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Is there more risk of OSA in patients with schizophrenia?

¿Existe un mayor riesgo de SAHS en esquizofrenia?

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SUMMARY

SUMMARY OF TABLES AND FIGURES

TABLES

FIGURES:

1. ABBREVIATIONS

AHI: apnoea-hypopnoea index.

BMI: body mass index.

CPAP: continuous positive airway pressure.

MetS: metabolic syndrome.

OSA: obstructive sleep apnoea.

RDI: respiratory desaturation index.

2. GLOSSARY OF TERMS

Apnoea: complete occlusion of airflow through the upper airway.

Apnoea - hypopnoea index: the sum of total apnoeas and hypopnoeas divided by total hours of sleep.

Atrial fibrillation: is an irregular, rapid heart rate that may cause symptoms like heart palpitations, fatigue, and shortness of breath.

Atypical antipsychotics: also known as second generation antipsychotics are a group of medications for the treatment of psychosis, mania, bipolar depression and other indications. They are less likely to cause extrapyramidal side effects than traditional antipsychotics such as haloperidol, but are still associated with other significant side effects including sedation, weight gain, impaired glucose tolerance, etc. Examples include clozapine, olanzapine, risperidone, quetiapine, etc.

Body mass index: defined as body weight divided by height squared (kg/m^2).

Co-morbidity: is the presence of one or more additional conditions with a primary condition.

Coronary artery disease: A disease in which there is a narrowing or blockage of coronary arteries (blood vessels that carry blood and oxygen into the heart).

Hypopnoea: partial occlusion of airflow through the upper airway.

Hypoxia: is a condition in which the body or a region of it is deprived of adequate oxygenation at tissue level.

Impaired glucose tolerance: a pre-diabetic state diagnosed as an elevated glucose level 2 h after a 75 g oral glucose challenge.

Major mental illness: is a behavioural or mental pattern that causes significant distress or impairment of personal functioning.

Menopause: the period in a woman's life (typically between 45 and 50 years old) when menstruation ceases.

Metabolic syndrome: cluster of medical disorders including (central) obesity, hypertension, lipid abnormalities and impaired glucose tolerance, which frequently coexist and are associated with higher risk of cardiometabolic disorders.

Negative symptoms of schizophrenia: symptoms that describe loss or reduction of normal behaviour, e.g., apathy, avolition, reduced speech, withdrawal and anhedonia.

Neuroleptic drugs: also known as antipsychotic drugs.

Obstructive sleep apnoea: sleep disorder characterized by repeated apnoeic and/or hypopnoeic periods during sleep due to the collapse of the upper airway. Common symptoms may include snoring, daytime sleepiness and cognitive impairment. Patients are at increased risk of cardiometabolic disease.

Orexigenic: a term used to indicate medications with the capacity to induce weight gain.

Polysomnography: a polymodal sleep study involving electroencephalography (EEG), electrocardiography (ECG), electromyography (EMG) and electrooculography (EOG), oximetry and respiratory effort monitoring.

Polycystic ovary syndrome (PCOS): is a condition that affects woman's hormone levels. Patients produce higher amounts of male hormones. This hormonal imbalance produces missed or irregular menstrual periods that impacts on fertility.

Positive symptoms of schizophrenia: Feelings or behaviours that are usually not present, such as: delusions, hallucinations and bizarre behaviour.

Psychosocial treatments (interventions): include structured counseling, motivational enhancement, case management, care-coordination, psychotherapy and relapse prevention.

Pulse oximeter: measures the proportion of oxygenated haemoglobin in the blood from pulsating vessels, especially finger or ear capillaries.

Schizophrenia: a serious chronic mental illness characterized by positive and negative symptoms and cognitive impairment, associated with onset in late adolescence/early adulthood and lifelong disability.

Sedative medication: A drug that calms a patient, easing agitation and allowing him to sleep.

Stroke: sudden death of brain cells. A stroke occurs when the blood supply to part of your brain is interrupted or reduced, depriving brain tissue of oxygen and nutrients. Two main types: ischaemic strokes and haemorrhagic strokes. Sudden loss of speech, weakness, or paralysis of one side of the body can be symptoms.

3. ABSTRACT

Background: Risk factors for obstructive sleep apnea (OSA) are common in people with schizophrenia. OSA may be prevalent and potentially under-recognized and under-treated in people with schizophrenia.

Aims: To determine, in people with schizophrenia: the prevalence of OSA; the physical and psychiatric correlates of OSA, associations between antipsychotic medications and OSA and the impact of treatment of OSA on psychiatric and physical health.

Methods: We reviewed major electronic databases (PubMed and Google Scholar) from 1980 until May 2019. Articles were included if reported prevalence of OSA determined by polysomnography (PSG) -an apnea-hypopnea index (AHI) >5 events/hr- and/or by pulse oximetry determined in patients with diagnosis of schizophrenia, according to structured clinical assessment and/ or meeting standardised diagnostic criteria.

Results: OSA prevalence assessed in people with schizophrenia was estimated between 13.6 and 57.1%. Most studies showed significant independent effect regarding age, body mass index (BMI), and chronic neuroleptic use, on the presence of OSA in psychiatric patients, with the schizophrenic group having significantly higher BMI and increased rates of sleep apnea.

Conclusion: People with schizophrenia have higher prevalence of OSA and this may negatively impact a range of health outcomes, therefore demands closer attention in clinical practice.

Keywords: Schizophrenia, Obstructive sleep apnoea, Metabolic syndrome, Continuous positive airway pressure, Review.

4. INTRODUCTION

4.1 SCHIZOPHRENIA

Schizophrenia is arguably one of the most disabling of the neuropsychiatric disorders, that affects approximately 1% of the population worldwide (Saha, Chant, Welham, & McGrath, 2005). It has been described as a neurodevelopmental disorder and probably encompasses a number of similar disorders, resulting from the complex interaction of multiple genes and environmental influences, including epigenetic factors (Fatemi & Folsom, 2009; van Os & Kapur, 2009). Generally, onset is in late adolescence or early adulthood with a lifelong course frequently marked by distressing symptoms, social and occupational impairment and exclusion (Mueser & McGurk, 2004).

The disorder is often characterized by incomplete recovery, and patients may variably exhibit persisting positive, negative, cognitive and affective symptoms, suicidal ideation, social withdrawal and unusual or personally maladaptive behaviours, all of which contribute to impairments in social role and occupational functioning (Elkis & Meltzer, 2010).

No cure for schizophrenia has yet been identified, but symptom control and better functional outcomes can be achieved -at least to some extent- using combinations of antipsychotic medications and adjunctive evidence-based psychosocial treatments (Dixon et al., 2010).

4.1.1 Schizophrenia and medical co-morbidity

Over recent years, both the medical literature and clinical practice have witnessed an ever-increasing awareness of the medical co-morbidity associated with schizophrenia and other major mental illnesses (Lambert, Velakoulis, & Pantelis, 2003; Meyer & Stahl, 2009).These patients are living with psychosis experience, poor physical health and shortened life expectancy; with higher prevalence of cardiometabolic risk factors (Galletly et al., 2012; Laursen, 2011) and cognitive impairment (Badcock et al., 2015; Morgan et al., 2014) that usually leads to impaired social and occupational functions (Badcock et al., 2015; Morgan et al., 2012; Mueser & McGurk, 2004).

Of particular note are high rates of cardiovascular risk factors: including obesity, hypertension, lipid and glucose metabolisms abnormalities (Bell, Farmer, Ries, & Srebnik, 2009; Bradley & Floras, 2009). This symptom cluster (other than clotting abnormalities) is referred to as the metabolic syndrome (MetS) and is found in 30-70% of individuals with schizophrenia (Meyer & Stahl, 2009). In addition to traditional risk factors for MetS such as at-risk ethnicity, age and family history, people with schizophrenia are particularly likely to have a poor diet and a sedentary lifestyle, which further increase the risk of developing the MetS (Holt & Peveler, 2006). Together with the sociodemographic deprivation so common in those with mental illness, these factors contribute substantially to weight gain even in those patients not taking

neuroleptics (Meyer & Stahl, 2009). In fact, high rates of obesity (Galletly et al., 2012)(Mitchell et al., 2013), tobacco smoking (N. Myles et al., 2012), alcohol consumption (Moore, Mancuso, Slade, Galletly, & Castle, 2012) and frequent sedative medication use (Al Lawati, Patel, & Ayas, 2009; Galletly et al., 2012) are risk factors shared with OSA, so they can contribute to its development in these particular patients.

4.2 OBSTRUCTIVE SLEEP APNOEA (OSA)

Obstructive sleep apnea (OSA) affects 2–4% of the general adult population(Young et al., 1993). OSA is characterized by repeated pharyngeal obstructions during sleep, resulting in airflow cessation (apnea) or reduction (hypopnea), frequent disruption of sleep, and hypoxic episodes (Liu et al., 2016).

Clinical symptoms include daytime somnolence, snoring and cognitive impairment (Kalucy, Grunstein, Lambert, & Glozier, 2013). A number of anatomical and muscular disorders can contribute to sleep apnoea. However, the most significant risk factors are obesity, male gender, increasing age and an increased neck circumference(Chang et al., 2011). While obesity is the most significant risk factor, others including smoking and use of sedative medications, have been found to play a significant role in OSA development (V Hoffstein, 2002; C. T. Li et al., 2014; Shirani, Paradiso, & Dyken, 2011). In addition, it should be kept in mind that, in women, menopause (Anttalainen et al., 2006), polycystic ovarian syndrome and episodes of atrial fibrillation are known as independent risk factor for OSA (Mansukhani, Calvin, & Kolla, 2013; A. Vgontzas, Legro, & Bixler, 2001).

4.2.1 OSA and medical co-morbidity

OSA is now known to be associated with an increased risk of stroke (Redline et al., 2010), hypertension (Devulapally, Pongonis, & Khayat, 2009), arrhythmias (Mehra et al., 2006), coronary artery disease and heart failure (Chang et al., 2011; Devulapally et al., 2009) and abnormal glucose metabolism (Aronsohn, Whitmore, Van Cauter, & Tasali, 2010; Muraki et al., 2010). Moreover, other reports have suggested that OSA is in fact a manifestation of metabolic syndrome (Iskander et al., 2009; A. N. Vgontzas, Bixler, & Chrousos, 2005). Actually recent data from the Cleveland Sleep Study demonstrated the co-aggregation of OSA with other components of the MetS (obesity, insulin resistance, hypertension and dyslipidaemia) for which Nock et al. have proposed the label “syndrome Z”(Nock, Li, Larkin, Patel, & Redline, 2009). Because of all the above mentioned, OSA is associated with poor cardiometabolic outcome (Bradley & Floras, 2009) increased risk of depression and anxiety, and impaired neurocognitive function (Kielb, Ancoli-Israel, Rebok, & Spira, 2012).

4.2.2 Diagnosis of OSA and their problems

Formal diagnosis of OSA is achieved using overnight polysomnography (PSG) and is defined as an elevation (usually above 5 events per hour) in the apnoea-hypopnoea index (AHI), which derives by dividing the sum of all observed apnoeas and hypopnoeas by the number of hours of sleep (Colten & Altebogt, 2006). An AHI of 5–15 means mild OSA; an AHI of 15–30 means moderate OSA and an AHI greater than 30 means severe OSA. However, questionnaires are also used and can determine risk for specific sleep disorders, such as the STOP-BANG used for OSA (Chung et al., 2008). So we have to take into account that diagnostic cut-offs vary between studies according to the methodology used to diagnose.

4.2.3 Treatment

Continuous positive airway pressure (CPAP) means wearing a mask at night that blows air into the nose so as to generate positive pressure (Rasmusson, Bidarian, Sennerby, & Scott, 2012). This improves oxygenation and increases lung volume. Is the first-line treatment but it has common side effects including: feelings of claustrophobia, nasal congestion and rhinorrhoea, skin irritation, dry eyes and airways and pressure sores from the mask. A Cochrane review has confirmed the effectiveness of CPAP delivered by nasal mask in controlling the symptoms of OSA (Giles et al., 2006). Despite its recognized efficacy, its effectiveness is frequently reduced due to non-adherence (Catcheside, 2010; Weaver & Grunstein, 2008).

On the other hand, proper perception of OSA severity, need and benefits of treatment may be some important factors helping in achieving adherence (Rasmusson et al., 2012; Weaver & Grunstein, 2008). Cognitive behavioural therapy was demonstrated to improve CPAP adherence, furthermore, for those unwilling or unable to comply with CPAP treatment, oral appliances can also provide good results, but only for those with the milder forms of OSA (V. Hoffstein, 2007; W. Li, Xiao, & Hu, 2013). However, evidence for other behavioural interventions including short-term education is minimal or lacking (Smith, Nadig, & Lasserson, 2009).

4 AIMS

The first aim of the present study is to determine if there is a higher incidence of OSA in patients with schizophrenia. Secondly, we will explore if the presence of OSA affects the evolution of schizophrenia in any way.

5 METHODOLOGY

We conducted a narrative literature review of the scientific evidence published regarding OSA and Schizophrenia. For this purpose, we searched through major electronic databases (PubMed and Google Scholar) from 1980 until May 2019, crossing "psychosis" and "Obstructive sleep apnea" terms.

5.1 SELECTION CRITERIA

Record titles, review articles and abstracts were screened. We included observational (clinical or population cohort) studies (prospective, retrospective or cross-sectional) that:

a. Included people with a diagnosis of schizophrenia according to a structured clinical assessment and/ or meeting standardised diagnostic criteria.

b. Reported the prevalence of OSA determined by polysomnography (PSG), an apnea-hypopnea index (AHI) >5 events/hr and by pulse oximetry, determined in schizophrenic patients.

We excluded articles not written in English and articles unrelated to OSA and schizophrenia.

When studies reporting data from the same sample at different time points were found, we used the most recent data and/or the largest data set.

5.2 LIMITATIONS

As it is a systematic review, it is important to highlight the methodological limitations arising from it. The publication bias is one of the main limitations. This is because studies with negative results, either not finding significant differences or going against the study hypothesis, are not published and therefore cannot be included in a systematic review. Similarly, even when these studies are published, a citation bias may occur, as studies with negative results are cited less than those with favourable results. Along with these two biases, we also find a selection bias, since the author of the systematic review could produce it by including or excluding studies based on their results. So, to prevent this, we have tried to clearly define the inclusion and exclusion criteria.

Other important biases that may have influenced the present work arise from the database, since we have only performed the bibliographic search using PubMed and Google Scholar. On the other hand, the language bias could be also present, as we have only considered studies in English, discarding other studies published in other languages. Finally, the validity and quality of the results of a systematic review is influenced and modified by the quality of the original studies and their results, as well as their variability.

6 RESULTS

6.1 STUDIES REPORTING PREVALENCE OF OSA IN POPULATIONS OF PATIENTS WITH SCHIZOPHRENIA

Table 1. Original research studies on OSA and schizophrenia

AUTHORS	PATIENTS	METHOD OF DIAGNOSIS	OSA RATES
(Alam, Chengappa, & Ghinassi, 2012)	100 psychiatric patients: • 56 with schizophrenia. • 18 with schizoaffective disorder.	STOP-BANG screening	69% of the patient population was at high risk for OSA; among them, 62% had a schizophrenia diagnosis.
(Ancoli-Israel et al., 1999)	52 outpatients with DSM-III-R schizophrenia (N=44) or schizo-affective disorder (N=8). Retrospective matched control group	Ambulatory sleep study	Cases: 48% (RDI >10), 31% (RDI >20). Controls: 45% (RDI > 10), 19% (RDI > 20)
(Anderson, Waton, Armstrong, Watkinson, & Mackin, 2012)	52 outpatients with major mental illness, 25 (48%) had a diagnosis of schizophrenia or schizoaffective disorder	PSG	Mild (AHI 5–15): 32% Moderate (AHI 15–30): 14% Severe (AHI > 30): 6%
(Annamalai, Palmese, Chwastiak, Srihari, & Tek, 2015)	175 with schizophrenia and schizoaffective disorder	NA	14.6% of all patients had a OSA diagnosis, 57.7% were at high risk.
(Benson & Zarcone, 1994)	141 patients undergoing sleep studies including: • 33 healthy controls. • 55 with schizophrenia. • 53 with other psychiatric disorders	PSG	Healthy controls: 15% Schizophrenia group: 14.5%. Other psychiatric disorders: 18.9%
(Haque, Anwar, Crowe, Brophy, & Stokes, 2008)	52 outpatients with schizophrenia	Ambulatory sleep study	44%
(Sharafkhaneh, Giray, Richardson, Young, & Hirshkowitz, 2005)	US Veterans from Health Administration database (n> 4 million)	Diagnostic codes for OSA	With 'psychosis': 1.6%. Without psychosis: 1.2%
(Stubbs et al., 2016)	138,700 patients with schizophrenia spectrum disorder	NA	The prevalence of OSA was 15.4%
(Takahashi et al., 1998)	101 inpatients with DSM-III-R schizophrenia. 48 healthy controls	Ambulatory pulse oximetry	Schizophrenia group: 19%(21.9% men, 13.6% women) Healthy controls: 23%(30.8% men, 13.6% women)
(Waters, Hanken, & Rock, 2013)	74 psychiatric patients: 52 with schizophrenia	NA	25% of patients with schizophrenia were at high risk for OSA.
(Winkelman, 2001)	364 consecutive psychiatric inpatient referrals to a sleep clinic; 46 with schizophrenia	PSG	33/46 (72%) patients analyzed for OSA risk. Males: 46.2%. Females: 57.1%

Abbreviations: BMI, body mass index; DSM-III-R, Diagnostic and statistical manual of the American Psychiatric Association third edition (revised); NA, not available; OSA, obstructive sleep apnea; PSG, polysomnography; RDI, respiratory desaturation index.

There are quite few studies reporting the prevalence of OSA in people with schizophrenia compared with control cases from general population. However, eleven surveys of selected patient samples were found as a result of an extensive database research (Table 1).

As described in Table 1, the former study of this revision by Benson and Zarcone reported a diagnosis of OSA in 14.5% of schizophrenic patients screened in their sleep laboratory (Benson & Zarcone, 1994). In this specific comparison they didn´t report patient's body mass index (BMI) or if they received treatment. In a more detailed report, Winkelman retrospectively evaluated rates of OSA in 364 consecutive psychiatric inpatient referrals to a sleep clinic. Of the 46 patients with schizophrenia, 75% were overweight and 50% were obese with a mean BMI of 35.5. All 46 patients were prescribed antipsychotic medication. Within the schizophrenia group, 72% (33 patients) underwent PSG. Rates of OSA, defined as an RDI >10, were significantly elevated in patients with schizophrenia/schizoaffective disorder (46.2% of males and 57.1% of females) compared to patients with other psychiatric diagnoses including depression, post-traumatic stress disorder, bipolar disorder or substance use disorders (Winkelman, 2001).

On the other hand, Takahashi and colleagues compared rates of "sleep disordered breathing" in a cohort of 101 Japanese inpatients with DSM-III-R schizophrenia and a group of 48 healthy controls of comparable BMI (within the normal range) and age (Takahashi et al., 1998). OSA was diagnosed using ambulatory pulse-oximetry devices, which are known to be less sensitive to OSA than PSG (Ryan et al., 1995) and was defined as an RDI >5 (as the number of desaturations greater than 4% below baseline/h). No significant difference in the RDI was found between cases and controls (19% of the schizophrenia group and 23% of the controls) and no relationship was identified between the RDI and antipsychotic medication use in the schizophrenia group. Of note, the mean BMI was within the normal range in both groups. Remarkably, a case-control study investigated an elderly schizophrenia group (N=44). Forty-eight percent of these patients had 10 respiratory events (apnoeas or hypopnoeas) per hour of sleep and reported more daytime sleepiness compared to a smaller group (N=8) of seasonal affective disorder patients, although these symptoms were unrelated to their BMI (Ancoli-Israel et al., 1999). When those participants over 65 years old were compared to a retrospectively matched healthy elderly controls, there was no difference in the rate of mild sleep apnoea but severe sleep apnoea (RDI >20) was more common in the schizophrenia group (31% vs 19%). Additionally, a cross-sectional study reported previously undiagnosed OSA in 23 of 52 (44.2%) Irish patients with schizophrenia attending a local mental health service and undergoing portable home sleep monitoring (with an Embletta apparatus). BMI, older age, waist circumference and waist-hip ratios were associated with OSA in this psychiatric patients (Haque et al., 2008). In agreement, a meta-analysis reporting a prevalence of 15.4% of OSA in schizophrenic patients also reported association with older age and higher BMI (Stubbs et al., 2016).

The largest study to date was a retrospective cross-sectional review of clinical codes indicating sleep apnoea, and psychiatric conditions recorded in the United States Veterans' Health Administration database, including inpatient and outpatient contacts, between 1998 and 2001 (Sharafkhaneh et al., 2005). A total of 118,105 out of 4,060,504 veterans were identified as having OSA (2.9%). Patients with psychiatric disorders were significantly more likely to have a co-morbid diagnosis of OSA. Sleep apnoea was diagnosed in 1.6% of patients with a 'psychosis' compared to 1.2% of patients without 'psychosis' (OR 1.49 (95% CI1.05-1.92)), although rates were not adjusted for BMI. Whilst this study is of impressive size, it suffers from selection bias as included only VHA patients, who are mainly male and middle aged or older, and documented only their VHA health contacts. Of note, also is the generally reduced availability of sleep medicine services in the VHA system compared to other health services in the US (Flemons, Douglas, Kuna, Rodenstein, & Wheatley, 2004) and people with schizophrenia have yet further reduced access to many forms of specialist care.(Mitchell, Malone, & Doebbeling, 2009). As it was also said for other studies, rates were not adjusted for BMI and in addition, the accuracy of database clinical diagnoses is also unclear.

One study in patients with severe mental illness treated at a primary care clinic found that 69% had high scores for the STOP-BANG, a screening questionnaire for OSA, and among this group 62% had a diagnosis of schizophrenia (Alam et al., 2012). It was reported that almost three quarters of patients with severe mental illness accepted referral for PSG and 85% of the patients were taking clozapine (N=42) meanwhile 69% of those were on risperidone (N=42), being both orexigenic treatments. In a more recent study of 175 outpatients with schizophrenia, a high prevalence of OSA (14%) was observed. BMI was found to be significantly higher in those patients diagnosed with OSA when compared with those without an OSA diagnosis (Annamalai et al., 2015). The management of these problems was with CPAP, and the treatment compliance was 53.8%. Similarly, Waters et al observed that high-risk schizophrenia patients were on more than one antipsychotic medication and on higher doses compared to other patients at low risk for OSA (Waters et al., 2013). And a previous study (Anderson et al., 2012), excluded subjects with previous OSA diagnosis, potentially reducing prevalence estimates. So they reported a negative correlation between quantitative measures of antipsychotic use (percentage of maximum dose) and AHI N 5 on univariate analysis, but no significant interaction between categorical benzodiazepine use and AHI on multivariate analysis.

In summary, most of the studies abovementioned (Alam et al., 2012; Ancoli-Israel et al., 1999; Annamalai et al., 2015; Haque et al., 2008; Stubbs et al., 2016; Waters et al., 2013; Winkelman, 2001) showed that age, BMI, and chronic neuroleptic use, all have a significant independent effect on the presence of OSA in psychiatric patients, with the schizophrenic group having significantly higher BMI and increased rates of sleep apnoea. Obesity is a likely factor responsible for the association between schizophrenia and OSA. We have to remember that excessive weight gain is a common side effect of antipsychotic medication. So, both genetically determined and medication-induced obesity can lead to OSA.

In contrast, studies in which there is no relationship between schizophrenia and OSA (Anderson et al., 2012; Benson & Zarcone, 1994; Sharafkhaneh et al., 2005; Takahashi et al., 1998), were either due to lack of knowledge of the patient's BMI, or because the patient were within the range of normality, or some variability in assessment measures and diagnostic thresholds for OSA.

With this information, we can conclude that studies assessing OSA in people with schizophrenia provide prevalence estimated between 13.6 and 57.1% which is higher than the one for the general population (Heinzer et al., 2015).

6.2 CASES REPORT OF OSA AND SCHIZOPHRENIA OR PSYCHOSIS

Table 2. Case series of OSA and schizophrenia.

AUTHORS	SUBJECT	DIAGNOSTIC METHOD	DIAGNOSIS	OUTCOME
(Berrettini, 1980)	Thirty-three year old man withpsychosis and recent weight gain	Polysomnography	OSA	Psychosis significantly improved with use of oropharyngeal airway
(Boufidis et al., 2003)	Thirty-six year old man with acute exacerbation of chronic schizophrenia and recent weight gain	Polysomnography	OSA	Psychotic symptoms resolved with a combination of CPAP, antipsychotic medications and weight loss
(Chiner, Arriero, Signes-Costa, & Marco, 2001)	Fifty-two year old man with chronic schizophrenia and recent weight gain	Polysomnography	OSA	Psychotic episode with onset 5 days after commencing CPAP. Psychotic symptoms resolved after ceasing CPAP and commencing neuroleptics
(Karanti & Landen, 2007)	Sixty-three year old female withchronic schizophrenia, type II diabetes, heart failure and obesity	Polysomnography	OSA	Psychotic symptoms and physical health significantly improved after commencing CPAP
(Lee, Chiu, & Chen, 1989)	Thirty year old with recurrent psychotic symptoms	Polysomnography	OSA	Psychosis resolved permanently following tonsillectomy to treat OSA
(Martin & Lefebvre, 1981)	Thirteen year old with congenital retrognathia and psychosis	Polysomnography	OSA	Psychosis resolved after surgical treatment of retrognathia
(Wirshing, Pierre, & Wirshing, 2002)	<u>Case 1</u> 45-year-old woman withschizophrenia and significantneuroleptic related weight gain,hypertriglyceridaemia and glucose intolerance <u>Case 2</u> 50-year-old man withschizophrenia and recent neuroleptic weight gain and type II diabetes	Polysomnography	OSA	Improvement in OSA after commencing CPAP

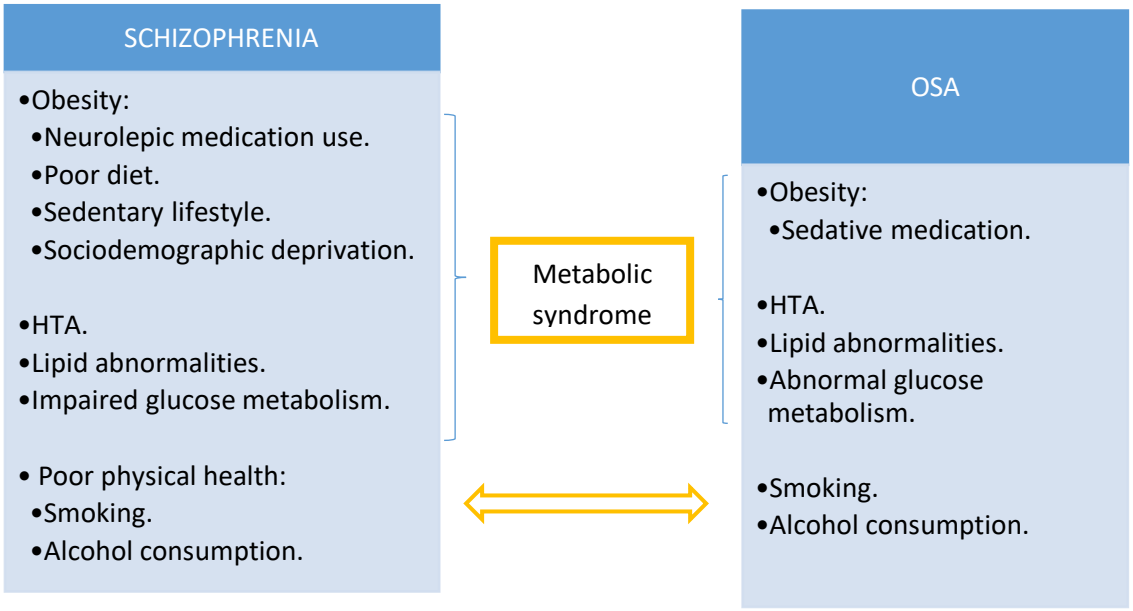
Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

7 DISCUSSION

7.1. HOW IS THE HIGHER INCIDENCE OF OSA IN PATIENTS WITH SCHIZOPHRENIA EXPLAINED?

Several studies have found a high prevalence of OSA in people with schizophrenia (Alam et al., 2012; Ancoli-Israel et al., 1999; Annamalai et al., 2015; Haque et al., 2008; Stubbs et al., 2016; Waters et al., 2013; Winkelman, 2001), but few studies have focused on OSA in people with psychosis (Kalucy et al., 2013; H. Myles et al., 2016; H. Myles et al., 2018; Seeman, 2014), although OSA and psychotic disorders, mainly schizophrenia, share many risk factors and poor clinical outcomes (Figure 1). One possible explanation for this association could be supported by the fact that MetS and OSA (Young, Peppard, & Gottlieb, 2002) share obesity as a principal risk factor. In fact, the two-fold higher prevalence of obesity and the MetS in schizophrenia (Meyer & Stahl, 2009) would seem likely that OSA would also be more prevalent (Boufidis et al., 2003; Winkelman, 2001) among these patients.

Figure 1. Common factors between schizophrenia and OSA



The high prevalence of obesity in schizophrenic people could be explained as:

a. Many psychotropic medications are orexigenic (Kim, Huang, Snowman, Teuscher, & Snyder, 2007).

b. People with schizophrenia are particularly likely to have a poor diet and a sedentary lifestyle, which further increase the risk of developing the MetS (Holt & Peveler, 2006).

c. Sociodemographic deprivation contribute substantially to weight gain, even in those patients not taking neuroleptics (Meyer & Stahl, 2009).

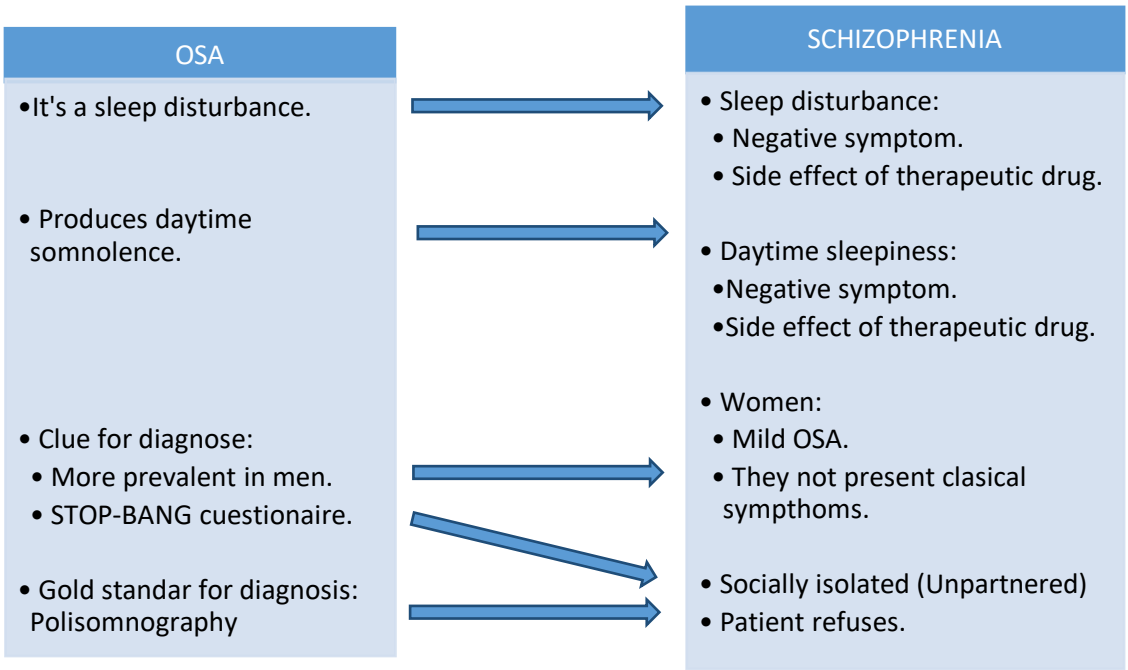
At the same time, there is evidence, albeit inconsistent, that smoking and alcohol abuse increase the risk for OSA. Both behaviours are very common in those with schizophrenia, potentially further increasing the risk of OSA in this population (McClave, McKnight-Eily, Davis, & Dube, 2010; McMillan, Enns, Cox, & Sareen, 2009).

In conclusion, all these risk factors/non healthy habits such as: high rates of obesity (Galletly et al., 2012)(Mitchell et al., 2013), tobacco smoking (N. Myles et al., 2012), alcohol consumption (Moore et al., 2012) and frequent sedative medication use (Al Lawati et al., 2009; Galletly et al., 2012) were observed in people with psychotic illnesses, and may contribute to the development of OSA and its higher prevalence in this particular group.

7.2 WHY IS THE RELATIONSHIP BETWEEN OSA AND SCHIZOPHRENIA NOT SO OBVIOUS IF THEY SHARE MANY COMMON RISK FACTORS?

Obstructive sleep apnoea (OSA) can be inordinately difficult to ascertain in the context of schizophrenia because of several reasons (Figure 2):

Figure 2. Overlap of clinical characteristics and symptomatology between OSA and Schizophenia



First of all, clinical symptoms of OSA include daytime somnolence, snoring and cognitive impairment (Kalucy et al., 2013). In patients with schizophrenia, daytime sleepiness, an important early clinical clue to OSA, is so commonplace (Poulin et al., 2010) that it is easily overlooked or attributed to the effects of therapeutic drugs. In addition, sleep disturbance and cognitive impairment are mistaken for negative symptoms of schizophrenia or medication side effects (H. Myles et al., 2016).

Furthermore, the relationship between OSA and Schizophrenia, especially in women, may go unrecognized. It has now been demonstrated that OSA is not as rare in women as previously thought, and that the general population male-to-female prevalence ratios are only 3:1 to 2:1 (Ye, Pien, & Weaver, 2009). However, male/female ratios are especially high (8:1) in clinical populations, which suggest that more than 90% of women with OSA are never clinically diagnosed. That's because women may not present with the classical picture: snoring, witnessed apnoeas, excessive daytime sleepiness. When they do present, women generally have a milder form of OSA and a higher BMI than men with OSA. Their clinical picture may be one of lack of energy (often from concomitant hypothyroidism), depression, and insomnia (Shah, Yaggi, & Redline, 2013; Ye et al., 2009).

As we have previously said, patients with schizophrenia are usually socially isolated so the commonly used screening instruments (STOP questionnaire) may be less useful in these patients relative to other patients because they rely, in part, on reports of snoring and gasping for breath at night as observed by a bed partner, whereas the majority of people with schizophrenia are unpartnered. In spite of all this, even when OSA is suspected, patients, frequently refuses to be physically examined (Iwata et al., 2011). The reasons are because of apathy, lack of understanding of the potential medical consequences of OSA or general suspiciousness, and may refuse sleep assessment. So the diagnose of OSA it's even more difficult for them (Iwata, Strydom, & Osborn, 2011). Even if they accepted, there is also the problem that PSG is considered the gold standard for diagnosis of OSA. However, requires a full night's stay at a sleep laboratory with a technician in attendance – a stressful and costly endeavour for many patients with schizophrenia.

7.3 WHAT WOULD WE HAVE TO TAKE INTO ACCOUNT TO DIAGNOSE THIS PROBLEM AND MAKE THE OSA SCHIZOPHRENIA RELATION MORE EVIDENT?

OSA is known to have strong familiar basis (Patel et al., 2012), also menopause is a known independent risk factor for OSA (Anttalainen et al., 2006). So, these factors could serve as a clue to diagnosis. Besides being aware of typical symptoms such as daytime sleepiness (which may confuse with the side effects of medication), in women specifically, special attention should be paid to those who suffer from schizophrenia and who refer to being tired (most common form of OSA presentation in women).

7.4 EVEN WHEN SUCCESSFULLY DIAGNOSED OSA CAN BE DIFFICULT TO TREAT IN SCHIZOPHRENIA PATIENTS

Even if the treatment is accepted, adherence with continuous positive airway pressure (CPAP), because of discomfort and side-effects, is difficult for most people and has been reported to be especially so for patients with schizophrenia (Lin & Winkelman, 2012). It should be noted that CPAP noise can remind patients of the auditory hallucinations they had. In addition, having no bed partner (Cartwright, 2008; Gagnadoux et al., 2011)(Baron, Gunn, & Czajkowski, 2012), unemployment (Gagnadoux et al., 2011) and poverty (Simon-Tuval et al., 2009) are all associated with poor adherence to CPAP and these all apply to most individuals with schizophrenia (Baron et al., 2012).

7.5 STILL, WHY IS IT IMPORTANT TO GET INVOLVED AND TRY TO SOLVE THE PROBLEM?

It is important to identify and treat OSA when co-morbid with schizophrenia, because daytime sleepiness leads to accidents. Also, because over time, the pathological sequel of OSA, including repeated episodes of hypoxia, sleep fragmentation, and oxidative stress, may precipitate or perpetuate psychopathological symptoms, cardiometabolic harms (Baguet, Barone-Rochette, Tamisier, Levy, & Pepin, 2012; Botros et al., 2009; Drager, Jun, & Polotsky, 2010; Drager, Polotsky, & Lorenzi-Filho, 2011; Jun & Polotsky, 2009; Redline et al., 2010) and cognitive impairment (Grigg-Damberger & Ralls, 2012; Lal, Strange, & Bachman, 2012; Verstraeten, 2007). The evidence is not clear yet about the effects of CPAP on metabolic and cognitive indexes (Iftikhar, Khan, Das, & Magalang, 2013). Nevertheless, attention, vigilance and perhaps memory appear to improve with continuous CPAP treatment (Ferini-Strambi, Marelli, Galbiati, & Castronovo, 2013), which makes this difficult diagnose worth the effort.

7.6 WHAT DO WE WANT WITH ALL THIS?

If the sleep-pause time is reduced and therefore the deep sleep improves, patients will be able to function better during the day as they will have less daytime sleepiness. By doing this, they may be able to have enough energy to exercise, which helps develop other healthy habits such as losing weight and starting a diet, and may even quit bad habits such as smoking and alcohol.

7.7 WHAT RECOMMENDATIONS SHOULD WE GIVE TO THIS PATIENT PROFILE?

Figure 3. Recommendations for patients with schizophrenia who presents OSA should take.

7.7.1 Regarding medication:

One of the most significant potentially reversible causes of obesity and MetS in schizophrenia is the selection of antipsychotic medication (Kahn et al., 2008; Newcomer, 2007). Among the most likely candidates which exhibit short-term weight gain are olanzapine, clozapine, chlorpromazine, quetiapine, and risperidone (Leucht et al., 2009). Furthermore, polypsychotropic prescription is common in schizophrenia and other frequently co-prescribed agents such as valproate and lithium are also associated with weight gain (Malhotra & White, 2002). So, sedating and weight-inducing medications should be withdrawn if possible.

All daytime sleepiness calls for safety measures and full scale investigation. So we also need to warn about the symptoms of drowsiness that patients may have with indicated medication. It is very difficult to avoid this symptom, but what we can do is prevention, specifically to prevent accidents from occurring: like traffic (Karimi, Eder , & Eskandari, 2013) and domestic accidents. Also we can recommend adjunctive evidence-based psychosocial treatments because of the fact that cognitive behavioural therapy was demonstrated to improve CPAP adherence.

7.7.2 Regarding bad habits:

Patients should be asked if they:

a. Drink alcohol, which could aggravate sleepiness and impair judgment.

b. Smoke, because the patient could fall asleep while smoking and inadvertently start a fire.

So diet, exercise, and counselling abstinence from tobacco and alcohol are first-line interventions.

7.7.3 Regarding sleep position:

It has been calculated that, in many patients with sleep apnoea, the sleeping position (supine versus non-supine) accounts for much of the apnoea index score (Joosten, O'Driscoll, Berger, & Hamilton, 2014; Ravesloot, Van Maanen, Dun, & De Vries, 2013; Sunnergren, Broström, & Svanborg, 2013). Various techniques and devices (pillows, alarms, vests) have been recommended to prevent sleeping on one's back. If patients can learn to avoid the supine position, a substantial number will have less trouble breathing at night (Ravesloot et al., 2013).

7.7.4 Regarding treatment with CPAP:

The clinician needs to screen for CPAP side-effects and assess patient's difficulties in using the equipment (adjusting the mask straps to prevent leaks and pressure sores, knowing how to connect and disconnect tubing). Once problems are identified, a constant encouragement from their psychiatrist is essential for patients to stay with their CPAP device. It should be noted that if adherence to treatment is not achieved, in cases of milder OSA frequently observed in women, oral appliances may be as effective as CPAP and better tolerated. So we can try this treatment in these particular cases.

8 CONCLUSIONS

Schizophrenia is associated with significantly increased physical morbidity and mortality, particularly secondary to cardiometabolic disorders. In people with schizophrenia, rates of obesity and the metabolic syndrome are higher compared to the general population. Whilst the weight gain secondary to antipsychotic medication is largely to blame, other factors include inactivity, poor diet and possibly the illness itself.

Obstructive sleep apnoea (OSA) may be associated with disabling symptoms including daytime sleepiness, cognitive impairment, depression, anxiety and long-term increases in morbidity and mortality secondary to cardiometabolic disease.

High rates of obesity (Galletly et al., 2012)(Mitchell et al., 2013), tobacco smoking (N. Myles et al., 2012), alcohol consumption (Moore et al., 2012) and frequent sedative medication use (Al Lawati et al., 2009; Galletly et al., 2012) observed in people with psychotic illnesses, may contribute to the development of OSA. In women also: postmenopause, with polycystic ovaries, and those with atrial fibrillation. Furthermore, a number of studies suggest a plausible relationship between weight gain, possibly enhanced by antipsychotic medication, and the development of OSA, and interestingly suggest a relationship between treatment of OSA and resolution (and in one case, exacerbation) of psychotic symptoms (Boufidis et al., 2003; Chiner et al., 2001; Karanti & Landen, 2007; Lee et al., 1989; Martin & Lefebvre, 1981). Recognition of OSA as an integral component of the MetS or, as it may come to be renamed, “syndrome Z”(Nock et al., 2009) may enhance the likelihood of diagnosis and treatment.

Health practitioners may be unaware of the need to screen for sleep apnoea in patients with schizophrenia and the disorder may be significantly under-recognised because of patient's daytime sleepiness may be erroneously attributed to their drugs. In addition, sleep disturbance, and cognitive impairment can be mistaken for negative symptoms of schizophrenia or medication side effects (H. Myles et al., 2016).

Treatment of OSA in people with schizophrenia has the potential to improve psychotic symptomatology, cognitive function, physical health and finally, quality of life.

9 TEACHING POINTS

- ✓ Schizophrenia and OSA share the metabolic syndrome as common risk factor, which is going to correlate both diseases.
- ✓ Sleep problems and, in particular, OSA symptoms should be included amongst general health screening for patients with schizophrenia.
- ✓ OSA poses immediate safety risks because of daytime sedation and long-term safety risks because of cardiovascular and metabolic sequel.
- ✓ Cognitive impairment, already present in schizophrenia, may be heightened when OSA coexists.
- ✓ Although more common in men, obstructive sleep apnoea (OSA) is not uncommon in women. This could serve as a clue to diagnosis.
- ✓ Daytime sleepiness in patients with schizophrenia may be erroneously attributed to their drugs.
- ✓ In addition to the daytime somnolence, sleep disturbance, and cognitive impairment are mistaken for negative symptoms of schizophrenia or medication side effects.
- ✓ Because they live alone, disordered breathing at night cannot be corroborated by STOP questionnaire to the bed partner.
- ✓ Diagnosis and treatment of OSA in people with schizophrenia may improve general physical health, mental health and quality of life.
- ✓ Diet, exercise, and counselling abstinence from tobacco and alcohol are first-line interventions.
- ✓ Sedating and weight-inducing medications should be withdrawn if possible.
- ✓ Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA, but adherence is difficult and needs to be encouraged and supported.

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