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Mini-Symposium: Pediatric Hypersomnolence Symposium

Treatment of narcolepsy and other organic hypersomnias in children

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Educational aims

The reader will be able to:

- Understanding the management steps for narcolepsy and other forms of organic hypersomnias.
- Understanding indications, dosing and potential adverse effects of various drugs.
- Appreciating emerging therapies for pediatric hypersomnia disorders.

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SUMMARY

The comprehensive management of chronic disorders such as hypersomnias of childhood requires combining life-style changes with rational pharmacotherapy that is based on treating the symptoms that are most bothersome, the age, comorbidities, and metabolic and endocrine status of the patient. The excessive sleepiness of narcolepsy and idiopathic hypersomnia is best treated with dextroamphetamine or methylphenidate preparations or modafinil/armodafinil. Cataplexy treatment requires sodium oxybate, tricyclic agents, selective norepinephrine reuptake inhibitors or selective serotonin reuptake inhibitors. Sodium oxybate is approved only for adults, thus its use in children is only on an off-label basis. Dual therapy, with both anti-cataplectic and stimulant medications may be required, as is close monitoring for treatment-emergent side effects.

Introduction

This manuscript will discuss treatment measures directed towards narcolepsy types 1 and 2, idiopathic hypersomnia and Kleine Levin syndrome (KLS). The treatment of daytime sleepiness related to narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia is similar; hence the discussion is for the most part combined for these disorders. Kleine Levin syndrome is addressed separately owing to likely different pathophysiologic mechanisms from other hypersomnia disorders.

Narcolepsy

General treatment measures

Since narcolepsy is a lifelong disorder, it is imperative that the diagnosis be firmly established on the basis of clinical features, nocturnal polysomnogram and the Multiple Sleep Latency Test (MSLT). At the time of starting treatment, it is necessary to reiterate the long-term management goals to the parents and patient – specifically for narcolepsy, sleep specialists may be able to enhance alertness, diminish cataplexy, enhance daytime function and improve the overall quality of life, but there is no cure.

General, supportive measures directed at changes in life-style, and the treatment of comorbidities such as depression, anxiety, and obesity are equally as important as pharmacological therapy. Approximately 20 per cent of type 1 narcolepsy patients may have coexisting major depression, and 10 per cent have an anxiety disorder [1,2]. The mood and anxiety disturbances are consequent to the underlying neurotransmitter imbalance or from life stresses that children with narcolepsy frequently encounter at school, home or socially – for instance, children with cataplexy may avoid social events such as attending birthday parties. Supportive *psychological counseling* helps both the patient and the parents – a very low threshold should be kept for providing this intervention. Referral to support groups such as the Narcolepsy Network (www.narcolepsynetwork.org) and Wake Up Narcolepsy (www.wakeupnarcolepsy.org), that enable interaction with other affected

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patients and families, should be encouraged. Interaction through social media may also help patients connect with and receive support from like-minded affected individuals.

Physical exercise is a good counter-measure for sleepiness, and should be encouraged to occur on a daily basis. It may also help manage the weight gain that is common at the onset of type 1 narcolepsy. In hypocretin knock-out mice, wheel running increased the total amount of wakefulness, although cataplexy also increased [3]. This animal study suggests that in clinical practice, in order to derive optimum benefit from physical exercise, one might need to optimize the control of cataplexy.

Avoidance of driving or working near sharp, moving machinery should be discussed. It is also important for patients to maintain regular sleep wake schedules and receive adequate sleep at night. Further, the use of alcohol should be discouraged as it tends to further disrupt sleep.

Vocational guidance about choosing a profession becomes important as teens graduate from high school and transition to college or other forms of higher education. Young people with narcolepsy seem best suited for professions that involve standing and moving around rather than desk work (author's opinion). This author has also come across several patients who have prudently decided to become elementary school teachers, physical therapists or store managers. The role of the sleep physician in proving this type of guidance cannot be over emphasized – it is our responsibility.

Medication management during pregnancy is now being encountered more by pediatric sleep specialists. Methylphenidate, dextroamphetamine, modafinil, armodafinil, sodium oxybate, fluoxetine and, venlafaxine have teratogenic potential in animal studies. They have been placed by the Food and Drug Administration (FDA) in category C, which includes drugs that have *"shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in human, but potential benefits may warrant the use of the drug in pregnant women despite potential risks*".

Thorpy et al. [4] one reasonable bit of advice for patients would be to ensure a planned pregnancy, after discussion with the sleep specialist and obstetrician. Given their potential teratogenic effects, some sleep specialists recommend stopping narcolepsy medications prior to conception. The symptoms of narcolepsy may be managed with conservative, non-pharmacological measures during the pregnancy. This suggestion about managing narcolepsy without drugs during pregnancy is based on clinical experience of sleep specialists rather than controlled clinical trials, but may need to be modified based upon the needs of the individual patient. For ethical reasons, controlled clinical studies have not been conducted in humans. With regard to breast-feeding, it should be avoided when the mother is taking narcolepsy medications as these drugs have a low molecular weight and tend to cross into breast milk [4].

Pharmacological therapy

Before starting drug treatment, it may be helpful to ask the patient what symptom is most bothersome -some narcolepsy patients are more bothered by cataplexy and others by sleepiness. The symptom that is most incapacitating is to be targeted first. Ancillary symptoms can be addressed gradually in a step-wise manner. Monotherapy is rarely effective in narcolepsy, and it is a common practice to combine medications for daytime sleepiness and cataplexy. Patient education efforts directed by the nursing staff are also helpful. The potential side effects of medications should be discussed. It should be emphasized that medicines are only modestly effective in improving symptoms of narcolepsy. Combining pharmacological therapy with lifestyle measures discussed earlier in this chapter is essential. The Fig. 1 provides a broad scheme for pharmacotherapy while the table provides additional drug-related information.

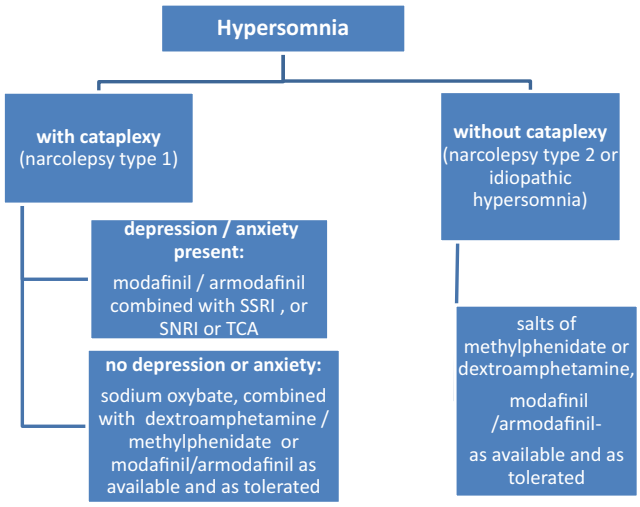

Fig. 1. Scheme for pharmacotherapy in hypersomnia. SSRI = selective serotonin reuptake inhibitor. SNRI = selective norepinephrine reuptake inhibitor. TCA = tricyclic agent.

Drugs for daytime sleepiness

There is no FDA – approved medications for children and adolescents for daytime sleepiness. The use of medications in the pediatric population therefore is on an empiric, off label basis.

Salts of amphetamine and methylphenidate are considered traditional stimulants. They are also used in the treatment of atten tion-deficit/hyperactivity disorder in children and adults [5]. D-amphetamine is four times more potent than l-amphetamine in enhancing alertness, but both enantiomers are equipotent when it comes to their rapid eye movement (REM) sleep suppressing property [6]. Methylphenidate and its derivatives are structurally similar to amphetamines. The mechanism of action of both amphetamine and methylphenidate is through enhanced release of dopamine and norepinephrine from the presynaptic terminals and inhibition of their reuptake [6]. In adults, there are three level 2 studies and four level 5 studies to support the effectiveness of traditional stimulants in treating daytime sleepiness [7]. Despite its relatively long half-life, dextroamphetamine seems to enhance alertness better with twice-a-day dosing. The potential side effects of stimulants include tics, anorexia, headache, nervousness, insomnia and weight loss [8,9]. Stimulants have not been FDA-approved for use in children below the age of six years. Amphetamine and methylphenidates preparations are generally avoided in children with known heart disease [5].

Table 1 lists medications that are commonly used for treating sleepiness. Even in adults, there are no head-to-head studies comparing the efficacy of modafinil to traditional stimulants such as methylphenidate or dextroamphetamine.

Modafinil and armodafinil are "wakefulness promoting" agents. The exact mechanism of action is not known, but they increase hypothalamic levels of catecholamines and histamine –the latter significantly enhances cortical arousal [6,10]. Armodafinil is the racemic derivative of modafinil. In comparison to the approximately 4-h half-life of modafinil, armodafinil has an approximately 15 h half-life. It is about twice as potent as modafinil [11,12]. Neither drug has been approved by the FDA for use below the age of 16 years, but off-label use is common in the pediatric population.

Table 1
Commonly used drugs in hypersomnolence disorders.

Symptom	Drug	Dose	Pharmacology	Side effects
Excessive sleepiness	Dextroamphetamine – 5, 10, 15 mg capsules (DEXIDRINE SPANSULES); solution 5 mg/5 ml;	5–30 mg in 2 divided doses	Half-life 16–30 h	Nervousness, tics, anorexia, insomnia, tremor
	Dextroamphetamine-amphetamine (ADDERALL) combination	2.5 mg twice a day to 20 mg twice a day	Half-life 11–14 h	Nervousness, tics, anorexia, insomnia, tremor
	Methylphenidate 5 mg/5 ml liquid preparation; Chewable tablets 25 mg, 5 and 10 mg; 5, 10, 20 mg tablets; Oral tablet, extended release (CONCERTA) 18, 27, 36 and 54 mg; Oral capsule, extended release (RITALIN LA) 10, 20, 30, 40 mg;	10–40 mg/day in 2 divided doses	Half-life approximately 3 h	Nervousness, tics, anorexia, insomnia, tremor
	Modafinil/armodafinil	Modafinil 50–400 mg/day in 2 doses	Half-life 9–14 h	Nausea, vomiting, headache, lowering effectiveness of oral contraceptives, Stevens Johnson syndrome
		Armodafinil 50–400 mg/day in 2 doses	Half-life 10–15 h	Same as modafinil
Cataplexy	Tricyclic agents (imipramine, clomipramine, protryptiline)	10–100 mg/day for imipramine, 10–150 mg/day for clomipramine, 2.5–5 mg/day for protryptiline	Significant anticholinergic effects, half-life 10–60 h	Dry mouth, blurred vision, weight gain, tremor, constipation
	Selective norepinephrine reuptake inhibitors (venlafaxine)	37.5–75 mg once a day	Inhibition of serotonin, norepinephrine and dopamine reuptake	Increased risk of suicidality in teens, adverse interaction with monoamine oxidase inhibitors, dizziness, headache, insomnia
	Sodium oxybate (powder, mix with water)	2–8 g at night in two divided doses – 1st dose at bedtime, 2nd dose 2.5–3 h later	GABAB receptor agonism; might also have other mechanisms not fully understood	Sleep walking, enuresis, exacerbation of sleep apnea, tremor, constipation, exacerbation of pre-existing depressive tendencies
Cataplexy with coexisting depression/anxiety	Fluoxetine	10–30 mg	Selective serotonin reuptake inhibitor; half-life 4–6 days	Tremor, insomnia, worsening of depression

Once-a-day dosing in the morning has been recommended, but a split dosing strategy, with one dose in the morning and a second dose at noon, has shown better alertness as measured on the Maintenance of Wakefulness Test in adult patients [13]. In children also, therefore, we recommend twice a day dosing (morning and early afternoon); it may help children perform better with after-school activities and completing their homework. There is no rebound in hypersomnolence when modafinil/armodafinil are stopped suddenly. Both drugs are expensive, hence in the United States, starting drug therapy with methylphenidate or amphetamine preparation is sometimes recommended, with a switch to modafinil or armodafinil if the former category of drugs is ineffective, or associated with significant side effects. The potential side effects of modafinil/armodafinil include headache and the development of Stevens Johnson reaction, which has been reported in one case [14]. The latter is a delayed hypersensitivity reaction that can develop days to weeks after initiation of therapy. There is sloughing of mucous membranes, cutaneous (progressive, maculopapular generalized rash) due to a systemic vasculopathy that can progress to hepatic or renal failure. Patients with Stevens Johnson should be admitted to the Hospital and modafinil/armodafinil stopped immediately. An immunologist should be consulted for management recommendations. Modafinil/armodafinil also have the potential for lowering the efficacy of concurrently prescribed oral contraceptives. Advice may need to be sought from a gynecologist about the concurrent use of a supplemental contraceptive, such as a barrier method.

There are 14 studies (including four level 1 and two level 2) in support of the use of modafinil/armodafinil for treating the daytime sleepiness of narcolepsy [7]. With regard to children and adolescents, the only evidence is a level 4 study by Ivanenko et al. [15]. There was subjective improvement in the level of sleepiness. Also, there was objective improvement in the mean sleep latency on the MSLT, with mean sleep latency rising from a baseline of 6.6 ± 3.7 min to 10.2 ± 4.8 min with modafinil therapy.

Histamine H3 receptor antagonists: Histamine is an excitatory neurotransmitter that is secreted in the tuberomammillary region. The histaminergic neurons project widely to the cerebral cortex and facilitate arousal. Histamine receptors, specifically relevant here being the H3 receptor, exhibit a negative feedback loop, which inhibits the histamine secreting neurons, thus promoting drowsiness. Pitolisant is a H3 receptor antagonist (also called an inverse agonist) that blocks this loop of presynaptic recurrent inhibition, consequently enhancing histamine activity and alertness, as assessed on the Epworth Sleepiness Scale [16]. It has been approved for use in the European Union, and has orphan drug designation in the United States [17]. Pitolisant is not felt to have drug abuse potential.

Drugs for cataplexy

Since cholinergic mechanisms tended to increase REM sleep intrusions, the anticholinergic effect of tricyclic agents has been found to be modestly effective in controlling cataplexy [18]. The agents commonly used in include imipramine, clomipramine, and protryptiline. Potential side effects of these agents include dryness of the mouth, blurring of vision, drowsiness, orthostatic hypoten-

sion and weight gain. In light of the inherent tendency for narcolepsy type 1 patients to gain weight due to hypocretin deficiency, the use of tricyclic agents can be problematic from the overweight/obesity standpoint. Nevertheless, tricyclic agents are relatively inexpensive, and may still be considered for an initial trial, with close monitoring for side effects. The doses utilized are shown in the table.

The second category of anti-cataplexy drugs are the selective serotonin reuptake inhibitors (SSRI), such as fluoxetine [7]. They are especially helpful when there is a component of anxiety or depression. Potential side effects include nervousness, insomnia and tremor. Further, there is a "black box" warning about increased suicidal ideation with SSRI agents in adolescents. Abrupt discontinuation of antidepressants (both tricyclics and SSRIs) may trigger status cataplecticus with almost continuous cataplexy episodes [19].

The third category of anti-cataplexy agents includes selective norepinephrine reuptake inhibitors like venlafaxine. The utility of venlafaxine in cataplexy management is based on isolated case reports and expert opinion only, based upon its good benefit: risk ratio [20].

Sodium oxybate or gamma hydroxy butyrate (Xyrem) is the fourth drug category. It is a gamma-hydroxybutyric acid B-subtype (GABAb) receptor agonist. It is available for restricted distribution through the Xyrem Success Program®. Presently the drug has an orphan drug designation. Following oral administration, the average time to peak concentration (Cmax) is 0.5–1.25 h. The elimination half-life is 0.5–1 h. There may be a non-linear increase in concentration of the drug after oral administration. Ingestion after a high-fat meal may lead to delayed absorption. It is metabolized via the Krebs tricarboxylic acid and beta oxidation [21,22]. As succinic semialdehyde dehydrogenase is an enzyme in the Krebs cycle, a contraindication from the metabolic standpoint for sodium oxybate use is congenital succinic semialdehyde dehydrogenase deficiency, as it may lead to toxicity from drug accumulation [23]. A urine organic acid assay may help exclude this rare inborn error of metabolism, if clinically suspected. The starting dose of sodium oxybate should be reduced by one half in the presence of liver disease. The exact mechanism of action of sodium oxybate is not known, but it likely stabilizes sleep architecture and decreases the number of night awakenings, with consequent improved daytime alertness and fewer REM sleep intrusions onto wakefulness, thereby reducing cataplexy episodes. There is a modest improvement in daytime alertness that is synergistic to that occurring from wake promoting agents or stimulants [24].

Because of the drug abuse potential with sodium oxybate, a detailed patient education session is recommended prior to initiation of drug therapy. Families should ensure they are available to receive the monthly shipment when it arrives at home, and also that it is securely locked up. Besides physicians, it may be helpful to involve nursing staff in this educational effort. The drug is available only in liquid form and the solution is salty to taste, which may be unpalatable to small children. The dose varies from 2 g nightly provided in two divided doses to 8 g nightly, in two divided doses. The first dose is administered right at bedtime, with the second dose being provided 2.5–3 h after the first dose. Potential side effects include nausea, vomiting, headache, somnolence (these are the most common side effects, occurring in 4–8% of subjects), followed by dizziness, weight loss, nocturnal enuresis, worsening of sleep apnea, sleepwalking, tremor and constipation. The drug may result in respiratory depression. By far the most significant concern is that of potential worsening of pre-existing depression/anxiety -it has been reported only in isolated instances [25]. Nevertheless, it is important to screen for pre-existing depression or anxiety and keep a low threshold for arranging supportive psychotherapy. If there is exacerbation of depression, consideration should be given to discontinuing sodium oxybate. Of note, this treatment-emergent depression seems to generally occur in the initial phases of drug therapy.

Sodium oxybate has a beneficial effect upon both cataplexy and daytime sleepiness. Presently, the drug is approved for use only in adults, though off-label use in children has been reported [25–28]. There is an ongoing clinical trial about the use of sodium oxybate and childhood narcolepsy – cataplexy that is sponsored by Jazz Pharmaceuticals (Jazz 13-005). Of note, sodium oxybate is recommended only when there is coexisting cataplexy. In our retrospective series of 15 children with a mean age of 11 (range 3–17) years, who were on a mean maintenance dose of 5 ± 2 g for a mean duration of 33 (range 3–90) months, excessive daytime sleepiness was reduced in 87% of the patients, with Epworth Sleepiness Scores dropping from a baseline median of 18 to a post-therapy median of 12 [27]. The median frequency of cataplexy attacks was also reduced from a baseline >38/week to <1/week after therapy. Limitations of this study are its small sample size, and potential parental recall bias. Strengths are that all subjects were uniformly evaluated and managed in our sleep clinic by a team of sleep specialist and nursing staff, and that all subjects had *bona fide* diagnoses of narcolepsy with cataplexy (type 1 narcolepsy).

Immunotherapy

Given the possible role of an immune-mediated disturbance in triggering narcolepsy type 1, some investigators have tried modulating humoral immunity soon after disease onset with intravenous immunoglobulin G (IVIG). The results have been inconclusive. Dauvilliers et al. treated four type 1 narcolepsy, CSF hypocretin-deficient patients with IVIG shortly after disease onset and noted a clear improvement in frequency and severity of cataplexy for up to seven months after therapy, without the aid of anti-cataplectic drugs [29]. The limitations of studies on IVIG therapy include the small sample size, open label design, and possible parental and physician observation bias towards improvement. One must also keep in mind the small possibility for spontaneous improvement of narcolepsy symptoms over time. No formal attempts have been made to target T-cell immunity in narcolepsy.

Kleine Levin syndrome

A recent Cochrane review that was conducted with the objectives of determining whether (a) pharmacological treatment for KLS was safe and effective, and (b) which drug or category of drugs was safe and effective, found that no drugs met inclusion criteria for a systematic review [30]. Agents like valproic acid, carbamazepine, lamotrigine and lithium has been used empirically to prevent recurrence of KLS episodes, with mixed results. By far the best clinical evidence for pharmacotherapy pertains to lithium carbonate. In an open-label, controlled study, the efficacy of lithium (130 cases, including 41 children) was compared to valproate acid (5 cases), contraceptive pills (5 cases) or no treatment (49 cases). The mean duration of KLS episodes (8 ± 20 vs. 2 ± 13 days), longest duration of episodes (18 ± 35 vs. 5 ± 13 days), and the frequency of episodes per year (2.6 ± 2.9 vs. 1.3 ± 2.78) decreased significantly in the lithium-treated group as compared to the untreated patients [31]. Side effects were noted in 50% of patients, were minor, and consisted of tremor, polydipsia, subclinical hypothyroidism or diarrhea.

Idiopathic hypersomnia

The excessive sleepiness in idiopathic hypersomnia generally starts in the second or third decade. This chronic sleepiness may

less severe than that seen in narcolepsy, but nevertheless, remains significantly incapacitating. Salts of amphetamine and methylphenidate and modafinil/armodafinil are the key agents used, in doses similar to those for narcolepsy [7]. Some patients with chronic hypersomnia syndromes have been reported to exhibit a positive allosteric modulator for ɣ aminobutyric acid (GABA) A receptors in the cerebrospinal fluid [32]. Clarithromycin was shown in this study to be a negative GABA-A modulator, and to alleviate daytime sleepiness in some patients. Large scale, randomized studies, however, are lacking.

Emerging therapies for hypersomnia disorders

The reader is referred to a recent, excellent review on this topic [33]. Progress has been hampered by the fact that hypocretin 1 or hypocretin 2 receptor analogs do not readily cross the blood-brain barrier. Development of hypocretin-1 analogs which cross the blood-brain barrier and do not have systemic side effects are still being explored. Asahi et al. discovered that the entire hypocretin protein is not necessary for biological activity, but rather that it is the C-terminus of hypocretin-1 and hypocretin-2 that is critical for passage into the brain [34]. Lang et al. performed multiple amino acid substitutions within the sequences of orexin A (hypocretin 1) and orexin B (hypocretin 2). They found that for orexin A, only the basic amino acids within the segment of residues numbered 6–14 were essential for activation of the hypocretin receptors [35]. Hopefully, their finding will lead to the development of smaller molecules that cross the blood-brain barrier. Gene therapy in the mouse model utilizing a replication-defective herpes simplex virus vector, and subsequently a recombinant adenovirus-associated vector, with delivery of the hypocretin gene into the lateral hypothalamus, has shown improvement in cataplexy [36,37]. Another class of agents with potential for therapy might be agonists of thyrotropin releasing hormone (TRH; 38). They may function via TRH-1 receptors that are restricted to the hypothalamus, or through the TRH-2 receptors that have a wider distribution. TRH analogs seem to reduce cataplexy in the canine model, without much effect on daytime sleepiness [38]. Histamine type 3 receptor antagonists (e.g. pitolisant) are also a class of drugs that may receive formal clinical trials, including in children [39]. The past two decades have led to incremental progress in the treatment of hypersomnia disorders -we are likely to see more rapid progress over the next 5–6 years.

Directions for future research

- Understand better the mechanism of sodium oxybate-related weight loss and its overall impact on somatic growth.
- Studies on the role of pitolisant in pediatric narcolepsy.
- Better understanding basic immunological mechanisms underlying the onset of narcolepsy-cataplexy.
- Consortium-level collaborative research on therapies for Kleine Levin syndrome.

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