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Obstructive sleep apnoea in severe mental disorders

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Summary

The prevalence of obstructive sleep apnoea (OSA) is estimated to be 3–7.5% in men and 2–3% in women. In mentally ill population it is even higher, as these patients are a high risk OSA group. The aim of the paper was a review of literature about the prevalence of sleep apnoea in patients with schizophrenia, bipolar disorder and recurrent depressive disorder.

The available data show that OSA is present in 15–48% of patients with schizophrenia, 21–43% of patients with bipolar disorder and 11–18% of patients with recurrent depressive disorder. The lack of diagnosis of OSA in people with mental illnesses has multiple negative consequences. The symptoms of sleep apnoea might imitate the symptoms of mental illnesses such as negative symptoms of schizophrenia and symptoms of depression, they might as well aggravate the cognitive impairment. A number of the drugs used in mental disorders may aggravate the symptoms of OSA. OSA is as well the risk factor for cardiovascular and metabolic diseases which are a serious clinical problem in mentally ill people and contribute to shortening of their expected lifespan. From the point of view of the physicians treating OSA it is important to pay attention to the fact that co-existing depression is the most common reason for resistant daytime sleepiness in OSA patients treated effectively with Continuous Positive Airway Pressure (CPAP). CPAP therapy leads to significant improvement of mood. However, in schizophrenia and bipolar patients it may rarely lead to acute worsening of mental state, exacerbation of psychotic symptoms or phase shift from depression to mania.

Key words: obstructive sleep apnoea, schizophrenia, depression, bipolar disorder

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Introduction

Obstructive sleep apnoea (OSA) is a common disease. It has been estimated that it affects 3–7.5% of men and 2–3% of women [1]. Similarly to other sleep disorders, OSA remains a disease which diagnosis and treatment is often neglected, because of need for interdisciplinary approach to its treatment. In the USA more than 80% of the mild and moderate OSA is undiagnosed [2]. It happens particularly often in psychiatric population. Those patients are still victims of stigmatisation, which worsens their access to the public health care [3]. At the same time, they constitute a group, in which OSA occurs more frequent or as often as in other medical conditions with a high risk of co-occurrence of OSA [4]. In the group of one hundred consecutive patients with severe mental illness, high risk of OSA was found in 69% of patients. Comparatively high proportion of patients with a significant risk of OSA was observed only in newly admitted patients with myocardial infarction. For comparison, among patients qualified for surgery, only 23% had a high risk of OSA [5]. Available data indicate that the high risk of OSA applies especially to patients with schizophrenia [5, 6].

Undiagnosed OSA in a mentally ill person has many negative consequences. Symptoms of sleep apnoea can imitate symptoms of mental disorders for example symptoms of depression or negative symptoms of schizophrenia, contribute to development of cognitive impairment [7, 8]. Some of the medications used to treat mental disorders may exacerbate the symptoms of sleep apnoea [9]. OSA is also a significant risk factor for cardiovascular disease and metabolic disorders, which are frequently present in psychiatric patients and contribute to their shortened life expectancy.

Aim

The aim of this paper is to review the literature on the prevalence of sleep apnoea in patients with schizophrenia, bipolar disorder and recurrent depressive disorder.

Obstructive sleep apnoea

Pathogenesis

Obstructive sleep apnoea (OSA) leads to repeated many times during sleep, complete (apnoea) or partial (hypopnoea) closure of upper respiratory tract (URT). Respiratory ways within the nasal cavity and the lower respiratory tract have a rigid support of cartilage and bone tissue, which prevents the loss of their patency. In contrast, the patency of the lower part of the upper respiratory tract depends only on stabilising tension of muscles of the pharynx, soft palate and tongue. When the negative pressure in the airway during inhalation is higher than stabilising muscle tension, URT are getting narrowed or completely closed. It might occur on the entire length, but it mainly takes place within central part of the pharynx, at the level of the soft palate and the tongue. This situation causes episodes of apnoea and then leads to frequent awaken-

ing or arousals, which result in disturbed sleep structure. Along with the progress of severity of the disease, there occur apnoeas hypoxic episodes associated with cardiac rhythm changes and blood pressure alterations [10, 11].

Risk factors

The most common risk factors for OSA include: obesity, male gender, older age (although the most severe form of apnoea occur in younger age groups), increased neck size (collar size ≥ 43 in men and ≥ 41 in women), hypothyroidism, acromegaly, drinking alcohol and tobacco consume [11, 12]. URT patency is also deteriorated by sleep in a supine position, elongated soft palate, enlarged tongue and tonsils, enlarged pharyngeal tonsil (especially in children), changes in the anatomical construction of facial and pharyngeal wall – excess of body fat and lymphoid tissue, and diseases deteriorating nasal patency (nasal septum deviations, mucosal polyps, hypertrophy of nasal turbinates). OSA is often associated with symptoms of metabolic syndrome [13]. For the co-occurrence of OSA with other components of the metabolic syndrome (obesity, insulin resistance, hypertension and dyslipidemia) Nock et al. proposed the term "Syndrome Z" [14]. Breathing disorders during sleep with obstruction of URT get worse after drinking alcohol, as well as during treatment with numerous drugs which have inhibitory effect on breathing or myorelaxant effect. Mainly the use of hypnotics and sedatives, anaesthetics, narcotic analgesics, neuroleptics, beta-adrenolytics is problematic in OSA patients.

An effective method to remember the risk factors for sleep apnoea is a mnemonic STOP-Bang abbreviation, created by anaesthesiologists to assess preoperative patients. It means: S – snoring loudly, T – tired in the daytime (daytime fatigue), O – Observed stop breathing (during sleep), P – blood pressure (hypertension). Bang: B – BMI > 35 kg/m^2, A – age (age > 50 years), N – neck circumference (neck circumference > 40 cm), G – gender (male). The finding of three of these eight factors indicates a high risk of apnoea [15]. Another way to assess the risk of sleep apnoea is the Berlin Questionnaire, which measures the risk of sleep apnoea in three categories. If the result of at least two categories is positive the patient has a high risk of OSA [16].

Symptoms

Symptoms of OSA are: loud, irregular snoring with pauses in breathing during sleep, restless sleep with frequent awakenings and increased physical activity during sleep as well as wake up with a feeling of suffocation, clogging, palpitations, frequent need to urinate at night, drowsiness, apathy during the day, morning fatigue, headaches, morning dry mouth [11].

OSA can be manifested by a wide spectrum of psychiatric symptoms such as increased irritability and impulsivity, the appearance of anxiety syndromes [17] and

depression [4, 18]. The diagnostic criteria for a depressive syndrome may occur even in 40–45% of patients suffering from OSA [19]. Night hypoxia, sleep structure disturbance and daytime sleepiness caused by OSA, are also associated with impaired cognitive processes, such as the decline in memory, executive function, visual-motor coordination, attention processes, and general mental deterioration [19, 20]. Severe forms of sleep apnoea can cause significant changes in behaviour and personality, resulting in motivation disorders and reduced control of emotions and behaviour. Such patients may be mistaken for suffering from organic mental disorders. Cases of incorrect classification of apathy and anhedonia caused by sleep apnoea as the negative and residual symptoms of schizophrenia are also being reported [8].

Diagnosis

The formal method of diagnosing OSA is full night polysomnography. For the diagnosis of OSA there should be found an increased apnoea and hypopnoea index (AHI), which is calculated by dividing the sum of all apnoeas and hypopnoeas by the number of hours of sleep. AHI values between 5 and 15/h are generally regarded as mild OSA, AHI between 15 and 30/h as moderate, AHI > 30/h as severe sleep apnoea. For the evaluation of the indications for the treatment of OSA, beside the AHI it is also important to evaluate mental and somatic symptoms – e.g. daytime sleepiness, coexisting cardiovascular diseases.

Currently it is discussed, whether in case of OSA diagnosed on the basis of the clinical interview with the patient and his/her bedroom partner, an assessment of the severity of OSA can be made with the polygraph test, instead of full polysomnography. Proponents of this approach emphasise its practicality, taking into account the high prevalence of sleep apnoea and inadequate availability and high cost of polysomnographic studies. Opponents of such a solution indicate that OSA is not only the pattern of breathing, heart rate, blood oxygenation and snoring, which are evaluated by polygraphic tests, but first of all a sleep disorder. Without assessing the impact of OSA on sleep structure, a full assessment of the severity of apnoea is not possible. It is worth to mention new methods of screening for sleep apnoea. One of them is based on measurement of PAT (peripheral arterial tone) signal. This method has been approved by the FDA for screening of OSA. In meta-analysis published in 2013, PAT analysis has been proved as a reasonable alternative to polysomnography [21]. The PAT test can be performed in cases of poor cooperation, e.g. in patients with mental illnesses and at home. Other methods for screening for OSA include analyses of: cyclic changes of heart rhythm variability (cyclic HRV) combined with oximetry, end-expiratory concentration of carbon dioxide ($EtCO_2$), the variability of the acoustic signals [22]. However, currently available data do not fully support the use of these methods.

Treatment

Having sleep apnoea diagnosed, modification of life style and behavioural recommendations should be implemented. That means: reductions in weight, avoiding sleeping medication and alcohol consumption before bedtime. When sleep apnoea is increased in supine position, the patients are advised to implant the sponge roller in the back of pyjamas to prevent sleeping in this position. Patients should also be referred to ENT specialist to evaluate the anatomy of the respiratory tract, particularly nasal obstruction and enlargement of the tonsils. In these two cases, surgery can lead to full recovery of the patients. In case of severe sleep apnoea, lack of efficacy of behavioural treatment, mild to moderate increase in AHI but with clear clinical symptoms and lack of indications for surgical treatment, the treatment with a positive airway pressure is recommended.

The consequences of untreated sleep apnoea

Repeated cycles of night hypoxia, negative pressure in the chest, arousals (partial disruption of sleep continuity) and awakenings (complete interruption of sleep) cause increase of sympathetic activity with a decrease of parasympathetic activity, decreased contractility and increased cardiac load, increased blood pressure, increased heart rate, oxidative stress, increased proinflammatory cytokine production, endothelial dysfunction and the activation of the coagulation cascade. OSA is a known risk factor for both ischemic and haemorrhagic stroke, high blood pressure, heart rhythm disorders, coronary heart disease and heart failure, pulmonary hypertension, impaired glucose metabolism, cognitive impairment and increased risk of motor vehicle and occupational accidents as a consequence of decreased vigilance and attention [8, 11].

Consequently, OSA significantly shortens life and reduces its quality. The average life expectancy evaluated in patients suffering from OSA is 58 years, compared to the average 78 years in healthy men and 83 in healthy women for [23]. Patients with severe mental illness have a life expectancy 20 to 25 years shorter than their healthy peers [24]. One of the reasons for this may be co-existing sleep apnoea, often regarded as insignificant by physicians who care for the mentally ill.

Obstructive sleep apnoea in mental illnesses

Obstructive sleep apnoea in schizophrenia

The fact that sleep disorders accompany schizophrenia is a commonly known and proved. However, very little data has been obtained considering the evaluation of frequency of OSA in this population. Several studies made on small groups of patients show that it can be as high as from 15 to 48% [8]. Taking into account the fact that obesity is a major risk factor for sleep apnoea [1] and in schizophrenia it is twice as frequent as in the general population, the incidence of OSA in patients with schizo-

phrenia should be higher than in the general population [6, 7]. In addition, there is evidence, however inconsistent [25], that smoking and drinking alcohol increases the risk of OSA. Both of these behaviours are very common in people with schizophrenia, which could potentially increase the risk of OSA even more. Diagnosis and treatment of OSA in patients with schizophrenia is important because OSA increases depressive symptoms, daytime sleepiness and cognitive impairment, which often hinder the lives of patients with schizophrenia. In several published studies there can be found a description of a case of a patient with schizophrenia and the concomitant sleep apnoea, in which the CPAP treatment resulted in a decrease in symptoms of depression and schizophrenia and moderate cognitive improvement [11]. The negative influence of atypical antipsychotics on symptoms of sleep apnoea also has been described. These drugs increase the likelihood of sleep apnoea by causing weight gain [6, 17] but also regardless this effect [25]. Patients receiving high doses of antipsychotics, who have a high BMI are at risk of OSA, which does not mean that sleep apnoea does not occur in other patients suffering from schizophrenia [25].

The reasons why it happens are not clear. The screening with the STOP-Bang method, in which the majority of the study population were patients with schizophrenia or schizoaffective disorder, found a high risk of sleep apnoea in 69% of the study group. Among patients with a high risk of OSA 62% had a diagnosis of schizophrenia. The highest risk of apnoea was found in patients treated with clozapine and risperidone [5].

The literature has also reported situations where in a patient with residual schizophrenia, the treatment of sleep apnoea with CPAP caused a reoccurence of acute psychosis with agitation, aggression and positive symptoms that required discontinuation of CPAP and intensification of antipsychotic treatment [26]. This was explained by increased dopaminergic activity or stimulation of GABAergic pathways that modulate cortical activity, and as a consequence, the increase of REM sleep and slow wave sleep after initiation of treatment with CPAP.

The adherence to medical recommendations in patients with schizophrenia is worse than in the general population [27]. For this reason some physicians give up the referral of patients with schizophrenia for diagnostic tests that require good compliance. Therefore, it is worth noting that among patients with schizophrenia at high risk for OSA, 71% of patients expressed their willingness to undergo sleep study towards OSA [5]. The question of the degree of the adherence of patients with schizophrenia to the treatment with CPAP is not entirely answered, and certainly requires further studies. OSA in schizophrenia is a subject worthy of attention because its effective treatment reduces cardiovascular risk, improves cognitive function, and hence, the quality of life of the patients.

Sleep apnoea in mood disorders

Sleep apnoea in depression

The links between sleep apnoea and depression were the subject of numerous studies. Their results, however, are inconclusive. The incidence of OSA in patients with depression is higher than in the general population and reaches about 11–18% [18], and the frequency of depression in patients with OSA, depending on the source, is estimated from 7 to as much as 63% [28]. Qhayon et al. examined 18,980 people from five countries with a telephone query and showed that the relationship between major depression and OSA remains significant even after excluding the impact of obesity and hypertension. People with diagnosed depression in a telephone interview were at five times higher risk of sleep apnoea. Both sleep apnoea and major depression were found in 0.8% of the surveyed people. 17.6% of people having one of these diagnoses turned out also to suffer from the other [18]. Some studies consider gender differences in the frequency of co-occurrence of depression in patients with OSA, emphasising that it is higher in women [29].

Large cohort study indicated that OSA is an important factor for developing depression [17] as it was shown in the analysis of the database of the clinic for veterans which included four million patients, of which 118,105 had sleep apnoea. It should, however, be noted that the data may be distorted by the over-representation of men in this study population.

In the paediatric population, an increased incidence of depressive symptoms in patients with OSA was also confirmed. The effective treatment of depression can improve the functioning of children with OSA [30].

It is worth noting that the majority of studies investigating the relationship between OSA and psychiatric disorders repeated some methodological problems. Some studies that reported co-occurence of depression and OSA as higher than in general population used assessment tools that have not been validated for patients with OSA such as MMPI (Minnesota Multiphasic Personality Inventory), Beck Depression Inventory, HAD-D (Hospital Depression Scale) and POMS (A Profile of Mood States) [31]. In addition, the above-mentioned depression assessment scales evaluate in a great majority symptoms that are common both in depression and sleep apnoea, such as fatigue, lack of energy, loss of interest, disturbed sleep, decreased libido and disturbed attention [32]. It has been suggested that for more effective recognition of depression in OSA we should consider cognitive spectrum of depressive symptoms such as guilt, worthlessness, rumination of unpleasant events, crying and suicidal thoughts [33].

There is important evidence that depressive symptoms in patients with OSA should not be considered only as a consequence of respiratory disorder. A multicentre study of 300 patients with depression and OSA treated with CPAP found that CPAP therapy in many patients does not result in resolution of symptoms of depression. Interestingly, daytime sleepiness, a core symptom of OSA seems to suggest the presence of coexisting depression. In a large cohort study, the highest association with daytime sleepiness was

not for sleep apnoea, but depression. Other factors associated with excessive sleepiness were high BMI, older age, longer duration of sleep, diabetes and smoking – the risk factors of sleep apnoea. The mere presence of OSA had no statistically significant effect on daytime sleepiness [34]. It was also found that when depression coexists with OSA, the daytime sleepiness persists despite the effective treatment with CPAP [35].

It would be misleading to claim that only depression with excessive sleepiness should bring attention to sleep apnoea. It has been shown that in depression with insomnia, OSA is more common than in depression without insomnia [36]. This observation is consistent with clinical experience indicating that OSA should be suspected not only in patients with excessive sleepiness, but also in those who report insomnia and the risk factors for sleep apnoea. The significance of the diagnosis and treatment of depression in OSA is also proved by the fact that depression is an independent risk factor for non-compliance with CPAP recommendations [37].

Neurobiological and pharmacological aspects of sleep apnoea in depression

The relationship of depression with OSA can be explained by the theory of neuroplasticity. According to it, chronic stress such as nocturnal hypoxia increases the levels of corticosteroids, which leads to atrophy of the hippocampal neurons and decrease of the expression of BDNF – brain-derived neurotrophic factor, responsible for neurogenesis and long-term memory. This leads to a decreased mood and cognitive disorders [38, 39]. Hypoxia also produces hyperintense subcortical lesions and their size is correlated with the intensity of depression [39–41]. It also induces inflammation and the production of inflammatory cytokines: TNFα, IL-1β, IL-2, IL-6, IL-12, which are an important component of the pathogenesis of depression.

The inverse relationship: depression as a risk factor of OSA, can be explained by serotonergic neurotransmission. Low serotonin levels is both a major cause of disturbed sleep in depression and a reduction in muscle tone of the URT. However, no significant efficacy of antidepressants that increase levels of serotonin has been proven in the treatment of OSA. This lack of response of OSA to serotonergic drugs is explained by reduced neuronal excitability as a consequence of oxidative stress induced by hypoxia [42]. However, there are data indicating that in patients with sleep apnoea who require sleep-promoting medication, sedative antidepressants are an important alternative to hypnotic drugs. A good example is trazodone, which significantly improves the quality of sleep, without worsening the AHI factor [20].

Bipolar disorder

Very few studies have been so far conduced on the coexistence of OSA and bipolar disorder. There are studies showing that the presence of sleep apnoea in patients with bipolar disorder may be as high as 21–47.5% [43].

Bipolar disorder is associated with a high risk of somatic diseases, e.g. cardiovascular diseases, that have many common OSA risk factors. Benzodiazepines and atypical antipsychotics, commonly used in bipolar disorder, increase sleep related breathing disorders, and therefore OSA co-existence should be excluded before choosing such treatment. The presence of OSA has an influence on the course of bipolar disorder. The presence of obesity, which is a risk factor for sleep apnoea, is associated with a worse course of bipolar disorder [44]. It is also known that all exogenous causes of sleep reduction, such as shift work and jet lag, can cause the phase shift in bipolar disorder [45]. In a similar way, phase shift can be caused by the sleep disruption caused by OSA [46].

Reports in the literature suggest a significant caution when initiating CPAP treatment in patients with bipolar disorder. A few cases of mania induced by CPAP were described, both in patients with unipolar depression, that have not been treated with mood stabilisers, and in patients with a diagnosis of bipolar disorder in a stable mental state, regardless whether the treatment with mood stabilisers was present [47]. In addition, the drugs used for treatment of mania, such as benzodiazepines and antipsychotics can cause respiratory failure in patients with bipolar disorder and OSA, which forces a switch to electroconvulsive therapy [48].

Recapitulation

Sleep-related breathing disorders often remain undiagnosed in patients with mental illnesses. This increases their risk for cardiovascular diseases, worsens cognitive functions, increases the symptoms of the mental disorders and causes that some drugs used in psychiatry can have negative influence on patients' health by increasing the severity of OSA.

Psychiatric hospitals should be an important place for recognition of sleep apnoea in patients with severe mental illnesses. Some symptoms of OSA, for example daytime sleepiness and problems with concentration, are nonspecific, and are often regarded by both patients and physicians as being associated with mental illness and current medication. Other more common symptoms of OSA, like snoring and apnoeas, require observation by partners of patients with OSA. However, in comparison with general population, mentally ill patients more often live alone, or sleep in separate bedroom. A stay in a psychiatric ward is therefore an opportunity to observe the patient during sleep by nursing staff and other patients in the room as well. The assessment of each patient with STOP-Bang criteria, also in mental health units, would effectively identify patients who need further evaluation. Taking into account the fact that the assessment with the STOP-Bang criteria can identify more than 50% of patients with severe mental illness as having high risk for sleep apnoea, it seems reasonable to carry out polygraph test before referring a patient to polysomnography. In uncooperative patients who also need an approximate assessment of the length and quality of sleep, a screening study with device using PAT technology can be considered. Physicians

should pay attention to obese patients because obesity is a modifiable risk factor for sleep apnoea. Recommendations for lifestyle changes and modification of pharmacotherapy towards the less metabolically active should be the next step in the procedure. The ways how to implement the recommendations for weight loss and using CPAP therapy in patients with mental illness still require further studies and individual approach to each patient is needed. From the point of view of the physicians involved in OSA treatment, it is important to note that depressive symptoms are the most common cause of persistent excessive sleepiness in patient with OSA effectively treated with CPAP. It is also important to note that in patients with schizophrenia and bipolar disorder CPAP therapy most often leads to improvement, however, in a few cases it might lead to deterioration of mental condition. This may be manifested in the onset of psychotic symptoms of schizophrenia or switching from depressive to manic phase in bipolar disorder.

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