Etiologies and Sequelae of Excessive Daytime Sleepiness

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ABSTRACT

Excessive daytime sleepiness (EDS), the primary complaint of patients seen in sleep clinics, affects up to 12% of the general population. The effects of EDS can be debilitating and even life threatening. Patients with EDS may exhibit psychosocial distress, decreased work or school performance, and increased risk for accidents. The differential diagnosis of EDS requires objective assessments, such as polysomnography and the Multiple Sleep Latency Test. There are four major causes of EDS: (1) central nervous system (CNS) pathologic abnormalities, such as narcolepsy and idiopathic CNS hypersomnia; (2) qualitative or quantitative sleep deficiencies, such as sleep apnea and insufficient nocturnal sleep; (3) misalignments of the body’s circadian pacemaker with the environment (eg, jet lag or shift work); and (4) drugs, which can increase sleepiness either therapeutically or as a side effect. Depending on etiology, management strategies for EDS include extension of time in bed, naps, surgery, various medical devices (eg, oral appliances, continuous positive airway pressure), and pharmacotherapy. Pharmacotherapy is generally achieved with stimulants, such as amphetamine sulfate, methylphenidate, and pemoline or newer, safer compounds like modafinil.

INTRODUCTION

Sleepiness is a physiologic drive. Just as hunger typically leads to food-seeking behaviors, sleepiness commonly leads to sleep onset. In most individuals, sleepiness is not severe and is usually alleviated after extended nocturnal sleep. For others, the drive to reduce sleepiness may be so overwhelming that it interferes with other activities and may even have health and safety ramifications.1,2

Excessive daytime sleepiness (EDS) affects up to 12% of the population.3 Although most normal individuals are occasionally affected by EDS, persistent EDS may be symptomatic of pathologic abnor-
malities, such as apnea or narcolepsy. EDS, rather than insomnia, is the most common complaint of patients seen in sleep clinics.4,5

Historically, the diagnosis and quantification of EDS were difficult, and sleep difficulties were generally not viewed as serious medical problems. Recent advances in patient assessment combined with an improved understanding of the societal ramifications of EDS are beginning to change this view. The emergence of the discipline of sleep medicine and improvements in educating the lay public are leading to the increasing perception of EDS as an important clinical and public health concern. This paper will review the assessment, morbidity, etiologies, and management of EDS.

**ASSESSMENT OF EXCESSIVE DAYTIME SLEEPINESS**

Behavioral and subjective signs of sleepiness may be influenced by motivational or other factors and may not be consistent with a physiologic assessment. Various self-report scales have been developed to standardize analyses of the degree of sleepiness.6,7 The Profile of Mood States, commonly employed in psychopharmacologic studies to assess overall mood, includes fatigue and vigor scales.8 The Stanford Sleepiness Scale is a seven-point scale widely used in sleep investigations; however, it may be unreliable in patients with chronic EDS.9 Unlike these scales, which measure isolated instances of sleepiness, the Epworth Sleepiness Scale is designed to evaluate the patient’s general level of sleepiness. Scores on this scale are generally correlated with Multiple Sleep Latency Test (MSLT) scores.7

The Sleep-Wake Activity Inventory is a multidimensional self-report test with an EDS scale designed to evaluate sleepiness apart from the influence of motivational and psychic distress factors. This test is predictive of MSLT scores and is sensitive to the changes resulting from the effective treatment of patients with apnea.6

Self-report assessments, however, are sometimes inaccurate and not reproducible. For instance, patients may occasionally rate themselves as alert even though they are falling asleep.10

**Multiple Sleep Latency Test**

An MSLT,11 usually performed the day after a nocturnal polysomnographic recording, is essential for determining the level of sleepiness. It is based on the assumption that sleep is a drive and that patients who are very sleepy, given the opportunity, will fall asleep faster than will patients who are not as sleepy. The test is a series of scheduled naps during which the time to sleep onset (sleep latency), as well as the stages of sleep during the naps, are recorded.12 The MSLT is also the main test for identifying narcolepsy.

**Polysomnography**

Polysomnography, which measures objective aspects of sleep, is necessary for proper clinical assessment of EDS. This common technique evaluates electroencephalographic, electro-oculographic, electromyographic, cardiovascular, respiratory, gastrointestinal, and other measures over an entire night’s sleep. Sleep stages are readily identified and evaluated via the record. Polysomnography is also used to detect specific abnormalities, such as sleep apnea and periodic limb movements, either of which might cause EDS.
Maintenance of Wakefulness Test

A variant of the MSLT, the Maintenance of Wakefulness Test (MWT), also called the Repeated Test of Sustained Wakefulness, places patients in a comfortable position in a darkened room and asks them to try to remain awake. Proponents of the MWT suggest that the test may measure different physiologic properties and may be better suited to evaluate the patient's ability to stay awake than the MSLT. However, measurement of the ability to stay awake may be confounded by other factors, such as the time of day, environmental conditions, and motivational factors.

MORBIDITY OF EXCESSIVE DAYTIME SLEEPINESS

The consequences of EDS reach far beyond the patient's sleep-wake cycle. Psychosocial function, school performance, and work performance may be affected; public safety may even be endangered. Economically, the cost of sleepiness-related accidents runs into the billions of dollars.

Psychosocial Functioning

Excessive sleepiness has a significant influence on psychosocial functioning. As one might expect, individuals who are chronically sleepy or fall asleep at inopportune times may be perceived by others as lazy. One third of the 180 narcoleptic patients surveyed in one study believed that others did not understand or tolerate their symptoms. Disruptions of family life and interpersonal relationships are common. Chronic EDS may even interfere with the enjoyment of recreational activities. Sixty-two percent of narcoleptic patients in one study had given up their favorite leisure activities.

Perhaps related to the above, clinical depression is frequently observed in EDS patients. One report found that two thirds of patients who sought treatment at a major sleep disorders center had displayed symptoms consistent with major depression within the previous 5 years, and half of the narcoleptic patients in another study had recurrent depression. A possible contribution to such depression is the fact that many patients with sleep disorders may remain undiagnosed (or misdiagnosed) for years. Individuals may not recognize EDS as a medical problem and may not seek treatment, or the physician may not be familiar with the diagnosis and treatment of sleep disorders.

Neuropsychologic deficits—including learning disabilities in children, memory impairments, and reduced cognitive function—have also been associated with EDS. These deficits are caused by impairment of daytime vigilance.

Accident Risk

The majority of published articles correlating sleepiness and accidents are concerned with motor vehicle accidents. For example, a study evaluating motor vehicle accidents in the midlands of England to which police were called found more than 20% of all accidents were sleep related.

Individuals with sleep disorders may pose a higher risk (discussed below); however, acute, rather than chronic, EDS may be responsible for many vehicular accidents in the general population. Normal individuals display a biphasic circadian rhythmicity of sleepiness, with maximum sleepiness between midnight and early
morning and a secondary peak in midafternoon.\textsuperscript{21,22} The distribution of automobile accidents through the day reflects this circadian rhythm of sleepiness.\textsuperscript{1,23} Daylight savings time, which entails a transient, 1-hour loss of sleep in the spring, is associated with increased traffic accidents the Monday after the time change.\textsuperscript{24}

**Work/School Performance**

Patients with EDS often show reduced productivity at work and school. Shift workers, for instance, who have an increased incidence of EDS have markedly impaired performance at work.\textsuperscript{8} Furthermore, in studies of narcoleptic patients, 78\%\textsuperscript{2} to 85\%\textsuperscript{17} have reported that their symptoms reduce their job performance.

In educational settings, 51\%\textsuperscript{2} to 64\%\textsuperscript{17} of all narcoleptic patients attribute poor grades to their symptoms. Even though narcolepsy is a syndrome that is only partially characterized by EDS (other symptoms include hypnagogic hallucinations, cataplexy, and sleep paralysis), in most studies narcoleptic patients report EDS to be their most problematic symptom.\textsuperscript{17,25-28} It is reasonable to conclude that EDS is a major cause of the work and school problems experienced by narcoleptic patients.

**Economic and Public Health Issues**

The diminished ability of excessively sleepy individuals to function normally has economic and public health ramifications. Certain concerns, however, hamper accurate assessment of these effects of sleepiness. Not only is it difficult to assign monetary values to degrees of human suffering and loss of life, the degree to which sleepiness caused an accident is often unclear. Unlike testing for ethanol, which is objective, rapid, and portable, there is no analogous method for assessing sleepiness. However, given that sleepiness may exacerbate the impairing effects of low doses of ethanol on driving performance,\textsuperscript{29} it is reasonable to assume that some ethanol-related accidents might not have occurred if sleepiness were not also involved.

Estimates of the cost of sleepiness-related accidents from narcolepsy and other causes vary widely,\textsuperscript{30,31} with even conservative estimates running into the billions of dollars per year.\textsuperscript{31}

Sleepiness becomes a public health issue when it compromises public safety. One survey showed that 37\% of narcoleptic patients reported having had automobile accidents due to their symptoms, and two thirds reported frequent near accidents.\textsuperscript{2} Another study, however, noted that many people with narcolepsy have developed effective coping skills (eg, cold packs, exercising at periodic stops) that allow them to successfully manage their sleepiness while driving.\textsuperscript{17} One study found that drivers with obstructive sleep apnea (OSA) have a greater accident risk than other drivers.\textsuperscript{32}

As can be expected, a driver who is asleep may have little or no warning before impact. A study of drivers who lost consciousness or had seizures estimated that 27\% did so because of excessive sleepiness; however, this cohort was responsible for 83\% of the fatalities. Moreover, only 16\% of the drivers with excessive sleepiness had been drinking.\textsuperscript{33}

There is no consensus as to how to prevent sleep-related accidents. A recent review of several countries' driving regulations pertaining to narcolepsy or sleep apnea revealed inconsistent rules or no rules at all.\textsuperscript{34} Regulatory guidelines may
also be needed for persons who are responsible for the safety of others (eg, military personnel, air traffic controllers, ship captains, pilots). A consensus report by a committee of the Association of Professional Sleep Societies suggests that public awareness and regulatory guidelines concerning excessive sleepiness could prevent accidents in which sleepiness appears to be a contributing factor.

MAJOR ETIOLOGIES OF EXCESSIVE DAYTIME SLEEPINESS

Sleep Fragmentation

Sleep fragmentation represents a qualitative, rather than a quantitative, deficiency of nocturnal sleep. An electroencephalogram of patients with a variety of sleep disorders displays brief arousal episodes of 3 to 15 seconds (Figure 1) that are usually not remembered by the patient. Fragmentation is correlated with EDS in a variety of patient groups. Moreover, patients who respond to treatment of sleep apnea show fewer arousals and a parallel decrease in sleepiness. Investigations by Bonnet show decreased performance the day after sleep fragmentation.

Figure 1. Sleep fragmentation as observed in an electrographic recording. LEOG = left electro-oculography; REOG = right electro-oculography; EMG = electromyography; EEG = electroencephalography; EKG = electrocardiography.

Further analysis of the relationship between arousal and EDS reveals differences between EDS patients and other individuals. The EDS patients had a positive correlation between the total number of arousals and sleepiness, while insomnia patients showed a negative correlation of these variables. Further analysis according to gradations of arousals found that in EDS patients, lower-level arousals were positively correlated and higher-level arousals were negatively correlated with sleepiness, whereas this pattern was reversed in insomnia patients.

Sleep Apnea

A conservative estimate suggests that, of working people aged 30 to 60 years, 4% of men and 2% of women have sleep apnea. Sleep apnea can be categorized into three major types: (1) obstructive apneas, in which the effort to breathe is maintained against an occluded airway; (2) central apneas, caused by a transient failure of the central nervous system (CNS) to activate the respiratory effort systems; and (3) mixed apneas, which include an initial pause followed by breathing efforts against an obstructed airway.
Functionally, mixed apneas are the same as obstructive apneas.

Sleep apnea is the most common diagnosis of EDS patients in US sleep disorders centers. At most centers, more than 75% of patients are diagnosed with OSA. Obesity is a major risk factor for OSA, along with male sex, older age, and craniofacial anomalies. Familial risks are also a factor, and evidence suggests that familial influence is both genetic and environmental. The fundamental problem underlying OSA is the collapse of the upper airway during sleep. The airway collapse leads to increased respiratory efforts, which in turn lead to arousals. Although these arousals may or may not be recalled during the day, their effect—sleep fragmentation—produces EDS.

Insufficient Nocturnal Sleep

The amount of nocturnal sleep is related to the degree of daytime sleepiness. The number of hours of sleep loss in normal volunteers is directly proportional to increased daytime sleepiness, as assessed by the MSLT. The effects of sleep deprivation may be cumulative. Insufficient sleep may be job related (eg, from working a late shift), may be the result of voluntary lifestyle decisions, or may be pathologic. The effects of chronic insufficient sleep may be countered by extending sleep time. In one study, extending nocturnal time in bed to 10 hours for 6 nights reduced sleepiness in patients with mean sleep latencies ≤6 minutes, although not to alert levels. A subsequent study showed that extended time in bed for 14 nights does normalize the MSLT in such patients.

There are substantial differences in the way individuals react to insufficient sleep. Sleep deprivation may lead to perturbations of mood, a famous example being the severe paranoid psychosis exhibited by a New York disc jockey who stayed awake for 200 hours. Others may react quite differently. One subject, a former world record holder for staying awake, did not display psychotic symptoms during a 264-hour wakefulness marathon. Factors unrelated to sleep deprivation (eg, personality) can account for differential responses to sleep deprivation.

Phase Alterations/Circadian Rhythms

Specific examples of phase alterations are jet lag and shift work. Jet lag represents a desynchronization of the individual with the environment. The extent to which it is experienced depends on the direction and length of the flight, as well as on substantial individual differences in susceptibility. Jet lag consists of three major components: (1) external desynchronization, in which the circadian rhythms of the traveler are out of phase with the environment; (2) internal desynchronization, in which various rhythms within the traveler are uncoordinated with each other; and (3) sleep loss, which is a result of the above two components.

Shift workers account for approximately 18% of the US workforce. Like those who suffer from jet lag, shift workers are also out of phase with respect to environmental cues. However, there are obvious and important differences between the two phenomena. In jet lag, environmental and social cues serve to assist the sufferer's realignment; however, these same cues are deleterious to shift workers, who must maintain their desynchronization in order to work at night and sleep during the day. Surveys report that shift workers lose approximately 5 to 7
hours of sleep per week when compared with their diurnal coworkers. Both EDS (actually excessive nighttime sleepiness in this case) and shortened, disrupted sleep are revealed in polysomnographic testing of night shift workers. One study, which typifies problems associated with shift work, examined firefighters working on a rotating shift schedule. When on the night shift, firefighters reported decreased amounts of sleep, greater sleepiness ratings, and decrements in mood.

**Drugs that Increase Sleepiness**

EDS is a common adverse effect of many medications, and there are several drug classes (eg, sedative-hypnotics and CNS depressants) that increase sleepiness. Polysomnographic testing reveals reduced sleep latency after the use of benzodiazepines, barbiturates, and ethanol, probably via facilitation of the actions of gamma-aminobutyric acid (GABA).

Ethanol is widely, though erroneously, self-prescribed as a sedative. Acute ethanol ingestion is known to have biphasic effects, initially promoting sleepiness, then disrupting it during the second half of sleep. In chronic ethanol administration, sleep is fragmented and disrupted by awakenings. An additional and dangerous effect of ethanol is its exacerbation of sleep apnea.

Barbiturates were once commonly prescribed as sedative-hypnotics, as they reduce nocturnal sleep latency and subsequent EDS. Barbiturates have been largely replaced by benzodiazepines due to the former drug’s lack of CNS specificity, lower therapeutic index, higher abuse potential, greater number of drug interactions, and more frequent development of tolerance. Although the benzodiazepines are effective sedatives, care should be taken to minimize their major side effects—residual sedation, anterograde amnesia, and rebound insomnia.

Antidepressant and antipsychotic drugs also have sedating effects. Depressed patients have rapid eye movement (REM) sleep that is more pronounced and have a shorter latency than that of normal individuals. Most antidepressants are REM suppressants and increase REM latency. Antipsychotics are a pharmacologically diverse group of drugs whose main action has traditionally been attributed to dopaminergic blockade. Members of this drug class may also affect serotoninergic and histaminergic systems, both of which influence sleep. Although the majority of antipsychotic drugs tend to increase sleepiness at therapeutic doses, members of this drug class do not have uniform effects on sleep.

Beta-blockers also have sedating effects; however, they may cause insomnia and nightmares.

**Narcolepsy**

Narcolepsy is a sleep disorder with an estimated frequency ranging from approximately 0.2 to 5.9 individuals per thousand in European countries, Japan, and the United States. This idiopathic CNS disorder is characterized primarily by EDS, and secondarily by cataplexy, hypnagogic hallucinations, and sleep paralysis. Because only 11% to 14% of narcoleptic patients display all of these symptoms, diagnosis can be difficult. An overnight polysomnographic recording followed by an MSLT the next day are crucial for an accurate diagnosis of narcolepsy.

Narcolepsy has a pathognomonic pattern of REM sleep. Unlike normal individuals in whom the first REM period is
approximately 90 minutes after sleep onset, narcoleptic patients display REM within 10 minutes of sleep onset (Figure 2).9 Such an occurrence is called a sleep-onset REM period. The sleep paralysis, cataplexy, and hypnagogic hallucinations associated with EDS in individuals with narcolepsy may be considered displaced manifestations of REM sleep that emerge during wakefulness or semiwakefulness.63

Although narcolepsy is of unknown origin, it appears to have a hereditary component.64,65 Recent evidence suggests that neuroanatomic degeneration and/or abnormal neurotransmitter function may also be involved.66

**Idiopathic Central Nervous System Hypersomnia**

As its name implies, idiopathic CNS hypersomnia is diagnosed by eliminating other potential causes of EDS. Idiopathic CNS hypersomnia is similar to narcolepsy in some respects. Both conditions are of unknown origin, are very disabling (potentially life threatening in certain instances), are currently incurable, and are characterized by EDS and impaired performance. Patients with idiopathic CNS hypersomnia, however, typically lack the cataplexy, hypnagogic hallucinations, and sleep paralysis seen in narcolepsy.67

**Miscellaneous Sleepiness Syndromes**

There are other sleep disorder syndromes that may reflect CNS pathologic conditions. One of these is Kleine-Levin syndrome, which is characterized by periodic hypersomnolence in male adolescents. This syndrome is typically accompanied by megaphagia, hallucinations, and sexual hyperactivity. Patients with
Kleine-Levin syndrome generally outgrow it by middle age.4

MANAGEMENT OF SLEEPINESS

The heterogeneity of etiologies of EDS is mirrored in the varied approaches to managing and treating it. In some cases treatment is effective enough to improve the patient’s quality of life and allow normal functioning. Yet many patients suffer from conditions of unknown origin, which complicate treatment and may limit treatment to symptom management at best.

Drugs that Increase Alertness

Certain drug classes, including stimulants, influence sleepiness by increasing alertness. Stimulants primarily reduce sleepiness by increasing catecholaminergic (particularly adrenergic) activity—a quality that may lead to abuse and side effects. Amphetamine, methylphenidate, and pemoline are used to alleviate the EDS of narcolepsy. Caffeine, one of the most popular stimulants, appears to enhance catecholaminergic function indirectly via antagonism of adenosine.

Modafinil is a new compound that appears to have minimal adverse effects. Modafinil has been shown to be effective for treating human narcolepsy68,69 and may be effective in normal persons for maintaining or recovering performance during prolonged sleep loss or continuous work.70,71

A summary of drugs that influence sleepiness or alertness is presented in the table.

Sleep Apnea

There are both nonsurgical and surgical treatments for OSA. Nonsurgical options include weight loss, medications, oral appliances, and, primarily, nasal continuous positive airway pressure. Nasal continuous positive airway pressure, the most popular and efficacious therapy for OSA, creates a pneumatic splint for the upper airway by delivering high-pressure air to the sleeping patient through a tight-fitting mask. Although EDS is reversed with this treatment, there are concerns about long-term patient compliance.41,72 Surgical options have evolved from tracheostomy to the present options, which include uvulopalatopharyngoplasty and maxillofacial procedures. Surgical procedures are performed only on patients with documented significant anatomic abnormalities.

Circadian Rhythms

Treatments for circadian rhythm disorders (including jet lag) focus on rapid entrainment of the sleep-wake cycle to the new time. Phase alterations are manipulations that offer some relief to jet lag sufferers. These may be achieved behaviorally or pharmacologically. Strategies such as realigning a person’s sleep-wake cycle before departure to approximate that of the new destination offer some relief to airline passengers. Phototherapy—exposure to bright lights—represents another way to reset the circadian pacemaker. Depending on the timing of exposure, either phase delays or phase advances may be achieved.73

Resetting the circadian pacemaker may also be achievable with melatonin, a pineal hormone synthesized and secreted at night, that can induce sleep in many individuals.74,75 Preliminary evidence suggests that melatonin may be useful to counter such circadian misalignments as jet lag76 and shift work.77 Although melatonin has recently received widespread
Table. Drug classes that influence sleepiness or alertness. (Examples of each drug class are given in parentheses.)

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<th>Drugs that Increase Sleepiness</th>
<th>Drugs that Increase Alertness</th>
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<tr>
<td>CNS depressants (ethanol)</td>
<td>CNS stimulants (amphetamine, caffeine, methylphenidate)</td>
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<td>Benzodiazepines (diazepam, lorazepam, temazepam, flurazepam)</td>
<td>Novel agents (modafinil)</td>
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<td>Barbiturates (phenobarbital)</td>
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<td>Beta-adrenergic blockers (propranolol)</td>
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<td>Other antihypertensives (methyldopa)</td>
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<td>Antidepressants (amitriptyline)</td>
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<td>Antipsychotics (chlorpromazine)</td>
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<td>Antihistamines (diphenhydramine)</td>
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<td>Anxiolytics (buspirone)</td>
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<td>Narcotic analgesics (hydrocodone)</td>
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<td>Other sedatives-hypnotics (meprobamate)</td>
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CNS = central nervous system.

exposure in the lay press, further scientific investigations are necessary.

Narcolepsy

The current treatment of narcolepsy is twofold. Stimulants are given to relieve the EDS, and tricyclic antidepressants are given to combat the remaining symptoms of the tetrad. Mitler et al. recently demonstrated the first example of normalization of function in narcoleptic patients by means of amphetamine therapy. However, high doses of methamphetamine (40 to 60 mg/d) were necessary to achieve this effect. These high doses could lead to social instability and psychologic dependence.

The compounds currently used to treat the EDS observed in narcolepsy enhance catecholaminergic function; however, other neurotransmitters may also partially mediate alerting effects. Modafinil, which appears to require an intact adrenergic system, has shown promising results for alleviating EDS in clinical trials. This compound may reduce GABAergic outflow, although the relationship between this action and wakefulness is unclear. Modafinil is reported not to disrupt normal sleep patterns, and it appears to lack clinically significant hypertensive action. Modafinil also appears to have a low abuse potential.

Idiopathic Central Nervous System Hypersomnia

Due to its unknown etiology, idiopathic CNS hypersomnia is treated only to relieve symptoms. Pharmacotherapy of this condition currently includes stimulants such as methylphenidate and dextroamphetamine. Newer compounds such as modafinil may prove to be as effective with fewer side effects.
CONCLUSION

EDS is gaining recognition as a clinical and public health concern. Despite recent advances in the diagnosis and treatment of sleep disorders, EDS remains a concern at both the patient and public health levels. Improvements in our understanding of the neurophysiology and pharmacology of sleep, the influence of circadian rhythms, and the effects of sleepiness will benefit not only the patient, but society as well. New approaches, both behavioral and pharmacologic, hold promise for the treatment of EDS.

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