodium oxybate, allowing the dose of sodium oxybate to be decreased. Concomitant use of other central nervous system (CNS) depressants may intensify the central depressant effects of sodium oxybate.

4. FT-218: (Controlled-release sodium oxybate): acts on the GABA-B agonist receptors and uses Micropump technology®, a microparticle platform that can be used to achieve prolonged or delayed delivery of orally administered small-molecule drugs. The dosage would therefore be only once a night. The FDA has currently designated it as an orphan drug.

   Dosage: 4.5–6-7.5 or 9 g once a night.

   Pharmacokinetics: A Phase III trial evaluating the bioavailability of FT218 compared to immediate-release sodium oxybate (Xyrem®) in healthy volunteers is currently under development.

   Efficacy: of FT218 is being evaluated in another phase III, multi-centre, double-blind, placebo-controlled REST-ON trial (Randomised study Evaluating the efficacy and SafeTy of a Once Nightly formulation of sodium oxybate). Adverse effects are expected to be similar to immediate-release sodium oxybate.

5. JZP-258: is a new low sodium oxybate product (combination of sodium oxybate, potassium oxybate, calcium oxybate and magnesium oxybate) and has 92% less sodium. It would therefore be more advisable for use in patients with hypertension, heart failure or renal failure). In addition, it is tolerated better because it does not leave an unpleasant taste and does not have as many gastrointestinal effects as sodium oxybate.

   Pharmacokinetics: lower Cmax, longer tmax and similar AUC were obtained compared to sodium oxybate.

   Efficacy: evaluated in a phase III multi-centre, randomised, phase III withdrawal study.

Adverse events: reported most frequently were headache (22.4%), nausea (13.4%) and dizziness (11.4%); treatment-related SAEs were reported in only two participants. In addition, a 24-week open-label safety study is underway.

6. SUVN-G3031: is an inverse agonist of the histamine 3 receptor (H3R) that is in phase II development.

   Anticataplectic and wakefulness-promoting effects have been observed in rodents, increasing acetylcholine, histamine, DA and NA levels in the cortex, but without altering DA levels in the striatum or nucleus accumbens, which might suggest a lower abuse potential. No adverse effects on ECG parameters, fertility, embryofoetal development or CNS safety concerns have been reported in preclinical studies.

7. TAK-925: is a selective agonist of the hypocretin/orexin 2 receptor (ORX2R). It has demonstrated wakefulness-promoting effects in wild mice and primates. It also increased wakefulness time and improved wakefulness fragmentation and cataplexy and attenuated weight gain in ORX/ataxin-3 transgenic mice without changing food intake. If the results are confirmed, it could be targeted to treat a wide range of symptoms without causing ORX2R desensitisation.

   Pharmacokinetics: A Phase I study with single ascending doses (7–240 mg, administered as an intravenous infusion over 9 hours) has been conducted in 36 healthy volunteers, evaluating safety, pharmacokinetics and tolerability. In addition, another placebo-controlled crossover study was carried out in 14 NT1 patients where doses of (5, 11.2 and 44.8 mg, as a 9 h intravenous infusion) were administered [9]. The exposure was proportional to the dose over the dose range studied and t1/2 was less than 2 h; PKs were similar in healthy volunteers and NT1 patients.

   Adverse events: increase in blood pressure and HR. Improved mean sleep latency as determined by the TMW maintenance of wakefulness test in NT1 patients (from 22.4, 37.6, and 40.0 min with TAK-925 5, 11.2, and 44.8 mg, respectively, compared to 2.9 min with placebo.

8. TAK-994a selective hypocretin/orexin 2 receptor agonist (administered orally), has been shown to increase wakefulness and reduce cataplexy-like episodes in mouse models and to improve wakefulness fragmentation in these models.

4. Future therapies

A. Administration of orexin peptides (ORXR2) as effective stimulants may also be of interest to decrease EDS in patients with NT2 and idiopathic hypersomnia and associated conditions with normal CSF ORX levels.

B. Neural transplantation of orexin: Hypocretin-1 does not cross the blood–brain barrier. In animal models, it has been observed that intraventricular administration of ORX suppressed narcolepsy symptoms in mice subjected to ORX/ataxin-3 neuronal ablation. Intrathecal ORX administration via an implantable pump was also proposed as a therapy for refractory patients with NT1. Unfortunately, these models have not been developed in humans, so the development of peptide analogues of hypocretin that cross the blood–brain

barrier and act centrally via non-invasive routes of administration would be the most viable future therapy. On the other hand, a non-invasive method through intranasal administration of ORX, directing the drugs to the brain along the olfactory and trigeminal neural pathways, could also be of interest as it has been shown to decrease the amount of REM sleep and REM sleep is more stable, but no effect has been observedin regard to drowsiness. At present, intranasal hypocretin is not a viable treatment [10, 11].

C. Transformation of stem cells into orexin neurons: in rats, patches have been transplanted with posterior hypothalamus cells causing a reduction in drowsiness. Hypothalamic neurons have been generated in vitro from embryonic stem cells and pluripotent stem cells. This therapy could therefore become a final option for very severe and drug-resistant narcoleptic patients.

D. Orexin-based gene therapy: the use of recombinant viruses has been postulated. Studies have been promising (improving symptoms in narcoleptics). More studies are needed to establish the safety and efficacy of the technique, but they could be future therapies.

E. Immune therapy: as mentioned above, by the time a patient is symptomatic, ORX neurons may already be irreversibly destroyed. A recent article used a highly sensitive method to detect rare T cell populations and found the presence of CD4+ T cells that recognised prepro-ORX peptide epitopes in NT1 and that have not been observed in healthy controls. Based on the model of immune-mediated hypocretinergic neurone destruction, immunotherapy applied at the onset of the disease to prevent neuronal death was postulated as a treatment. To date, several studies have been conducted implementing this methodology in narcoleptics, but the existing data are based on a very small number of patients, and they are uncontrolled case studies. Some of the different therapeutic strategies that have been tried include: corticosteroids, intravenous immunoglobulins (IVIG), plasmapheresis, rituximab, etc. with variable efficacy, possibly due to the lack of safety if the treatment was applied at the onset of the disease and not when the situation was already irreversible. A study has been published of a patient who received treatment with IVIG for 15 days right at the onset of the disease, completely reversing the clinical symptoms (EDS and cataplexy) and normalising the levels of ORX in CSF, which were initially undetectable. Regarding new immune-based therapies. A recent review has been published, presenting several treatments targeting NT1, including: Natalizumab, Fingolimod, Abatacept, monoclonal antibodies targeting T or B cells, TNF alpha inhibitors, Anakinra, antigen-specific therapies or Cyclophosphamide. In another study they propose that for future trials with immunotherapy, patients should have a specific profile with clear selection criteria, benefiting above all, those with ongoing inflammatory or autoimmune processes [12].

5. Conclusion

Recent years have seen a resurgence of new lines of therapy for the treatment of narcolepsy. These new future prospects predict a promising prognosis in terms of being able to guarantee a better quality of life for patients with narcolepsy, perhaps even a possible correction of the hypocretin deficit, completely resolving the symptomatology and achieving complete control of the disease. Future lines of research

should be based on the discovery of new reliable biomarkers to be able to identify the patients who best respond to immunomodulators and, of course, on the discovery of the underlying mechanisms related to the destruction of hypocretin-producing neurons. On the other hand, we have highlighted the lack of clinical trials in some specific groups, such as pregnant women or the elderly population. In addition, further trials in patients with common comorbidities such as psychiatric disorders or cardiovascular risk factors would be of interest.

Conflict of interest

The authors declare that they have no conflicts of interest.

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