Review

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OBSTRUCTIVE SLEEP APNEA-HYPOPNEA SYNDROME. MODERN VIEW ON THE PROBLEM

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Obstructive sleep apnea syndrome is a common chronic syndrome that significantly affects the quality of life of patients and often requires lifelong care. This review deals with modern ideas about the prevalence, causes, clinical presentation, diagnosis and treatment of obstructive sleep apnea syndrome. Using modern methods of diagnosis and the correct approach to such patients helps prevent unwanted effects and significantly improves quality of life.

KEY WORDS: obstructive sleep apnea-hypopnea, sleep disorders

СИНДРОМ ОБСТРУКТИВНОГО АПНОЕ-ГІПОПНОЕ СНУ. СУЧАСНИЙ ПОГЛЯД НА ПРОБЛЕМУ

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Синдром обструктивного апное сну є поширеним хронічним синдромом, яке значно погіршує якість життя пацієнтів і часто вимагає довічного догляду. У цьому огляді розглянуто сучасні уявлення про поширеність, причини, клінічну картину, діагностику та лікування синдрому обструктивного апное сну. Використання сучасних методів діагностики і правильний підхід до такого роду пацієнтів дозволяють запобігти небажаним наслідкам і значно поліпшити якість життя.

КЛЮЧОВІ СЛОВА: синдром обструктивного апное, порушення сну

СИНДРОМ ОБСТРУКТИВНОГО АПНОЭ-ГИПОПНОЭ СНА. СОВРЕМЕННЫЙ ВЗГЛЯД НА ПРОБЛЕМУ

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Синдром обструктивного апноэ сна является распространенным хроническим синдромом, которое значительно ухудшает качество жизни пациентов и часто требует пожизненного ухода. В настоящем обзоре рассмотрены современные представления о распространенности, причинах, клинической картине, диагностике и лечении синдрома обструктивного апноэ сна. Использование современных методов диагностики и правильный подход к такого рода пациентам позволяют предотвратить нежелательные последствия и значительно улучшить качество жизни.

КЛЮЧЕВЫЕ СЛОВА: синдром обструктивного апноэ, нарушения сна

People spend about 30 % of their lives asleep. Sleep is essential for a variety of restoration and biochemical processes in the body, such as tissue repair, growth of the organism, recovery of immune reserves, synthesis of anabolic hormones, ontogeny, information processing, formation of memory and knowledge[1-3]. Sleep plays a vital role in good health and well-being throughout life. Getting enough quality sleep at the right times can help protect mental health, physical health, quality of life, and safety [4, 5].

In 1965, independently of one another the German and French researchers have described many detrimental effects of sleep disorders related to sleep apnea and snoring [6].

Snoring not only creates certain social problems, but also is a harbinger and one of the main symptoms of obstructive sleep apnea-hypopnea (OSAHS) [7-9]. In severe forms of OSAHS up to 400-500 pauses in breathing per night can be observed for a total duration of 4-5 hours, which leads to acute and chronic deficiency oxygen saturation during sleep [10]. This, in its turn, greatly reduces the quality of life of the patient, significantly increases the risk of developing metabolic syndrome, erectile dysfunction, hypertension, cardiac arrhythmias, myocardial infarction, stroke and sudden death during sleep [11, 12].

Unfortunately, today in Ukraine insufficient attention is paid to the diagnosis of sleep-related breathing stops. Moreover, these patients do not complain of sleep apnea, snoring is considered a symptom that unworthy of attention of the doctor, patients do not report the relevant complaints. Severe forms of OSAHS often remains undiagnosed and untreated, which significantly affects the quality of life and prognosis in these patients.

DEFINITION

OSAHS is a condition wherein a patient has multiple, repeated respiratory standstills because of complete or partial narrowing of the airways in the throat accompanied by cessation of pulmonary ventilation during sleeping with continued respiratory efforts characterized by the presence of snoring, decrease of oxygen level in blood, coarse fragmentation of sleep with frequent awakenings and excessive daytime sleepiness [13]. Herewith awakening serves as a protective mechanism in which the activation of the muscles - upper airway dilators occurs and warns of asphyxia from OSAHS [14, 15].

PREVALENCE

The prevalence of the OSAHS is 5–7 % of the total population over 30 years (predominantly male). Severe forms of the syndrome occur in about 1–2 % from above [16-18]. Frequency of occurrence of this syndrome increases with age. In persons older than 60 years occurrence of occurrence OSAHS is about 30 % in men and 20 % women; In persons older than 65 years - about 60 % [19]. These figures exceed the prevalence of the bronchial asthma [20].

The prevalence of clinically significant OSAHS is 15 % for patients in the therapeutic profile hospitals [21-23]. In cardiac patients the prevalence of OSA is even higher. In patients with systemic arterial hypertension, the figure is 30 % [24], and in refractory forms of hypertension reaches 83 %. [19, 25]. In patients with nocturnal bradyarrhythmia OSAHS is detected in 68 % of cases [26]. In patients with coronary heart disease (CHD) and heart failure II-IV functional NYHA class, OSAHS prevalence reaches 43 % [27]. Frequency of occurrence of ischemic cerebral stroke in patients with OSAHS is 2-10 times higher than in the general population and have a higher risk of car accidents in 4-6 times compared with the average data [19]. The prevalence of OSA is also very high in obese patients with metabolic syndrome, diabetes mellitus, hypothyroidism. [28].

AETIOLOGY AND PATHOPHYSIOLOGY

The basis of the syndrome is a periodic cessation of breathing due to subsidence of airways on the level of the pharynx. The airways can be completely occluded and then develops into apnea. Apnea is a cessation of airflow (pulmonary ventilation) for 10 seconds or more. With a partial loss patency of the respiratory tract patients have hypopnea. It is a significant reduction in air flow (over 50 % from baseline), accompanied by a decreased arterial oxygen saturation of 3 % or more [29]. In severe forms of OSAHS, breathing may be missing for 5 hours per night which leads to a dramatic lack of oxygen during sleeping. If the rate of oxygen in the blood is 96-98 %, episodes of obstructive apnea during sleeping could cause severe intermittent hypoxia and retention of CO2, with a fall in arterial oxygen saturation during the pauses to less than 60 % i.e. development of prohibitive hypoxia (according to resuscitators, reduction
of saturation below 50 % for 2 minutes causes the death of the cerebral cortex). In intensive care where the oxygen level in blood is less than 80 % doctors make intubation and mechanical ventilation [30].

Acute shortage of oxygen in arterial blood leads to the stress response, accompanied by activation of sympathetic nervous system and the rising in blood pressure [15, 30].

Eventually the negative information from different organs and systems causes a partial awakening of brain (micro activation). The brain regains control over the pharyngeal muscles and opens airways quickly. Then person snorts loudly and makes few deep breaths [31]. The normal oxygen content restored in the body, the brain calms down and falls asleep again. The patient falls asleep, and these events repeat again, breaking sleeping continuity [32].

The causes of the oropharynx collapse are a significant reduction of pressure in the upper inspiratory airway and the inability of the muscles which extend the throat to keep it open [33]. The reduction of muscle tone of the upper airway during sleeping and weakening of their reflex reaction on the fall of airway pressure plays a decisive role [34].

Most people have structural abnormalities of upper respiratory tract. Sometimes it's rough anatomical changes for example adenoids, curvature of the nasal septum, polyps, macroglossia, retrognathia (underdevelopment and rearward displacement of the upper and / or lower jaw), but basically there is just a slight reduction of the oropharynx size [35, 36].

A number of diseases promote the narrowing of the upper airway:

- obesity – the deposition of fat in the soft tissues of the pharynx or squeezing of the throat by massive subcutaneous tissue of the neck;
- hypothyroidism- weight gain, global decrease in muscle tone and edema of visceral tissues with lower thyroid function;
- acromegaly- disproportionate growth of individual organs and the tongue that causes narrowing of the throat at the base of the tongue, etc. [19].

Muscle relaxants (hypnotics, alcohol) often provoke the collapse of the oropharynx. As they cause selective relaxation of these muscles and prevents activation which interrupts each apnea [37]. Smoking also has different negative impacts on upper respiratory tract which foster the development of respiratory disorders during sleeping [38].

CLASSIFICATION

There are three types of sleeping apnea: central, obstructive and mixed (CSA, OSA and MSA). Airway collapse during ongoing respiratory effort is observed in obstructive sleep apnea (respiratory center function maintained).With central sleep apnea (Cheyne-Stokes and other forms) there is a decrease of function or stoppage of the respiratory center and the cessation of respiratory effort. Thus airways are still open. The concept of mixed apnea includes the features of both above types [39].

Standard criteria of classifying of OSAHS are the frequency of apneas and hypopneas per hour - the apnea / hypopnea index (AHI). It is inappropriate to count separately the number of apneas and hypopneas, as they carry on similar risks to the development of cardiovascular disease and other complications. Currently, the majority of international consensus and clinical guidelines adhere to the following classification of the severity of OSAHS in adults based on IAG: mild form - from ≥ 5 to < 15; Mild (moderate) form - from ≥ 15 to < 30, Severe ≥ 30 [40].

The additional criteria for classifying the severity of OSAHS may be the amount of desaturation on the background of episodes of apnea / hypopnea index, the degree of structural failure of a night's sleeping, cardiovascular complications associated with respiratory disorders (myocardial ischemia, arrhythmias and conduction, hypertension) and the severity of cognitive deficits [41].

SYMPTOMS AND SIGNS

Generally, symptoms of OSAHS begin insidiously and are often present for years before the patient is referred for evaluation. The characteristic symptom of OSAHS is excessive daytime sleepiness, also known to be a common predisposing factor for accidents, reduced productivity, neurocognitive impairment and interpersonal and/or social problems [42]. Snoring is one of the main symptoms of OSAHS, which is usually loud, habitual, and bothersome to others. Also patients commonly experience repeated awakenings from sleep, feelings of choking or gasping, flailing or thrashing during sleep, restless sleep, with patients often experiencing frequent arousals and tossing or turning during the night, decreased capacity for concentration, impaired functioning in daily activities, morning headaches and sexual dysfunction. Deteriorations in quality of life and affect, which can include irritability, depression, and anxiety, are common among patients with OSAHS [43].

Every stoppage of breathing leads to a sharp deterioration of the quality of sleeping.

The patient may wake up from the effects of long pauses with a sense of heart, rapid breathing, breathlessness, anxiety, profuse sweating. Headache, increased blood pressure, angina may disturb in the morning [44, 45]. Marked hypersomnia throughout the day and also irritability, poor mood [46]. The attacks of severe drowsiness are especially dangerous while driving. The risk of traffic accidents may increase because of this [47]. Memory and attention become worse, body weight increased, libido decreased and impotence develops [48].

DIAGNOSIS

The presence or absence and severity of OSAHS must be determined before initiating treatment in order to identify those patients at risk of developing the complications of sleep apnea, to guide selection of appropriate treatment and to provide a baseline to establish the effectiveness of subsequent treatment. Diagnostic criteria for OSAHS are based on clinical signs and symptoms determined during a comprehensive sleep evaluation, which includes a sleep oriented history and physical examination, and findings identified by sleep testing [49].

The diagnosis of OSAHS starts with a sleep history that is typically obtained in one of three settings: first, as part of routine health maintenance evaluation, second, as part of an evaluation of symptoms of obstructive sleep apnea, and third, as part of the comprehensive evaluation of patients at high risk for OSAHS. High-risk patients include those who are obese, those with congestive heart failure, atrial fibrillation, treatment refractory hypertension, type 2 diabetes, stroke, nocturnal dysrhythmias, pulmonary hypertension, high-risk driving populations (such as commercial truck drivers), and those being evaluated for bariatric surgery [50].

The physical examination can suggest increased risk and should include the respiratory, cardiovascular, and neurologic systems [51].

Particular attention should be paid to the presence of features that may suggest the presence of OSAHS include obesity (body mass index: > 30 kg/m^2), an enlarged neck circumference (men: > 43 cm; women: > 37 cm), and hypertension [52]. Other clinical pointers may include craniofacial and soft tissue enlargement associated with upper airway resistance such as retrognathia, deviated nasal septum, low-lying soft palate, enlarged uvula and base of the tongue, congenital narrowing of upper airway can be detected radiographically or by acoustic pharyngometry [53, 54].

A diagnosis of OSAHS must be established by an acceptable method. The two accepted methods of objective testing are; in-laboratory polysomnography (PSG) and home testing with portable monitors (PM). The American Academy of Sleep Medicine guidelines for the indications and performance of PSG include the following [55]: electroencephalogram (EEG), electrooculogram (EOG), chin electromyogram, airflow (using both a thermal sensor and a nasal pressure transducer), oxygen saturation, respiratory effort (using inductance plethysmography), and electrocardiogram (ECG) or heart rate. Additional recommended parameters include body position and tibialis electromyogram (EMG) derivations. The breathing pattern is analyzed for the presence of apneas and hypopneas as per definitions standardized by the American Academy of Sleep Medicine [40].

A PM records airflow, respiratory effort, and blood oxygenation. PM for the diagnosis of OSAHS should be performed only in conjunction with a comprehensive sleep evaluation. PM may be used to diagnose OSAHS when utilized as part of a comprehensive sleep evaluation in patients with a high pretest likelihood of moderate to severe OSAHS. PM testing is not indicated in patients with major comorbid conditions including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease, or congestive heart failure, or those suspected of having a comorbid sleep disorder [56]. PM testing may also be indicated for the diagnosis of OSAHS in patients for whom in-laboratory PSG is not possible by virtue of immobility, safety or critical illness and to monitor response to non-continuous positive airflow pressure (CPAP) therapies [57].

The multiple sleep latency test (MSLT) is not routinely indicated in the initial evaluation and diagnosis of OSAHS or in an assessment of change following treatment with nasal CPAP. However, if excessive sleepiness continues despite optimal treatment, the patient may require an evaluation for possible narcolepsy, including the MSLT. The MSLT has a reasonably high test-retest reliability over periods of months in normal subjects. However, the MSLT is very cumbersome, time

consuming and expensive to perform. It takes all day, both for the subject and the polysomnographer and is not easy to justify as a routine test for all patients [58].

There are other methods of assessment of sleep disorders. The Stanford sleepiness scale (SSS) is a quick and simple test. It involves the subject's own reports of symptoms and feelings at a particular time. Visual analogue scales (VAS) of sleepiness/alertness have also been used, however, these tests do not attempt to measure the general level of daytime sleepiness, as distinct from feelings of sleepiness at a particular time [59]. The Epworth sleepiness scale (ESS), designed to measure sleep propensity in a simple, standardized way. The scale covers the whole range of sleep propensities, from the highest to the lowest and is a validated method of assessing the likelihood of falling asleep in a variety of situations. The Scale should be completed independently by both the patient and their partner as the patient may underestimate the severity of their sleepiness due to its insidious onset, or in order to hide concerns over driving ability [60].

Thus, by questioning patients with high confidence a diagnosis of OSAHS can be made, and for diagnosis objectification patient should be send to the sleep laboratory.

OUTCOMES AND COMPLICATIONS

Frequent episodes of breathlessness and severe hypoxemia in conjunction with disruption of the structure of sleeping could cause the development of cardiovascular diseases [44], metabolic, endocrine, neurological and psychiatric disorders [48, 61].

Acute and chronic lack of oxygen increases the risk of development of cardiac arrhythmias, the development of acute myocardial infarction, acute stroke, sudden death during sleeping [60]. Frequent respiratory arrest leads to a sharp deterioration of the quality of sleeping and disruption of sleeping structure. As a result, there are frequent nocturnal awakenings, loss of deep stages of sleeping, restless sleeping, excessive daytime sleepiness, irritability, poor concentration, loss of memory [62].

It is proved that OSAHS is an independent risk factor for hypertension [63-66], 50 % patients with hypertension have OSAHS [67, 68]. In the 7-th Report of the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) sleeping apnea is at the first place among all causes of secondary hypertension, this highlights the high prevalence and clinical significance of hypertension caused by OSAHS [69]. Patients with OSAHS have absence of blood pressure reduction at night («non-dipper») or even its excess over the daily pressure («night peaker») [70]. Increase in blood pressure (mainly diastolic) in the morning has been also marked [71]. Significant reduction of the blood pressure in 20-30 minutes after waking up without any medical intervention is an interesting feature which patients with OSAHS have. According to Logan and co-authors [25] 41 patients with refractory hypertension (blood pressure > 140/90 mm Hg), who are not treatable with three or more drugs had obstructive sleeping apnea (AHI > 10 per hour) in 83 % of cases. So you should always assume the presence of OSAHS in patients with predominantly nocturnal and morning hypertension, especially refractory to treatment.

After 12 years observation it was noted a threefold increase in fatal and 4-5-fold increase in non-fatal cardiovascular events among patients with untreated severe OSAHS. In fact, the risk of dying or getting a heart attack or stroke was 50 % during the 12 years of observation. Patients who had constant CPAP therapy for OSAHS had the same frequency of complications as the patients without OSAHS [72].

Wisconsin cohort study showed an increased risk of cardiovascular mortality by 5,2 times during the 18 year follow-up of patients with untreated OSAHS [48]. During the observation 35 % of patients with untreated severe OSAHS compared with 7 % in the group without OSAHS died. Another study demonstrated that for moderate and severe forms of OSAHS risk of death from any cause within 14 years of observation is 6,24-fold higher ($p < 0,002$) compared with the control group, comparable in age, gender, body mass index, mean blood pressure, smoking, coronary heart disease and diabetes, the level of total cholesterol and high density lipoproteins. [37].

OSAHS is a cause of progression of visceral obesity and the metabolic syndrome by disrupting hormone production during the night, such as cortisol and insulin, thus in patients with metabolic syndrome prevalence

of OSAHS is approximately 50 %, and with the Pickwick syndrome – 90 % [73].

Impaired Peaks in the production of growth hormone and testosterone secretion which are found in the deep stages of sleeping develops in severe forms of OSAHS. When patient has OSAHS he practically doesn't have deep stages of sleeping which leads to their lack of production. The mobilization of fat from the depot and its transformation into energy and muscle mass is one of the functions of growth hormone in adults. With a lack of the hormone a person begins to gain weight, and any effort either diet or medications aimed at weight loss give poor results , and fat at the neck leads to further narrowing of the airways and the progression of OSAHS. Lack of testosterone in the body leads to impotence and reduction of men's libido [74].

Negative impact of OSAHS on beta cell function and insulin sensitivity is proved. The prevalence of OSAHS in patients with type 2 diabetes is 36 %. With this in mind, the International Diabetes Federation published clinical guidelines, which urged health professionals working with patients with type 2 diabetes or OSAHS, in the case if a patient has one of the diseases not to exclude the possibility of the other disease [75].

MODERN APPROACHES TO THERAPY:

Approach to the treatment of patients with snoring and OSAHS should be comprehensive and flexible [76]. Modern guidelines for the management of such patients include the following categories:

1. Patient Education

Sleep hygiene. An integral component of the treatment of all forms of sleep disorders is the culture preparation for sleep, which includes the following recommendations [77]:

- go to bed and get up at the same time;
- exclude naps, especially in the afternoon;
- do not eat at night tea or coffee;
- reduce stress, mental workload, especially in the evening;
- arrange for physical activity in the evening, but not later than 3 hours before bedtime;
- regularly use water treatments before bedtime;
- exclude watching television for 2 hours before bedtime.

Positional therapy. Body position greatly affects the number and severity of episodes of obstructive sleep apnea, with at least twice as many apneas occurring in people who lay on their back as in those who sleep on their side. This may be due to the effects of gravity, which cause the throat to narrow when a person lies on the back. A special pillow that helps to stretch the neck may reduce snoring and improve sleep for people with mild sleep apnea. Sleeping in an upright position may improve oxygen levels in overweight people with sleep apnea. Elevating the head of the bed may help. Some people are helped by special oral appliances to keep the airway open during sleep [78-80].

Weight loss. All patients with obstructive sleep apnea who are overweight should attempt a weight-reducing program. Weight loss certainly reduces snoring and apnea/hypopnea episodes in many people, sometimes stopping it completely. It also improves sleep and significantly reduces daytime sleepiness [81-83].

Smoking, alcohol and drugs.

- Smokers should quit, since smoking worsens apnea. Smoking causes chronic chemical trauma of airway at the throat, which leads to their swelling and decrease in muscle tone at the level of the pharynx, and this in turn contributes to the progression of snoring and OSAHS [35].
- Avoid sedatives and sleeping medications. Most of these drugs have a muscle relaxant and depressing influence of respiratory function, that impairs breathing disorders during sleep [84].
- Avoid alcohol within 4 hours of sleep. Alcohol has a double negative effect in OSAHS. First, it acts as a muscle relaxant and that leads to the relaxation of the pharyngeal muscles and more frequent collapse airways. Secondly, ethanol increases the threshold of the brain's response to adverse stimuli. In this situation, respiratory arrest last longer and develop more severe hypoxemia [85].

Exercise. Training tongue muscles and lower jaw is also advisable to apply. If the muscles are trained, even in a relaxed state (in a dream), they maintain a certain tone, providing an increase in the lumen of the pharynx and reducing snoring. Training can be carried out by a course of special set of exercises or by electrical stimulation of upper pharyngeal muscles [86].

2. Medication

To alleviate uncomplicated snoring there are pharmacological agents based on essential oils with methyl salicylate, which have a local tonic, anti-inflammatory and antiseptic action, they are sprayed directly on the back of the throat and uvula, but the effectiveness of their use remains controversial [87]. There are also studies on the use of glucocorticoids in patients with sleep apnea amid allergic rhinitis [88]. Pharmacologic therapy is generally not a part of the primary treatment recommendations. Acetazolamide, medroxyprogesterone, fluoxetine, and protriptyline have been used to treat OSAHS; however, these medications are not recommended. Modafinil is approved by the US Food and Drug Administration (FDA) for use in patients who have residual daytime sleepiness despite optimal use of CPAP [89, 90].

3. Treatment with the equipment

Treatment for OSAHS depends on the severity of the problem. At this time, the most effective treatments for sleep apnea are devices that deliver slightly pressurized air to keep the throat open during the night. There are a number of such devices available [35].

The best treatment for obstructive sleep apnea is a system known as CPAP. It is safe and effective for people of all ages, including children [91].

The device itself is a machine weighing about 3 pounds that fits on a bedside table. A mask containing a tube connects to the device and fits over just the nose.The machine supplies a steady stream of air through a tube and applies sufficient air pressure to prevent the tissues from collapsing during sleep [92].

The standard CPAP machine delivers a fixed, constant flow of air. Variations on CPAP include:

Autotitrating positive airway pressure (APAP) devices automatically respond to changes in the sleeper's breathing patterns by adjusting and varying the air pressure flow throughout the night. Some patients find this makes CPAP easier to tolerate [93].

Bilevel positive airway pressure (BPAP) systems deliver two different pressures, a higher one for inhalation (breathing in) and a lower one for exhalation (breathing out) [94].

For patients with OSAHS, CPAP therapy is usually prescribed as first-line treatment, a recommendation supported by high-level evidence for efficacy of CPAP in preventing upper airway collapse and relieving symptoms such as daytime sleepiness and mounting data suggesting that CPAP therapy may favorably impact cardiovascular outcomes and reduces mortality [95-97].

4. Surgery

Surgical modifications of the upper airway have been performed for decades as a treatment for OSAHS.Yet, the role of such procedures in the management of OSAHS remains controversial [98]. Critics point to the lack of high-level, controlled studies in the surgical literature and the absence of standardized criteria to define surgical «success,» while proponents cite ethical and logistical limitations to controlled surgical studies and contend that the «all or none» principle of eradication of OSAHS (an apnea-hypopnea index < 5) as the standard of care is flawed and impractical for many patients [99, 100].

All patients with OSAHS should have ongoing, long-term management for their chronic disorder. Those on chronic therapy should have regular, ongoing follow-up to monitor adherence to therapy, side effects, development of medical complications related to OSAHS, and continued resolution of symptoms. Those with elimination of OSAHS should be monitored for continued risk factor modification and to look for return of symptoms.

CONCLUSION

Obstructive sleep apnea syndrome is an actual problem in modern medicine because of the high prevalence in the population, increasing the risk of cardiovascular, neurological and metabolic complications of this syndrome, as well as a significant deterioration in the quality of life of patients.

At the moment the doctor informed about this issue, has the ability to accurately diagnose this potentially lethal syndrome. Designated timely treatment can in most cases prevent unwanted effects and significantly improve the quality of life of the patient.

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