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Sleep disorders in neurology

French consensus. Management of patients with hypersomnia: Which strategy?

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INFO ARTICLE

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ABSTRACT

Central hypersomnias principally involves type 1 narcolepsy (NT1), type 2 narcolepsy (NT2) and idiopathic hypersomnia (IH). Despite great progress made in understanding the physiopathology of NT1 with low cerebrospinal fluid hypocretin-1 levels, current treatment remains symptomatic. The same applies to NT2 and IH, for which the physiopathology is still largely unknown. Controlling excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis and disturbed night-time sleep are key therapeutic targets in NT1. For IH and NT2, reducing EDS is the main objective. Based on European and American directives for the treatment of narcolepsy, we propose French recommendations for managing central hypersomnias as well as strategies in the case of drug-resistance. Stimulating treatments target EDS, and Modafinil is the first-line treatment. Other stimulants such as methylphenidate, pitolisant, and exceptionally dextro-amphetamine can be prescribed. Selective serotonin and noradrenaline reuptake inhibitor antidepressants are effective for the management of cataplexy in NT1. Sodium oxybate is an effective treatment for several symptoms, including EDS, cataplexy and disturbed night-time sleep. Treatment of central hypersomnia must also take into consideration frequent cardiovascular, metabolic and psychiatric comorbidities, particularly in NT1. New therapies are currently under study with the development of new stimulants and anti-cataplectics. The next few years will see innovative emerging therapies, based on a physiopathological approach, aiming to restore hypocretinergic transmission or to interrupt the autoimmune processes causing the loss of hypocretin neurons.

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1. Introduction

Central hypersomnias principally involve type 1 narcolepsy (NT1, hypocretin deficiency syndrome, characterised by excessive daytime sleepiness or EDS and cataplexy), type 2 narcolepsy (NT2, narcolepsy without cataplexy with normal hypocretin-1 in the cerebrospinal fluid), and idiopathic hypersomnia [1–5]. Excessive daytime somnolence (EDS) is often the most disabling symptom and the most frequent reason for consultation. Cataplexy may be a highly disabling NT1-specific symptom, and the best clinical diagnostic marker of the disease. Other symptoms such as sleep-related hallucinations, sleep paralysis, even if non-specific to narcolepsy, are frequent and found in 50% of patients with narcolepsy but rarely in patients with IH. To date, no cure is available to treat central hypersomnias, and treatment is purely symptomatic and therefore long term, especially for patients suffering from NT1. European and American directives for the treatment of narcolepsy were developed a few years ago [6,7]. Stimulant treatments target EDS, antidepressants target cataplexy, and sodium oxybate acts on both symptoms. While the ANSM, the French National Agency for Drug Safety, and the EMA, the European Drug Agency, approve the use of some pharmacological stimulants (market approval/product licence), other molecules are prescribed off-label due to their recognised usefulness in treating the symptoms of central hypersomnia. The management and follow-up of these patients should ideally be conducted in a Hypersomnia-Narcolepsy Reference or Competence Centre.

2. Narcolepsy

2.1. *Treatment of excessive daytime sleepiness*

2.1.1. *Non-drug measures*

Healthy sleep behaviour measures (implementation of regular sleep schedule, avoidance of sleep deprivation situations) and programming planned naps (often short < 15 minute naps) can reduce EDS [8]. Due to the chronic character of the disease (notably for type 1 narcolepsy), educating patients about the disease, its prognosis and treatment is essential to good management.

Recommendations

- *Programming planned naps is effective in reducing EDS in narcolepsy (grade C).*
- *Programmed planned naps and adopting healthy sleep habits are recommended in addition to pharmacological treatment of EDS in narcolepsy (grade C).*

2.1.2. *Pharmacological treatment*

Modafinil (MODIODAL®), methylphenidate (RITALINE®), and more recently pitolisant (WAKIX®) benefit from French Drug Authority approval with the indication ''excessive daytime sleepiness'' in narcolepsy with or without cataplexy (type 1 or 2). Sodium oxybate (XYREM®) benefits from French Drug Authority approval in the treatment of narcolepsy in adult patients with cataplexy. Dextroamfetamine (DEXAMFETAMINE®) can be prescribed in special conditions after a specific authorisation and after other prescribed treatments have been unsuccessful. Prescriptions of mazindol (DIMINEX®) followed the same rules but came to an end in 2016. No other treatment has French Drug Authority approval for this indication.

2.1.2.1. *Modafinil.* Modafinil (MODIODAL®) is the first-line treatment for EDS. Its mechanism of action is poorly understood, but principally acts by increasing the extracellular concentration of dopamine by inhibiting its transporter. The dosage usually prescribed is between 200 and 400 mg/d, taken once or twice a day, with doses up to 600 mg prescribed in some cases although this is off-label.

Four major level 1 studies have demonstrated the efficacy of modafinil on EDS at doses between 200 and 400 mg [9–12]. Modafinil is, in general, well tolerated, with main side effects being headaches, irritability, nausea, tachycardia and insomnia. Before treatment, a clinical interview to determine personal and family history of cardiac disease and sudden and unexpected death, a physical examination and an ECG are necessary to rule out arterial hypertension, cardiac arrythmias or pre-existing cardiac disease. Three-monthly follow-up of cardiac frequency and blood pressure is adequate. A cardiac ultrasound or a Holter ECG is not required before or during modafinil treatment, except in the case of cardiac symptoms such as dyspnoea, tachycardia, chest pain, or limb oedema.

Modafinil is an enzymatic inductor of P450 cytochrome activity. Hence, it increases the metabolism of oral contraceptives. Consequently an oral contraceptive containing at least 50 μg of ethinylestradiol must be prescribed if modafinil is used. The use of modafinil is not recommended during pregnancy but can, exceptionally, be prescribed on a case by case basis. A benefit-risk analysis should be carried out in a Reference Centre taking into account the current recommendations of the CRAT (the French Reference Centre for Teratogenic Drugs).

Recommendations

- *Modafinil is effective in the treatment of EDS in type 1 narcolepsy (grade A).*
- *Modafinil constitutes the first-line therapy for this indication (grade C).*
- *Assessment prior to therapy includes establishing personal and family cardiovascular history as well as an electrocardiogram (grade C).*
- *Blood pressure and heart rate should be followed up every three months (grade C).*
- *An electrocardiogram or trans-thoracic cardiac ultrasound are not recommended in routine follow-up in the absence of clinical indications (grade C).*

2.1.2.2. *Methylphenidate.* Methylphenidate (RITALINE®, RITALINE LP®, CONCERTA LP®, QUASYM LP®, MEDIKINET LP®)