Narcolepsy

Signs, Symptoms, Differential Diagnosis, and Management

Phillip M. Green, MD; Michael J. Stillman, PhD

Narcolepsy is a chronic neurologic disorder characterized by excessive daytime sleepiness and cataplexy and less often by hypnagogic hallucinations and sleep paralysis. While patients report excessive daytime sleepiness and cataplexy as the more frequent symptoms of this condition, excessive daytime sleepiness is generally believed to be the most debilitating. Narcolepsy often is undiagnosed or misdiagnosed for a variety of reasons. Although confirmation of an initial diagnosis requires monitoring of physiologic variables conducted at a sleep center by specialists, the primary care physician has a critical role in the identification and management of this incurable affliction. This article provides recommendations for the diagnosis and management of narcolepsy. The cataplexy associated with narcolepsy can be managed with tricyclic antidepressants. The excessive sleepiness is managed with stimulants, but newer agents, such as modafinil, which will be marketed as Provigil, and selegiline hydrochloride, with fewer adverse effects and less abuse potential, may offer means of promoting daytime wakefulness. Groups such as the National Sleep Foundation, Washington, DC, and the Narcolepsy Network, Cincinnati, Ohio, can provide patients with needed support and information.

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OVERVIEW OF NARCOLEPSY

Narcolepsy is characterized predominantly by EDS and cataplexy (sudden loss of muscle tone) and less often by hypnagogic hallucinations, sleep paralysis, and disrupted nighttime sleep. The most prevalent and the most debilitating symptom of the narcolepsy tetrad is EDS. The following tabulation indicates the percentages of patients with each symptom.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of Patients With Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDS</td>
<td>100</td>
</tr>
<tr>
<td>Cataplexy</td>
<td>70</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>30-50</td>
</tr>
<tr>
<td>Sleep-related hallucinations</td>
<td>20-40</td>
</tr>
<tr>
<td>All 4 symptoms</td>
<td>11-14</td>
</tr>
</tbody>
</table>

Narcolepsy can have serious consequences. Automobile accidents and related deaths are caused by drivers losing consciousness. People with narcolepsy are particularly prone to such accidents because they can fall asleep at the wheel without warning. A person with narcolepsy also may suffer injuries at home; falls during cataplectic attacks and burns caused by falling asleep while smoking are common.

Many aspects of the life of the patient with narcolepsy are impaired by EDS. Although the diagnosis of narcolepsy generally is not made until adulthood, symp-
and interpersonal relationships,¹,⁹ experience disruption of family life theret.
Persons with narcolepsy may often is misperceived as lazy or apa-
grade reduced job performance or poor performance in general is illus-
reduced job responsibility at school or work. Many persons with narco-
eos EDS or cataplexy. Be-
terates DR2 and DQwl,¹³,¹⁴ this asso-
3 = high chance of dozing

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
</tr>
<tr>
<td>Sitting, inactive in a public place (eg, a theater or a meeting)</td>
<td></td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in the traffic</td>
<td></td>
</tr>
</tbody>
</table>

Thank you for your cooperation

The Epworth Sleepiness Scale, a self-administered test to determine excessive daytime sleepiness. Numeric scores from each question are summed to obtain a total score, which can range from 0 to 24. A score of more than 16 indicates a high level of sleepiness. The survey, designed to overcome differences in daily routines, was validated in patients with confirmed diagnoses of sleep disorders. From Johns.²⁵ Used by permission.

Although a suspected diagnosis of narcolepsy should be confirmed by sleep studies, the primary care phys-
can work toward deter-

RECOGNIZING THE KEY SIGNS AND SYMPTOMS OF NARCOLEPSY

The Epworth Sleepiness Scale is a validated method to measure excessive daytime sleepiness (EDS). It consists of ten questions, each rated on a four-point scale (1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing, 4 = would never doze). The total score can range from 0 to 24, with higher scores indicating greater daytime sleepiness.

**Situation** | **Chance of Dozing**
--- | ---
Sitting and reading |                  |
Watching TV |                  |
Sitting, inactive in a public place (eg, a theater or a meeting) |                  |
As a passenger in a car for an hour without a break |                  |
Lying down to rest in the afternoon when circumstances permit |                  |
Sitting and talking to someone |                  |
Sitting quietly after a lunch without alcohol |                  |
In a car, while stopped for a few minutes in the traffic |                  |

**Table 1**

The Epworth Sleepiness Scale is a self-administered test to determine excessive daytime sleepiness. Numeric scores from each question are summed to obtain a total score, which can range from 0 to 24. A score of more than 16 indicates a high level of sleepiness. The survey, designed to overcome differences in daily routines, was validated in patients with confirmed diagnoses of sleep disorders. From Johns.²⁵ Used by permission.

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Table 1. Differential Diagnoses for Excessive Daytime Sleepiness (EDS)*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Distinguishing Characteristics</th>
<th>Diagnostic Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-disordered breathing</td>
<td>Middle age, male sex, obesity, history of loud snoring, hypertension, or cardiac arrhythmias*</td>
<td>Interview of bed partner for description of patient’s sleep behavior (loud snoring, pauses in breathing), physical examination, polysomnograph*27</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>EDS plus other symptoms of the narcoleptic tetrad</td>
<td>Interview patient about cataplexy, referral for MSLT to screen for rapid onset of NREM</td>
</tr>
<tr>
<td>Sleep deprivation or circadian</td>
<td>Altered sleep-wake cycle owing to job, activity schedule, jet lag, shift work</td>
<td>Thorough history, referral for polysomnogram (should be normal)</td>
</tr>
<tr>
<td>misalignment</td>
<td></td>
<td>Thorough history, physical examination, bed partner’s reports of leg movements</td>
</tr>
<tr>
<td>Restless legs syndrome (Ekbom</td>
<td>Compulsion to move the legs, reports of various leg sensations, possible vasculopathies, neuropathies, iron deficiency anemia, or metabolic abnormalities*24</td>
<td></td>
</tr>
<tr>
<td>syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance use or abuse</td>
<td>History of substance dependency or signs of current drug abuse or dependence</td>
<td>Thorough history and drug screening</td>
</tr>
<tr>
<td>Depression</td>
<td>Severe mood disturbance; indecisiveness; somatic preoccupations; changes in appetite, weight, bowel habits, or the capacity to experience pleasure</td>
<td>Thorough history, referral for psychiatric examination, referral to sleep center to rule out narcolepsy (the disorder should respond to antidepressants)</td>
</tr>
<tr>
<td>Kleine-Levin syndrome</td>
<td>Male sex (M/F ratio, 3:1), adolescence, compulsive overeating, hallucinations, sexual hyperactivity (a rare syndrome)</td>
<td>Thorough history</td>
</tr>
<tr>
<td>Idiopathic hypersomnia</td>
<td>Prolonged nocturnal sleep times, absence of multiple brief sleep attacks or of nocturnal insomnia, few alert periods, relative lack of wakefulness, severe lethargy on awakening in the morning*26</td>
<td>Thorough history, may refer to sleep center for MSLT</td>
</tr>
<tr>
<td>Infection</td>
<td>Hypersomnia only, signs of current infection</td>
<td>Diagnose infection (EDS should resolve with treatment of underlying disease)</td>
</tr>
</tbody>
</table>

*MSLT indicates Multiple Sleep Latency Test; NREM, nonrapid eye movement.

Differential Diagnosis of Causes of EDS

Sleep-Disordered Breathing. Sleep apnea is the most common diagnosis of patients who seek care at US sleep centers because of EDS. An estimated 15% of men and 5% of women have mild sleep apnea (10 or more episodes of apnea and hypopnea per hour of sleep). In sleep apnea, the patient’s airway is occluded periodically during sleep because of loss of tone in the muscles of the upper airway, excessive pharyngeal tissue, or structural abnormalities. The result is increased respiratory effort and frequent arousals throughout the night. The patient may be unaware of these arousals the following day, yet these arousals produce sleep fragmentation, resulting in EDS. Risk factors for sleep apnea include obesity, male sex, and certain craniofacial anomalies (eg, the mandibular maldevelopment that occurs in the Pierre Robin syndrome or the Treacher Collins syndrome). Because sleep apnea is associated with loud snoring and pauses in breathing, the patient’s bed partner should be interviewed whenever possible to obtain a description of the patient’s sleep behavior. The patient can be referred for polysomnography or equipped with a portable device for analysis of heart rate and respiratory efforts so that the apneic events can be documented.

Narcolepsy. While EDS is often the first symptom of narcolepsy, additional symptoms of the narcolepsy tetrad may develop over time. Approximately 11% to 14% of patients report all 4 symptoms* (see the tabulation). The baseline objective criteria for diagnosing narcolepsy are given in Table 2. The symptoms of narcolepsy and their recognition are described in the following paragraphs.

Cataplexy. Cataplexy, a sudden loss of muscle tone, can be precipitated by an emotional event such as anger or laughter. Some experts consider cataplexy to be an excellent discriminating factor for narcolepsy, especially the combination of a history of cataplexy and the incidence of a sleep onset–REM period (Table 2). Narcoleptic symptoms may range from mild to severe. Mild attacks can cause facial weakness, slurred speech, drooping eyelids, weakened grip, head nodding, or buckling of the knees. Severe attacks can result in physical collapse. Once a physician establishes that the patient has EDS and suspects narcolepsy, the physician can ask questions that might reveal whether the patient has experienced cataplexy: After an emotional or physically active time, have you ever noticed that your speech was slurred or that you had periods of stuttering? Have you felt you were overly clumsy at these times? In such circumstances, have you ever collapsed suddenly, without warning?

Hypnagogic Hallucinations. Some patients with narcolepsy report hypnagogic hallucinations, which are hallucinations that occur just before falling asleep (those that occur on awakening are termed hypnopompic hallucinations). Hypnagogic hallucinations may be visual, auditory, or tactile, and they seem to differ from normal dreams because they are frightening and lifelike. Although they may be mistaken for symptoms of schizophrenia, the patient with narcolepsy does not have an intrusive thought disorder. The hallucinations experienced in narco-
Sleep Paralysis. Sleep paralysis, an inability to speak or move at sleep onset or on awakening, also can occur. Episodes of sleep paralysis may terminate spontaneously or on tactile or auditory stimulation. This symptom, which is associated with the atonia of REM sleep, may be observed during intoxication or withdrawal from drugs in these classes.2 Thorough questioning about substance use or drug screening may be warranted if this diagnosis is suspected.

Infection. Excessive daytime sleepiness also can be the result of infections such as encephalitis. Mononucleosis may be associated with EDS. These conditions do not involve other symptoms of the narcoleptic tetrad and, therefore, usually can be distinguished readily from narcolepsy. However, caution is advised in ruling out narcolepsy, since younger patients with narcolepsy may have only EDS; the other features of narcolepsy may not develop for several years. Physicians should look for other signs of disease if they suspect that EDS is caused by infection.

Depression. Narcolepsy may be mistaken for depression. Although some persons with depression report EDS, most have difficulty falling or staying asleep, or they awaken prematurely. However, unlike the short, fragmented, nocturnal sleep observed in many older patients with narcolepsy, persons with mood disorders may have prolonged nocturnal sleep.2 Patients whose chief complaint is depression or disturbed sleep should be evaluated for the presence of the other condition. Although a causal relationship has not been established, many patients with narcolepsy have depressive symptoms. In 1 study, more than 50% of patients with narcolepsy complained of recurrent depression compared with 29% of control subjects.3 Thus, physicians must be careful to differentiate depression associated with narcolepsy from depression as the primary cause of the sleep disorder.

Sleep Deprivation or Circadian Disorders. In sorting through the potential causes of EDS, the physician should not overlook the patient’s recent sleep history. The patient who seeks care because of EDS may be sleep deprived, perhaps voluntarily. Patients who have jet lag or who work nonstandard shift schedules probably are sleepy because of circadian misalignments rather than narcolepsy. The physician also should be mindful of the variability in sleep requirements. Many people require 8 hours of nocturnal sleep and show performance decrements if even 1 hour of sleep is lost38; others require more sleep, while some function properly on less. Thus, there is no universal sleep requirement below which a diagnosis of exhaustion is given—this should be assessed individually during diagnosis. A diagnosis of narcolepsy for a patient with EDS requires a regular sleep-wake schedule with adequate nocturnal sleep. Although sleep-deprived persons may have sleep paralysis or hallucinations, cataplexy is not observed.3

Other Causes of EDS. Patients with primary (idiopathic) hypersomnia differ from persons with narcolepsy because they have more difficulty awakening, more persistent daytime sleepiness, longer and less disrupted nocturnal sleep, REM latency, and no sleep onset–REM periods.3

In addition to temporary (eg, jet lag) or voluntary (eg, shift work) circadian misalignments, some persons, colloquially referred to as “night owls,” may suffer from a type of circadian rhythm sleep disorder termed delayed sleep phase. On

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**Table 2. Diagnostic Criteria for Narcolepsy**

| A. | Excessive sleepiness or sudden muscle weakness |
| B. | Recurrent daytime naps or lapses into sleep that occur almost daily for at least 3 mo |
| C. | Sudden bilateral loss of postural tone in association with intense emotion (cataplexy) |
| D. | Associated features |
|   | Sleep paralysis |
|   | Hypnagogic hallucinations |
|   | Automatisms |
|   | Disrupted major sleep episode |
| E. | Polysomnography demonstrates 1 or more of the following: |
|   | Sleep latency less than 10 min |
|   | Rapid eye movement sleep latency less than 20 min |
|   | Multiple Sleep Latency Test that demonstrates a mean sleep latency of less than 5 min |
|   | Two or more sleep-onset rapid eye movement periods |
| F. | Human leukocyte antigen typing demonstrating DR2 and/or DQw1 positivity |
| G. | Absence of medical or psychiatric disorder that could account for the symptoms |

*Minimal criteria for a diagnosis of narcolepsy: B and C or A and D and E and G.*
their own (ie, without an alarm clock), persons with delayed sleep phase awaken and fall asleep at delayed, although consistent, times and experience normal sleep. Enforced sleep deprivation by a work or school schedule often leads to EDS. If not elucidated in the initial evaluation, the normalcy of the polysomnogram distinguishes this disorder from narcolepsy.

In the restless legs syndrome (also called Ekbom syndrome), paresthesia in the legs is relieved by sporadic movements. Diagnosis is based on the history of the patient. The essential features of the restless legs syndrome are unpleasant limb sensation, precipitated by rest and relieved by activity, compelling motor restlessness, and worsening of symptoms during early evening or later at night, usually resulting in insomnia. These movements often disrupt nocturnal sleep, resulting in EDS. Periodic leg movements are not always associated with restless legs syndrome. At times, these movements occur as repetitive, somewhat arrhythmic flexion movement of the legs during sleep that last 0.5 to 5 seconds, usually at intervals of 20 to 40 seconds. When these movements are common, especially in older people, and may fragment sleep to the point of resulting in insomnia. These movements often disrupt nocturnal sleep, resulting in EDS. Periodic leg movements are not always associated with restless legs syndrome. At times, these movements occur as repetitive, somewhat arrhythmic flexion movement of the legs during sleep that last 0.5 to 5 seconds, usually at intervals of 20 to 40 seconds. These movements are common, especially in older people, and may fragment sleep to the point of resulting in EDS. The patient may be unaware of the movements during sleep associated with the restless legs syndrome or periodic leg movements, but the patient's bed partner may help elucidate this condition.

Various conditions, such as epilepsy, Parkinson disease, cerebrovascular disease and endocrine dysfunctions, and Huntington disease, also may disturb nocturnal sleep and lead to EDS. Chronic fatigue syndrome, like narcolepsy, may manifest as EDS and disturbed nocturnal sleep. However, the presence of cataplexy, sleep-related hallucinations, or sleep paralysis can help the physician distinguish narcolepsy from another condition. In addition, head trauma may induce narcolepsy symptoms in persons who previously experienced normal sleep.

Kleine-Levin Syndrome. Kleine-Levin syndrome, a rare condition, is characterized by periodic hypersomnia, predominantly in male adolescents. It is typically accompanied by compulsive overeating, hallucinations, and sexual hyperactivity. Although there is no cure for Kleine-Levin syndrome, patients generally outgrow it by middle age.

Further Diagnostic Tools

Referral to a specialist (eg, a neurologist or a sleep specialist or center) is usually recommended when narcolepsy is suspected. An examination of physiologic functions at a sleep center, including a nocturnal polysomnogram and a Multiple Sleep Latency Test (MSLT) the next day, can confirm a diagnosis of narcolepsy. There are more than 250 sleep centers in the United States, many of which are affiliated with teaching hospitals. These centers are equipped with the sophisticated monitoring equipment necessary to perform the polysomnogram and the MSLT.

The polysomnogram, a nighttime record of electromyographic, electroencephalographic, and electrocardiographic data, may include other (eg, respiratory and gastrointestinal) measures during sleep. The polysomnogram can indicate whether other conditions that could cause EDS, such as sleep apnea or periodic leg movements, are present.

In the MSLT, the sleep latency (ie, the number of minutes required to fall asleep) in 4 or 5 naps and the stages of sleep during these naps are recorded. Patients with narcolepsy have much shorter sleep latencies (approximately 5 minutes or less) than do healthy patients (latencies between 10 and 20 minutes). The assessment considers normal diurnal variations in sleep latency, eg, patients assessed in midafternoon may be experiencing the normal circadian-cycle sleepiness that occurs at this time. The MSLT also can document the appearance of sleep onset–REM periods.

TREATMENTS AND COPING STRATEGIES

The realization that narcolepsy is a debilitating chronic illness has encouraged the development and refinement of pharmacological treatments. Stimulants, such as pemoline, amphetamine sulfate, and methylphenidate hydrochloride, are the primary treatment options for EDS. Methylphenidate and dextroamphetamine seem to work by enhancing catecholaminergic function and may lessen EDS in many patients with narcolepsy. However, they are associated with undesirable adverse physical effects (eg, increased blood pressure and heart rate) and psychological effects (eg, psychosis and hallucinations). Methylphenidate psychosis may occur in a small number of patients treated for narcolepsy. Tolerance to the drug may develop in patients receiving long-term stimulant therapy, creating the need to increase dosage to achieve the same control. Also, amphetamine and methamphetamine have a high potential for abuse and are classified as schedule II substances, which restricts the writing of prescriptions and limits the availability of these medications.

Antidepressants, principally tricyclic antidepressants, are the best treatment for cataplexy, hypnagogic hallucinations, and sleep paralysis because they suppress REM sleep. The tricyclic antidepressant clomipramine hydrochloride, the treatment of choice for many years in Europe, is now available in the United States. Imipramine hydrochloride, desipramine hydrochloride, protriptyline hydrochloride, and, to a lesser extent, the serotonin reuptake inhibitor fluoxetine also have been effective.

Some patients with narcolepsy benefit from nonpharmacological coping strategies. Therapeutic naps of 15 to 30 minutes each can improve daytime functioning, nap therapy not only may alleviate the severity of EDS, but also may permit the reduction of medication dosages for some persons. Some patients benefit from prospectively “mapping out” their day. For a patient with narcolepsy who has a long drive ahead, this would entail a temporal distribution of medications and naps to make falling asleep during the drive less likely. Other strategies for safe driving used by patients with narcolepsy include applying cold packs, singing along with the radio, stopping for naps, and exercising at periodic stops.
Maintaining a regular sleep-wake schedule is important for everyone, but especially for persons with sleep disorders. Patients with narcolepsy should go to sleep and awake at the same times every day, including weekends. Creating a comfortable environment helps to maintain uninterrupted sleep. Because nicotine and caffeine may fragment sleep, patients with narcolepsy should avoid these agents.

**POTENTIAL NEW THERAPIES FOR EDS**

Because their abuse potential and adverse effects make stimulants far from ideal agents, effective alternative compounds with fewer adverse effects and lower abuse potential are under development or consideration for the treatment of narcolepsy.

A wakefulness-promoting agent, modafinil, which will be marketed as Provigil in the United States and released in the late fall or early winter of 1999, is structurally distinct from methylphenidate and amphetamine. Although the exact mechanism of action is unknown, modafinil acts through a mechanism that differs from the traditional dopaminergic- and catecholaminergic-enhancing stimulants. Modafinil is effective in promoting wakefulness in patients with EDS associated with narcolepsy. It is generally well tolerated, with minimal adverse effects and low abuse potential, and does not disrupt normal sleep patterns. Modafinil lacks clinically significant hypertensive action.

Selegiline hydrochloride, a compound used to treat Parkinson disease, initially showed no or slight improvements in patients with narcolepsy in open-label studies. More recent studies suggest that selegiline can increase REM latency in persons with narcolepsy. However, caution is warranted pending further research with selegiline because of its decreasing efficacy in Parkinson disease after long-term (6 months to 2 years) administration. The concerns about possible increased mortality in selegiline-treated patients do not seem to be supported by review of the total experience with this medication.

Treatment with gamma-hydroxybutyrate seems to improve the clinical symptoms of cataplexy, sleep paralysis, hypnagogic hallucinations, and EDS. However, considerable work must be done to determine the appropriate and safe dosage of this medication. Gamma-hydroxybutyrate is in early phase 3 clinical trials in the United States. Concern about the abuse potential of this medication exists, and it may have difficulty obtaining approval from the Food and Drug Administration. The medicine has been associated with date rape.

**SOCIETIES AND SUPPORT GROUPS**

Several organizations offer support for persons with sleep disorders. The American Sleep Disorders Association, Washington, DC, is active in professional education and the development of standards and guidelines for patient care. The National Sleep Foundation, Washington, is a nonprofit organization dedicated to improving the quality of life of persons with sleep disorders and to preventing catastrophic sleep-related accidents. The National Sleep Foundation provides patients with a wide variety of sleep disorders with up-to-date educational literature about the specific disorder. Persons with narcolepsy also may take advantage of disorder-specific programs. The Narcolepsy Network, Cincinnati, Ohio, a patient-support group, disseminates information to lay audiences. The National Center on Sleep Disorders Research, Bethesda, MD, is also an important resource. In addition, other organizations, hospitals, and private sleep clinics have sites on the World Wide Web that can be accessed through the Internet. However, patients should be warned that information available on the Internet (if not an official statement of one of the aforementioned legitimate organizations) may be incorrect, unreliable, unclear, or outdated.

**INSURANCE CONCERNS**

Many patients may be justifiably concerned about whether visits to sleep centers will be covered by their health insurance plan or by health maintenance or preferred provider organizations. At Kalamazoo Neurology, Kalamazoo, Mich, the technical costs of sleep studies are billed by the hospital, but the interpretations and patient follow-up visits are billed through the physician's office. The structure of billing and the site of service for different sleep centers may vary. A letter justifying the procedure and documenting the need to complete the testing may be necessary to obtain approval from various health plans.

**CONCLUSIONS**

Patients with sleep disorders, including patients with narcolepsy, now benefit from the recognition of sleep medicine as a medical discipline. The greater awareness of narcolepsy as a medical problem has spurred research into new pharmacological treatments. Early recognition and appropriate treatment of EDS and other symptoms associated with narcolepsy are essential to improving the patient's quality of life. The primary care physician can make an important contribution to the care of patients with narcolepsy by obtaining a thorough history from patients who complain of sleepiness. The use of new treatments in conjunction with coping strategies can substantially improve the outlook for patients with narcolepsy.

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