REVIEW

Narcolepsy: a review

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Abstract: Narcolepsy is a lifelong sleep disorder characterized by a classic tetrad of excessive daytime sleepiness with irresistible sleep attacks, cataplexy (sudden bilateral loss of muscle tone), hypnagogic hallucination, and sleep paralysis. There are two distinct groups of patients, ie, those having narcolepsy with cataplexy and those having narcolepsy without cataplexy. Narcolepsy affects 0.05% of the population. It has a negative effect on the quality of life of its sufferers and can restrict them from certain careers and activities. There have been advances in the understanding of the pathogenesis of narcolepsy. It is thought that narcolepsy with cataplexy is secondary to loss of hypothalamic hypocretin neurons in those genetically predisposed to the disorder by possession of human leukocyte antigen DQB1*0602. The diagnostic criteria for narcolepsy are based on symptoms, laboratory sleep tests, and serum levels of hypocretin. There is no cure for narcolepsy, and the present mainstay of treatment is pharmacological treatment along with lifestyle changes. Some novel treatments are also being developed and tried. This article critically appraises the evidence for diagnosis and treatment of narcolepsy.

Keywords: narcolepsy, cataplexy, hypocretin, modafinil, gamma hydroxybutyrate

Introduction

Narcolepsy is a debilitating lifelong rapid eye movement (REM) sleep disorder. It is characterized by the classic tetrad of excessive daytime sleepiness with irresistible sleep attacks, cataplexy (sudden bilateral loss of muscle tone), hypnagogic hallucination, and sleep paralysis.[1] Other features include fragmented night sleep and automatic behavior, loss of concentration and memory, and blurry vision.[2–5] The presentation is variable in terms of symptoms and intensity over time, and only about 10% of patients concurrently exhibit all components of the tetrad.[6] There are two distinct groups of patients, ie, those having narcolepsy with cataplexy and those having narcolepsy without cataplexy.

It often coexists with other sleep disorders, like obstructive sleep apnea syndrome, periodic limb movements in sleep, REM sleep behavior disorder, and nocturnal eating disorder.[7–12]

Epidemiology

The prevalence of narcolepsy in European countries varies from 0.02% to 0.05%.[13–15] It shows marked ethnic variation in prevalence rate, being 0.0002% in Israel and 0.16% in Japan.[16,17] The varying prevalence rates may be as a result of varying disease definitions, varying study designs, varying age group inclusion in studies, or an actual varying disease prevalence due to other factors.[18,19] It has been suggested that the differences in

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prevalence may be partly related to the association between narcolepsy and the prevalence of the human leukocyte anti-gen (HLA) DQB1*0602 phenotype.[14] The subgroup having narcolepsy without cataplexy may represent 10%–50% of the narcolepsy population.[20] The estimated incidence rate is 0.74/100,000 per year for narcolepsy with cataplexy and 1.37/100,000 per year for both narcolepsy with cataplexy and narcolepsy without cataplexy.[21] The incidence rate is highest in the second decade, and the disorder is more common in men.[21]

Pathophysiology
Genetic and environmental basis
Although most cases are sporadic, there are definite cases with familial clustering. The risk of narcolepsy in first-degree relatives of patients is 10–40 times higher than in the general population.[22] There is an environmental contribution as well, as shown by reported concordance rates of 25%–31% in monozygotic twins.[23] The nature of possible environmental triggers is unknown. Nevertheless, the onset is frequently associated with nonspecific environmental factors, such as head trauma, stroke, and change in sleep-wake cycle.[23] Moreover, recent studies have shown an association with streptococcal infection,[24,25] HIN1 vaccination or infection,[26] and exposure to heavy metals, insecticides, and weed killers.[27]

HLA haplotype
More than 85% of patients having narcolepsy with cataplexy have HLA DQB1*0602, often in combination with HLA DR2 (DRB1*1501), while only half of patients having atypical, mild, or narcolepsy without cataplexy have HLA DQB1*0602.[28] Other alleles of HLA also affect the predisposition to narcolepsy with cataplexy.[29,30] Occurrence of the HLA DQB*0602 allele is not limited to narcolepsy with cataplexy, and is found in 12%–38% of the general population.[23] Moreover, there are some rare patients with definite cataplexy who do not have HLA DQB1.[31] Overall, the poor discriminatory ability of HLA typing limits its usefulness and makes it unsuitable as a routine diagnostic test.

Hypocretins
Hypocretins 1 and 2, also called orexins A and B, are two dorsolateral hypothalamic neuropeptides that function in regulating sleep-wake cycles, food intake, and pleasure-seeking behavior.[32] Amongst the areas of the brain that the neurons producing hypocretins project to are the locus ceruleus, tuberomammillary nucleus, raphe nucleus, and ventral tegmental areas.[32] These areas correspond to norepinephrine, histamine, serotonin, and dopamine secretion, respectively.

Deficiency of hypocretin could lead to malfunctioning of these systems and therefore abnormalities of REM sleep and excessive daytime sleepiness.[33] Hypocretin neurons also project to other areas of the hypothalamus, olfactory bulb, cerebral cortex, and thalamus.[34,35] The evidence for hypocretin deficiency is as follows.

In 1979, Foutz et al showed that narcolepsy was inherited in a single autosomal recessive pattern in Doberman Pinschers.[36] Lin et al later identified this as a mutated hypocretin receptor 2 gene.[37] One of the earliest reports of hypocretin deficiency in narcolepsy with cataplexy was that of Nishino et al in 2000. Their study showed that whilst seven of nine patients having narcolepsy with cataplexy had no detectable hypocretin, the neuropeptides were detectable in all their eight matched controls.[38] Further studies have supported hypocretin neurotransmission deficiency in narcolepsy with cataplexy.[31,39,40]

It was subsequently found that, unlike in animals, hypocretin deficiency in humans having narcolepsy with cataplexy was not due to mutation in hypocretin genes but rather secondary to loss of hypocretin neurons in the dorsolateral hypothalamus.[39,40] Peyron et al found only one patient (an atypical case with onset of narcolepsy with cataplexy at the age of 6 months) with hypocretin mutation among 74 patients screened for mutation. She also found global loss of hypocretin neurons in the brains of six deceased patients who had suffered from narcolepsy with cataplexy.[40] Furthermore, Thannickal et al found the number of hypocretin neurons to be reduced by 85% to 95% in association with evidence of gliosis.[39] These studies collectively suggested that the loss of hypocretin neurons in patients having narcolepsy with cataplexy might be inflammatory in nature.

Autoimmunity
The combination of HLA antigens, hypocretin deficiency, hypocretin neuron loss, the rarity of hypocretin gene mutations, and onset in the second decade of life points strongly towards an autoimmune etiology.[38–40] Initial efforts at isolating an autoantibody proved unsuccessful.[41,42] However, there was indirect evidence for an autoimmune nature of narcolepsy, such as its temporary response to steroids.[42,43] Recently, methods have been developed to demonstrate the presence of autoantibodies. There has been a demonstration of an autoantibody which disrupts colonic migrating motor complexes.[44] A Tribbles homolog 2 (*Trib2*) transcript (an autoantigen in autoimmune uveitis[45]) has been shown to be enriched in hypocretin neurons from genetically engineered mice.[46] Enzyme-linked immunosorbent analysis was used in turn to

show that sera from patients having narcolepsy with cataplexy had higher Trib2-specific antibody titers compared with those in normal controls or patients with other neurological diseases.[46] Moreover, serum from a patient having narcolepsy with cataplexy showed specific immunoreactivity with over 86% of hypocretin neurons in the mouse hypothalamus.[46] This finding was replicated in another study that found autoantibodies against Trib2 in 26.1% of patients having narcolepsy with cataplexy compared with 2.3% of healthy controls.[47] Thus, a subgroup of patients having narcolepsy with cataplexy might be suffering from anti-Trib2 autoimmune disorder. Furthermore, another study has found an association between narcolepsy with cataplexy and polymorphism in the T cell receptor alpha genetic locus (encoding the major receptor for HLA peptide presentation in any disease) in three ethnic groups compared with normal matched controls.[48]

Further support for an autoimmune etiology comes from cytokine studies showing higher interleukin-6, tumor necrosis factor-α, and tumor necrosis factor receptor p75 levels in patients having narcolepsy with cataplexy.[49–51] However, Fontana et al have suggested that immune-mediated destruction of hypocretin cells might occur independent of T cells.[52] Moreover, a lack of hypocretin is not specific to narcolepsy with cataplexy. It has also been reported in patients with Guillain–Barré and Miller Fisher syndromes.[53,54]

Loss of hypocretin-producing neurons definitely causes narcolepsy with cataplexy.[31,39,40,55] Other neurological insults, lesions of the hypothalamus or nearby structures, and global traumatic, vascular, or inflammatory insults to the brain could also cause narcolepsy.[56–58] All this could affect the levels of hypocretin either transiently or permanently (see Table 1).[55]

Diagnosis

The first step in the diagnosis of narcolepsy is history-taking from the patient and from partners, relatives, and friends. Apart from atonia and areflexia in patients having active cataplexy, the physical examination should be normal.[5] The current *International Classification of Sleep Disorders* (ICSD-2)

Table 1 Primary and secondary etiologies of narcolepsy

Hypocretin deficiency
Hypothalamic lesions
Inherited disorders eg Neimann–Pick disease type C
Brain tumors
Craniocerebral trauma
Cerebrovascular disorders
Encephalomyelitis
Neurodegenerative diseases
Demyelinating disorders

definition for narcolepsy is shown in Table 2.[59] It is based on history, polysomnography, multiple sleep latency tests (MSLT), and measurement of hypocretin levels in cerebrospinal fluid. It classifies narcolepsy into three types (see Table 2). Excessive daytime sleepiness is the most constant feature of narcolepsy[6] and measuring it accurately is important. There are a number of subjective and objective scales to measure this.

Subjective measures of excessive daytime sleepiness

The main advantages of subjective measures of excessive daytime sleepiness are that they are less cumbersome, less time-consuming, and less expensive compared with objective tests.[60] Their main drawback is their inconsistent reliability in correlating with objective tests.[61]

The Epworth Sleepiness scale was developed by Murray Johns in Australia in 1991 and was validated using 150 consecutive clinic patients with a range of sleep disorders and 30 hospital worker controls.[60] Thus, the study sample was from neither the normal population nor from the same population. The Epworth Sleepiness scale is a self-administered questionnaire in which patients rate their likelihood of falling asleep in eight different life situations.

Table 2 *The International Classification of Sleep Disorders* for narcolepsy[59]

Narcolepsy with cataplexy
Excessive daytime sleepiness almost daily for at least 3 months
Definite history of cataplexy
Diagnosis should be confirmed, whenever possible, by one of the following:
Polysomnography[a] and MSLT[b]; mean sleep latency should be $\leq$8 minutes and at least 2 SOREMS[c]
CSF[d] hypocretin level $\leq$110 pg/mL or 1/3 of mean normal controls
Hypersomnia is not better explained by another disorder or medication
Narcolepsy without cataplexy
Excessive daytime sleepiness almost daily for at least 3 months
Definite cataplexy is not present
Diagnosis must be confirmed by polysomnography or MSLT
Mean sleep latency should be $\leq$8 minutes and $\geq$2 SOREMs
Hypersomnia is not better explained by another disorder or medication
Secondary narcolepsy (narcolepsy due to medical condition)
Excessive daytime sleepiness almost daily for at least 3 months
One of the following is present: definite history of cataplexy; if cataplexy is not present, diagnosis must be confirmed by polysomnography and MSLT; mean sleep latency should be $\leq$8 minutes and at least 2 SOREMS; CSF hypocretin level $\leq$110 pg/mL
Underlying medical or neurological condition accounts for the sleepiness
Hypersomnia is not better explained by another disorder or medication

Abbreviations: MSLT, Multiple Sleep Latency Time; SOREM, sleep onset REM; CSF, cerebrospinal fluid.
Note: Reproduced with permission from American Academy of Sleep Medicine. *The International Classification of Sleep Disorders, Diagnostic and Coding Manual.* 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.

Each situation is scored from 0 to 3 and the total score varies from 0 to 24. It has been validated in different clinical situations and languages.[62–65] It correlates best with the objective tests in comparison with other subjective tests.[60]

Other subjective measures include the Stanford Sleepiness scale which rates excessive daytime sleepiness according to the subjects' perception of their sleepiness/alertness at a particular time,[60] and the visual analog scale, with which subjects indicate their levels of sleepiness along a continuous line between two points. These two tests only measure sleepiness at a particular time rather than general daytime sleepiness. Thus, their main application is in research rather than in the clinic, when they can only be used for point-in-time estimation of sleepiness.[61] Based on the above considerations, our recommended clinical subjective measure is the Epworth Sleepiness scale.

Objective measures of excessive daytime sleepiness

Polysomnography is a method which is usually performed overnight in a sleep laboratory before MSLT. Data such as breathing, movement, time spent asleep, heart rate, and electroencephalography are obtained.[18,66,67] Patients may have audio and video monitoring that could reveal snoring, sleep talking, movement, and complex behavior during sleep.[18] Thus, it can reveal the etiology of excessive daytime sleepiness and other sleep pathologies. However, performing polysomnography itself can cause disruption to sleep, potentially affecting MSLT on the following day.[18] Thus, it is recommended that at least 6 hours of sleep is recorded on the night before MSLT.[67]

MSLT is the accepted standard objective measure for excessive daytime sleepiness and has good inter-rater and intrarater reliability.[18,60,66] It consists of five scheduled naps during the day, each lasting 20 minutes and 2 hours apart. Ideally, it is carried out under conditions that best help patients to fall asleep, eg, appropriate temperature and limited stimulation. Patients are required to stay awake between each nap opportunity. During the tests, physiological data are gathered, such as time taken to fall asleep and the presence or absence of REM sleep.[18] When REM sleep occurred within 15 minutes of onset, it is termed sleep-onset REM sleep (SOREM). It is common in narcolepsy but rare in normal individuals.[18] Patients should spend at least 8 hours in bed per night in the preceding week in order to avoid erroneous results.[68] This can be confirmed using a documented sleep log or, more objectively, by the use of wrist actigraphy,[69] which entails wearing a motion-sensitive

device that uses lack of movement as a surrogate for the period spent asleep.[68]

The current ICSD-2 MSLT criteria shown in Table 2 might not be specific for narcolepsy, as shown by Allen[70] who carried out polysomnography and MSLT in 289 normal males and 267 normal females, and analyzed subject variables such as age, gender, body mass index, and HLA typing against their results on MSLT. Allen found that 4.2% and 0.4% of males and females, respectively, had two SOREMS and an excessive daytime sleepiness score of ≥11 on the Epworth Sleepiness scale (ICSD-2 criteria for narcolepsy without cataplexy, see Table 2). Furthermore, shift work, use of non-REM-suppressing antidepressants, a positive HLA DQB1*0602, decreased oxygen saturation, and a sleep diary showing a 1-hour decrease in sleep the night before polysomnography, are all related to two or more SOREMs. Therefore, several other factors and sleep disorders could result in two SOREMs, and two SOREMs are not as specific for narcolepsy as suggested by ICSD-2 criteria.

Moreover, a recent case series showed five patients diagnosed as having narcolepsy with cataplexy based on history alone (consistent with ICSD-2 criteria) but whose diagnoses were later found not to be corroborated by MSLT, and all were HLADQB1*0602 negative.[71] Thus, the diagnosis of narcolepsy irrespective of whether it is narcolepsy with cataplexy or narcolepsy without cataplexy should be based both on clinical symptoms and MSLT, and reliance on either alone may be insufficient.

The maintenance of wakefulness test is a variant of the MSLT, and measures the ability to stay awake. It consists of 4–5 trials of trying to remain awake while in the recumbent position in a dark room. This is repeated every 2 hours. Each trial is terminated if no sleep occurs after 40 minutes.[45] It is subject to the same caveats as the MSLT.[60] It has been found to measure alertness rather than sleepiness.[72] Thus, it is used to measure the ability to stay awake in individuals with jobs that require a high level of alertness and also to assess response to treatment by those with excessive daytime sleepiness in pharmacological trials,[61] rather than to make a diagnosis. The correlations between the Epworth Sleepiness scale, MSLT, and maintenance of wakefulness test are generally not impressive.[61,73]

Laboratory testing for HLA typing adds little to the diagnostic evaluation because its sensitivity is highest in patients having narcolepsy with cataplexy, a group in which additional diagnosis is rarely necessary.[18,19,28,31] Testing for hypocretin suffers from the same problem. In addition, it needs a lumbar puncture, which is an invasive

procedure with potential complications. Nevertheless, hypocretin measurement should be considered in the following situations: following an equivocal MSLT result; in patients who cannot follow the instructions for MSLT; individuals who are unable to stop medications that could affect the result of MSLT; those with complex psychiatric, neurological, or medical disorders that could compromise the result of MSLT; in the patient who gives an excellent history of narcolepsy with cataplexy but who has normal polysomnography and MSLT. In these patients, a hypocretin-1 level below 110 pg/mL in cerebrospinal fluid is highly indicative of narcolepsy, but a higher level does not necessarily exclude the diagnosis.[55]

In terms of neuroimaging, magnetic resonance studies are presently inconclusive in their findings, while magnetic resonance spectroscopy has revealed abnormal metabolism in the hypothalamus. Functional neuroimaging has revealed hypoperfusion and hypermetabolism in the hypothalamus, limbic cortex, and cerebrum.[45,74–81] Overall, neuroimaging is not useful in the diagnosis of narcolepsy.

Differential diagnoses

- Sleep deprivation, sleep apnea, idiopathic hypersomnia, recurrent hypersomnia (Kleine–Levin syndrome), restless legs syndrome, and periodic limb movement disorder.[82]
- Neurological conditions commonly associated with sleepiness and REM sleep behavioral disorder, eg, Parkinson's disease, Alzheimer's disease, and other neurodegenerative conditions, including multiple sclerosis, stroke, epilepsy, neuromuscular disorders, and structural brain disorders (bithalamic or bicortical lesions affecting midline projecting systems).[82–84]
- Medical conditions commonly associated with sleepiness, such as respiratory disorders (eg, chronic obstructive pulmonary disease and asthma), cardiac disorders (eg, congestive heart failure), renal disorders (eg, chronic renal failure), rheumatologic disorders (eg, arthritis), inflammatory disorders (eg, lupus), hepatic disorders (eg, liver failure), and malignancy.[82]
- Major psychiatric disorders sharing symptoms of functional impairment, insomnia, and hypersomnia with narcolepsy;[85] reduced REM latency is common to major episodes of depression and narcolepsy;[4,86,87] REM sleep-related disorders in narcolepsy share some psychotic features with schizophrenia, eg, hypnagogic/hypnopompic hallucination;[88–90] some features of narcolepsy, such as sleep paralysis and sleep behavior disorder, could be misinterpreted as psychosis.[91]

- Stimulants used in the treatment of narcolepsy can give rise to psychotic symptoms.[92]
- Differences between the core symptoms of psychosis and symptoms of narcolepsy have been elaborated elsewhere[93] in a study comparing 148 narcolepsy patients, 21 schizophrenic patients, and 128 healthy subjects, which found that episodes of hallucination in narcolepsy were sleep-related and posture-related, and more likely to be visual and kinetic (83% and 71% in narcolepsy, respectively, compared with 29% and 5% in schizophrenia);[93] the drawback of the study included discordant sample sizes for the groups, and the groups were also from different populations.
- In children, narcolepsy may present with only excessive daytime sleepiness, and the behavioral problem associated with excessive daytime sleepiness might be misdiagnosed as ADHD.[94]
- Malingering
- Cataplexy has been misdiagnosed as epilepsy or recurrent syncope.[95–97]

Treatment
Excessive daytime sleepiness and sleep attacks
Conventional treatments are essentially symptomatic, given that no cure has been found for narcolepsy. American Academy of Sleep Medicine classification of the levels of evidence that the authors follow in this paper are shown in Table 3.[98]

There is no randomized controlled trial to support the efficacy of nonpharmacological therapy. There is Level III evidence from a nonblinded controlled study that taking naps reduces excessive daytime sleepiness both subjectively and objectively,[99] while hypnotherapy has only Level IV evidence from a case series.[100] Furthermore, there is Level IV evidence from an open-label study that a low-carbohydrate, high-protein diet can improve wakefulness.[101] Overall,

Table 3 Oxford Centre evidence-based medicine levels of evidence[98]

Evidence level study design or description
I. Randomized controlled trial with narrow confidence intervals
II. Randomized trials without narrow confidence intervals, or with methodological problems, or cohort studies
III. Nonrandomized concurrently controlled studies or case-control studies
IV. Case-control or cohort studies with methodological problems, or case series
V. Expert opinion, or studies based on physiology or bench research

Note: Abbreviated with permission from Centre for Evidence-based Medicine. Levels of evidence 2009 [web page on the Internet]. Oxford: Centre for Evidence-based Medicine; 2009 [updated April 15, 2011]. Available from: http://www.cebm.net/index.aspx?o=1025. Accessed April 20, 2011.

nonpharmacological therapies are not adequate alone as primary therapy for narcolepsy. According to an American Academy of Sleep Medicine report: "Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy for narcolepsy."[102]

Pharmacological therapy is the mainstay of treatment for excessive daytime sleepiness. There is only Level III and IV evidence of efficacy from trials using earlier medications. The earliest medication used in the treatment of narcolepsy was caffeine, but its cardiovascular side effects prohibited its use at higher doses.[103] Other treatments included insulin-induced hypoglycemia (reported in 1952)[104] and trazodone used to supplement methylphenidate.[105] Both were case reports that led to temporary improvement. Other older treatments include mazindol, which was studied in a nonrandomized controlled trial with a short follow-up,[106] and propranolol, which was found to be effective in a case report[107] but not in an open-label study.[108] Overall, these earlier medications are no longer used routinely in the treatment of narcolepsy.

Ritanserin is a serotonin antagonist with Level II evidence from two studies. One study demonstrated an improvement in subjective daytime sleepiness but not in sleep latency on MSLT when ritanserin 5 mg/day was added to usual medication in 28 patients.[109] The second study compared ritanserin 5 mg and 10 mg with placebo in 134 patients, and did not find improvement in any of the objective measures, but did report an improvement in subjective sleep quality.[110] According to an American Academy of Sleep Medicine report: "Ritanserin may be effective treatment of daytime sleepiness due to narcolepsy."[102] Its most appropriate use is as an add-on medication.

Selegiline, a monoamine oxidase type B inhibitor, has a Level II study that demonstrated its efficacy for excessive daytime sleepiness and cataplexy.[111] The American Academy of Sleep Medicine report has expressed some reservations about its use as the preferred initial choice for treatment of excessive daytime sleepiness,[102] on account of its potential for drug and diet interactions.[102]

Traditional stimulants have been in use since the 1930s, initially caffeine and ephedrine, then amphetamines, methamphetamine, and dexamphetamine, and thereafter, their derivatives pemoline briefly and methylphenidate later.[33,103,112] At low doses, stimulants release dopamine and noradrenaline through reversal of action of their presynaptic transporters. At higher doses, amphetamine inhibits vesicular monoamine transporter 2.[113] The side effects of stimulants include irritability, headache, nervousness, palpitations, insomnia, and less often, orofacial dyskinesia, anorexia,

nausea, excessive sweating, psychosis, and myocardial infarction.[113–115] Tolerance may develop in up to one-third of patients, and these have a potential for addiction.[113] There is limited evidence to support their use. The only Level III evidence available for the efficacy of traditional stimulants was provided by Mitler et al[116] who compared eight patients with narcolepsy and eight healthy matched controls. The patients received 0 mg, 20 mg, or 40–60 mg, while the controls received 0 mg, 5 mg, or 10 mg of methamphetamine. MSLT sleep latency increased in both groups, from 4.3 to 9.3 minutes in patients and from 10.4 to 17.1 minutes in controls.

Pemoline selectively blocks dopamine reuptake. It has the potential to cause fatal hepatotoxicity.[113] On account of this, it has been withdrawn from the market and is no longer recommended.[82]

Methylphenidate, an N-methyl derivative of amphetamine, has a shorter half-life, milder side effects, and low abuse potential.[33] It has Level II and Level IV evidence for its use. A nonrandomized controlled study compared the response of narcoleptic patients allocated to four treatment groups (methylphenidate, pemoline, protriptyline, and dextroamphetamine) and one placebo group. Each group had three dose regimens. Improvement in the maintenance of wakefulness test was used as the objective measure. All doses of methylphenidate and dextroamphetamine were efficacious, while doses of pemoline <112.5 mg and doses of protriptyline up to 60 mg/day were not efficacious.[117] Honda et al reported a dose-related improvement in 92% of 106 patients treated with methylphenidate (50 patients had more than 5 years of treatment).[118] However, the improvement might not have been solely due to methylphenidate because many of the patients were also receiving concurrent hypnotics or tricyclic antidepressants. Stimulants including amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for the treatment of daytime sleepiness due to narcolepsy.[102] However, treatment should be individualized, and patients should be closely followed up to ensure efficacy and detection of side effects.[102]

Modafinil and its R enantiomer, armodafinil, are wake-promoting agents that have an additional phenyl group and an amide instead of an amine group in their chemical structure when compared with amphetamine.[113] Although the mechanism of action of modafinil is unclear, it is believed to work through the dopaminergic, adrenergic, and histaminergic systems.[33] Recently, a functional neuroimaging study has shown that modafinil increases extracellular levels of dopamine in the human brain.[119] Furthermore, another study has

shown that modafinil indirectly inhibits gamma aminobutyric acid by activating potassium ATP channels in animals.[120] Its side effects include headache, dry mouth, insomnia, nausea, vomiting, anxiety, tachycardia, palpitation, chest pain, and dermatological reactions, like Stevens–Johnson syndrome.[18] Unlike the stimulants, the efficacy of modafinil has been evaluated by double-blind, placebo-controlled, randomized trials (Level I evidence).[121–123] These trials are summarized in Table 4.

Furthermore, recent crossover, randomized, controlled trials have shown more sustained wakefulness with higher doses and superior results with a split dose of modafinil.[124,125] This occurred when the maintenance of wakefulness test was performed in the evenings rather than 1 hour after administration of medication, as performed in the randomized controlled trials shown in Table 4. Modafinil does not seem to impair night-time sleep as shown by a nonrandomized control study (Level III evidence), which compared the effect of modafinil on night-time sleep with that of dextroamphetamine in healthy volunteers.

The subjects received 100 mg and 200 mg of modafinil and 10 mg and 20 mg of dextroamphetamine in a crossover design. Dextroamphetamine reduced total night sleep time and REM sleep time, but these were unchanged in placebo and modafinil patients.[126] An open-label study (Level IV evidence) is suggestive of lack of development of tolerance to modafinil. In this study, the investigators followed up patients with narcolepsy treated with modafinil for 40 weeks. The subjects demonstrated sustained improvement in excessive daytime sleepiness and quality of life for the 40-week duration of the trial.[127]

Armodafinil 150 mg and 250 mg has also been shown by a randomized controlled trial to lead to an improvement in both morning and late maintenance of wakefulness test, sleep latency, and Clinical Global Impression of Change score when compared with placebo.[128] However, there are no direct comparisons of armodafinil and modafinil. Modafinil and armodafinil are effective for excessive daytime sleepiness, and are recommended for the treatment of excessive daytime sleepiness due to narcolepsy.[102,129]

Table 4 Double-blind randomized controlled studies of modafinil

Study	Placebo group	Treatment group 1	Treatment group 2	Outcome measures	Duration	Results	Drawbacks
US 18-center study[121]	n = 92	Modafinil 200 mg n = 96	Modafinil 400 mg as a single dose n = 95	MWT, MSLT, ESS, CGI-S	0, 3, 6, 9 weeks	MWT, MSLT, CGI-S, ESS, significantly reduced in the 2 treatment groups compared with placebo but no significant difference between the 2 treatment groups ($P < 0.001$)	Drug company sponsored Short follow-up
US 21-center study[122]	n = 93	Modafinil 200 mg n = 89	Modafinil 400 mg as a single dose n = 89	MWT, MSLT, ESS, CGI-S	9 weeks	MWT, MSLT, CGI-S, ESS, significantly improved in the 2 treatment groups compared with placebo but no significant difference between the 2 treatment groups ($P < 0.001$). Dropout rate 6%, return of EDS after discontinuation of modafinil but no withdrawal effect	Drug company sponsored Short follow-up MWT tested 1 hour after
Canadian nine-center crossover study[123]	Each of 75 patients received in order: Placebo first 2-week	Second 2-week period 200 mg of modafinil	Third 2-week period 200 mg twice daily of modafinil	MWT, ESS, patient sleep diary	6 weeks	MWT and ESS significantly improved. No significant difference between the doses, 5% dropout rate, well tolerated by patients	Drug company sponsored No washout periods MWT tested 1 hour after administering medication

Abbreviations: EDS, excessive daytime sleepiness; MWT, maintenance of wakefulness test; MSLT, multiple sleep latency time; ESS, Epworth Sleepiness scale; CGI-S, Clinical Global Impression of Change.

Cataplexy, sleep paralysis, and hypnagogic hallucination

A report of the effectiveness of imipramine in the treatment of cataplexy in 1960 led to widespread use of tricyclic antidepressants.[130] Their effect could be due to an ability to inhibit the reuptake of catecholamines, increase muscle tone, or suppress REM sleep.[131–133] Side effects include nausea, anorexia, dry mouth, urinary retention, constipation, and sexual dysfunction. Rebound cataplexy, which may be severe and prolonged (status cataplecticus), may occur on sudden withdrawal from tricyclic antidepressants.[33] There are only case reports and case series (level IV evidence) for their efficacy.[134]

Selective serotonin reuptake inhibitors inhibit presynaptic serotonin reuptake and also nocturnal REM sleep. Femoxetine has Level II evidence for treating cataplexy from a crossover, placebo-controlled study involving 10 patients. Only case series and reports (Level IV evidence) are available for other selective serotonin reuptake inhibitors.[135,136]

Other antidepressants, including noradrenergic reuptake inhibitors, such as venlafaxine, duloxetine, reboxetine, and viloxazine, are being used.[137,138] There is a Level III single-blind, crossover, placebo-controlled study of viloxazine involving 23 patients, with one dropout.[139] There are only case series (Level V evidence) available for venlafaxine and duloxetine.[137,140]

Overall, there is a lack of good evidence for the use of antidepressants in treating cataplexy. Nevertheless, according to the American Academy of Sleep Medicine report: "Based on consensus and clinical experience ... they may be an effective treatment for cataplexy, hypnagogic hallucination and sleep paralysis."[102]

Cataplexy and excessive daytime sleepiness

Gamma hydroxybutyrate, marketed as sodium oxybate, is a natural metabolite of gamma aminobutyrate (GABA), and is a $GABA_B$ receptor agonist at a pharmacological dose.[18] Its exact mechanism of action is not known, but it increases slow wave sleep, decreases arousals, and has a variable effect on latency and amount of REM sleep.[141,142] Level I evidence for the efficacy of gamma hydroxybutyrate was provided by three multicenter, randomized, double-blind, placebo-controlled studies of the short-term and long-term efficacy of gamma hydroxybutyrate.[143–145] In the first trial, 136 narcolepsy patients with 3–249 cataplexy attacks weekly were enrolled to receive 3.6 g or 9 g of gamma hydroxybutyrate or placebo taken in equal divided doses on retiring to bed and 2.5–4.0 hours later for 4 weeks. The primary measure of efficacy was a change in baseline weekly cataplectic attacks, while secondary measures included excessive daytime sleepiness using the Epworth Sleepiness scale, inadvertent daytime naps, and night-time awakenings. In total, 88% of participants completed the trials. Weekly cataplectic attacks started to decrease at a 6 g dose and became significant at a 9 g dose, and excessive daytime sleepiness was reduced at all doses, becoming significant at the 9 g dose. The frequency of inadvertent daytime naps and night-time awakenings reduced at all doses, becoming significant at the 9 g dose.[143] The second trial included 55 patients stabilized on nightly doses of gamma hydroxybutyrate for at least 6 months. They were then randomized into two arms, ie, one abruptly changing to placebo and the other continuing on gamma hydroxybutyrate for 2 weeks. Cataplexy gradually returned in those patients that were changed onto placebo over 2 weeks, but none of the patients suffered withdrawal symptoms.[144] This suggests lack of development of tolerance to gamma hydroxybutyrate.

The third trial compared the effect of nightly gamma hydroxybutyrate 4.5 g, 6 g, or 9 g with placebo in 228 adult patients over 8 weeks.[145] The patients showed a significant dose-related increase in duration of stage 3 and 4 sleep, reaching a median duration of 52.5 minutes in patients receiving gamma hydroxybutyrate 9 g nightly. Frequency of nocturnal awakening and stage 1 sleep were each significantly decreased at nightly doses of gamma hydroxybutyrate 6 g and 9 g. This study showed that gamma hydroxybutyrate decreased the sleep disruption and fragmentation that are usually associated with narcolepsy. Moreover, two Level IV (open-label) studies have demonstrated the tolerability and sustained efficacy of gamma hydroxybutyrate.[146,147]

From the gamma hydroxybutyrate trials, common side effects have included dizziness, headache, nausea, pain, somnolence, sleep disorder, confusion, infection, vomiting, and enuresis.[33] Illicit use in high doses could result in addiction and withdrawal. Sudden deaths have been reported in patients who have risk factors for obstructive sleep apnea.[148] Overall, gamma hydroxybutyrate is effective, and is recommended for treatment of cataplexy, excessive daytime sleepiness, and disrupted sleep due to narcolepsy.[102]

Future treatments

Introduction of hypocretin-1 into the cerebral ventricular system was found to be useful in mice but not in hypocretin-2 mutated dogs.[149] Intranasal administration is promising, as well as transplantation of neonatal hypothalamic stem cells into the brainstem.[149,150] Narcolepsy with cataplexy is strongly

suspected to be an autoimmune disorder. However, attempts to modify immune processes, including use of steroids, plasmapheresis, and intravenous immunoglobulin, have been met with limited and short-term success.[151–153] Histamine 3 receptors regulate the release of histamine. Antagonism of the histamine 3 receptor enhances wakefulness, while stimulation causes sedation.[154] Histamine 3 receptor antagonists have been shown to be effective in canines and mice.[155,156] Other promising novel treatments include thyrotrophin-releasing hormone and the nicotine patch.[156,157]

Conclusion

Our understanding of the pathogenesis of narcolepsy continues to advance, with substantial evidence that autoimmune loss of hypocretin neurons is the main cause of narcolepsy with cataplexy. The standardized criteria for narcolepsy and diagnostic measures are generally accepted, but might need to be reviewed in the future. There is established pharmacotherapy for symptomatic treatment of narcolepsy. Future treatment modalities, such as hypocretin analogs and histamine receptor antagonists, should aim to tackle the cause of narcolepsy.

Disclosure

The authors report no conflicts of interest in this work.

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