



Metabolic syndrome among patients taking second generation antipsychotics: does obstructive sleep apnoea and sleep quality play any role?

Abstract

Background: Metabolic syndrome (MetS) is common among patients who have been exposed to second generation antipsychotics (SGA). Obstructive sleep apnoea (OSA) and sleep quality may also contribute to MetS. **Aims:** To study the contribution of sleep quality and OSA on the development of MetS in patients taking SGA. **Methods:** Total 60 patients taking SGA for more than three months were taken for the study. It was an observational, cross-sectional study. The diagnosis of OSA was done using Hindi translation of Berlin questionnaire. Hindi version of the Pittsburg Sleep Quality Index was used to assess the sleep quality. MetS was diagnosed using Adult Treatment Panel III criteria. **Results:** Forty two subjects did not have MetS, out of which 35 had low risk of OSA and seven had high risk of OSA, while 18 subjects had MetS of which nine each had high and low risk of OSA. The results were highly significant with a p-value of 0.007 ($p \leq 0.05$). Subjects without MetS ($n=42$) comprised four good sleepers and 38 poor sleepers. Subjects with MetS ($n=18$) comprised of one good sleeper and 17 poor sleepers. The results were non-significant with a p-value of 0.525 ($p \geq 0.05$). The high risk of OSA had around seven times higher likelihood of contribution to MetS. **Conclusions:** Sleep quality did not play a significant role in increasing the likelihood of MetS and OSA increased the likelihood of MetS in subjects exposed to SGA by seven times.

Keywords: Syndrome X. Berlin Questionnaire. The Pittsburg Sleep Quality Index. Adult Treatment Panel III. DSM-5.

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INTRODUCTION

Metabolic syndrome (MetS) is common among patients seen in psychiatric clinics, especially among subjects with schizophrenia and the risk further worsens in patients who have been exposed to antipsychotics.[1] MetS, also known as Syndrome X is defined by the third Adult Treatment Panel (ATP III) of the National Cholesterol Education Programme (NCEP) criteria.[2] The diagnosis is based on the presence of three or more of the following criteria: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), elevated triglycerides (≥ 150 mg/dl), decreased high density lipoprotein cholesterol (<40 mg/dl in men or <50 mg/dl in women), systemic hypertension (blood pressure $\geq 130/85$ mm Hg), or hyperglycaemia (fasting plasma glucose ≥ 100 mg/dl).[2] Studies have found that second generation antipsychotics (SGA) may induce weight gain which is one of the risk factors for development of obstructive sleep apnoea (OSA).[3,4] OSA also contributes to MetS which has been attributed to several mechanisms such as intermittent hypoxia, oxidative stress, and cytokines.[5] Sleep quality also predisposes to MetS as assessed by sleep deprivation.[6]

Aims and objectives

To study the contribution of sleep quality and OSA on the development of MetS in patients taking SGA.

METHODS

The study was conducted over a period of 12 months, between January 2017 and December 2017 at Himalayan Institute of Medical Sciences, Dehradun, India after institutional scientific and ethics committee clearance. Total 60 samples were taken fulfilling the inclusion criteria of study. Only patients with primary diagnosis of schizophrenia spectrum disorder or bipolar disorder or major depressive disorder as per the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[7] were included. Both male and female subjects between 18-60 years of age constituted the samples. It was an observational, cross-sectional study. Patient taking SGA for more than three months only were included. The diagnosis of OSA was done clinically and using Hindi version of Berlin questionnaire.[8] Hindi version of the Pittsburg Sleep Quality Index was used to assess the sleep quality.[9,10] MetS was diagnosed using ATP III of NCEP criteria.[2] A written informed consent was taken from them.

Their demographic data, information regarding the present illness (total duration, course, number of episodes, and symptomatology of the present episode), details regarding comorbid psychiatric illness was recorded in a self-designed proforma. Diagnosis of psychiatric disorder was made using DSM-5 criteria.[7] Information regarding other medical disorders was recorded. Treatment history included type of medication taken, dose and duration of treatment.

RESULTS

A total of 81 subjects were recruited for the study of which 21 were excluded owing to various reasons such as pregnancy, poor compliance to SGA. Sixty subjects were finally included in the study which were analysed. However, samples which were included and those which were excluded were comparable in various domains.

Subjects with absence of MetS were more frequent (42 [70.0%]) while subjects with presence of the metabolic syndrome were fewer (18 [30.0%]). Subjects with poor sleep quality had a very high frequency of 55 (91.7%) while subjects with good sleep quality had a lower frequency rate of five (8.3%) only. Subjects with low risk OSA score had a higher frequency rate of 44 (73.3%) while subjects with high risk OSA score had a frequency rate of 16 (26.7%).

Forty-two subjects did not have MetS, out of which 35 had low risk of OSA and seven had high risk of OSA. Subjects

Table 1: Frequency of OSA score in the subjects with and without MetS

MetS	OSA score		p-value
	Low risk	High risk	
Absent	35	7	0.007
Present	9	9	
Total (n=60)	44	16	

OSA=Obstructive sleep apnoea, MetS=Metabolic syndrome

Table 2: Association between MetS and sleep quality showing frequency of subjects

MetS	Sleep quality		p-value
	Good sleepers	Poor sleepers	
Absent	4	38	0.525
Present	1	17	
Total (n=60)	5	55	

MetS=Metabolic syndrome

Table 3: Binary logistic regression for likelihood ratio of various factors contributing to MetS

MetS	Significance	Exp(B)	95% confidence interval for exp(B)	
			Lower bound	Upper bound
Sleep quality	0.541	2.130	0.189	24.024
Physical activity	0.338	0.273	0.019	3.889
Sex	0.970	1.025	0.289	3.635
OSA	0.007	6.923	1.707	28.066

MetS=Metabolic syndrome, OSA=Obstructive sleep apnoea

with MetS had low and high risk for OSA in equal number of subjects each, i.e. nine. The results were highly significant with p-value of 0.007 ($p \leq 0.05$) (Table 1).

Subjects without MetS (n=42) comprised four good sleepers and 38 poor sleepers. Subjects with MetS (n=18) comprised of one good sleeper and 17 poor sleepers. The results were non-significant with p-value of 0.525 ($p \geq 0.05$) (Table 2).

The high risk of OSA had around seven times higher likelihood of contribution to MetS, with p-value of 0.007. On the other hand, the sleep quality had two times higher likelihood of contribution to MetS; however, this was not statistically significant ($p=0.541$) (Table 3).

DISCUSSION

One-third of the subjects in the present study fulfilled the criteria for MetS. However, the biochemical parameters such as fasting blood sugar and complete lipid profile did not reveal any abnormality in the studied sample. Hence, it could be suggested that the diagnosis of MetS is primarily done on the basis of clinical history, examination, and anthropometric measurements. Prevalence of MetS among subjects taking SGA was found to vary between 12.8% to 29.3% in the Indian population.[11,12] However, higher prevalence ranging between 26.9%-43.9% was reported in studies that had included western and non-Indian Asian populations.[13,14]

It was observed in the present study that nearly one-fourth of the subjects taking SGA were at high risk for OSA. Also, approximately one-third of the total sample had MetS. However, among the group with high risk of OSA, more than half (nine out of total 16) had MetS (Table 1). Binary logistic regression analysis has proven that following control of other factors, OSA appeared to have a major contribution towards causation of MetS (Table 3). In addition, in this study, almost all of them had poor quality sleep, except for a few (Table 2).

A number of studies have reported higher prevalence of OSA among subjects taking antipsychotics.[3,4] Prevalence was found to vary between 20.9% to 57.7% among subjects taking atypical antipsychotics across studies.[15,16] Results of the present study also confirmed that nearly one-fourth of the subjects were at a higher risk for OSA, in a population that was comparable with subjects included in previous studies.[15,16] This is an important issue for the patients taking antipsychotics, especially when many of them required long-term treatment. Risk of OSA increases with age in

normal population and patients taking antipsychotics were at a higher risk. OSA was associated with increased frequency of cardiovascular disorders, sudden cardiac death, diabetes, dyslipidaemia, stroke, and congestive heart failure.[17] Thus, clinicians must pay attention to presence of OSA in subjects exposed to antipsychotics.

A shift in our understanding regarding pathophysiology of MetS becomes important in view of the finding of the present study where OSA was found to increase the likelihood of MetS by seven folds (Table 3), as discussed. The present and previous studies mentioned in the literature have shown that a significant proportion of subjects exposed to SGA have MetS and OSA. Is it possible that OSA explains the relationship between the two? Is it possible that OSA produces certain physiological changes that then paved the way for MetS? These questions become pertinent in light of past literature which suggests that association between OSA and MetS is independent of obesity.[18]

The present study reported that most of the subjects were having poor sleep quality. The disease itself or the effect of antipsychotic medications could mediate this. Poor quality sleep has been reported in subjects suffering from schizophrenia who were on antipsychotics earlier.[19] On an average, poor quality sleep has been reported among 30-80% subjects suffering from schizophrenia.[20] Though subjects with schizophrenia spend more time in sleep at night, their sleep latency is longer and is characterised by multiple awakenings. However, these studies have included subjects maintained well on antipsychotic medications and hence, effect of disease and medications could not be differentiated, similar to the present study.[19, 21]

Findings of the present study though preliminary, still add on to the existing knowledge and have multiple implications in the field of public health and clinical medicine. These findings reiterate the need for the psychiatrist to at least recognise OSA, especially in high-risk population, e.g. those exposed to antipsychotic. Optimal management and timely recognition of OSA can potentially reduce the development of metabolic abnormalities, which in turn induces cardiovascular disorders in the population.[22]

Though this study provided us with some future implications regarding role of OSA in occurrence of MetS in subjects exposed to SGA, however, a number of questions yet remains to be answered. Is there a cause and effect relationship between sleep disorders and MetS? The degree of relative contribution of OSA, poor quality sleep, and restless legs syndrome towards MetS in the population needs to be ascertained. The role of pharmacodynamic properties of medications needs to be determined. Do the antipsychotic medications have a dose effect with regards to MetS or does a ceiling effect appear? Queries whether metabolic consequences are preventable or reversible still needs to be answered. The amount of contribution of obesity which is a risk factor for OSA, poor quality sleep as well as MetS needs to be unveiled. These questions should be answered in future in well-designed studies with a larger sample size after controlling for other confounding factors.

Conclusion

Sleep quality increases the likelihood of MetS by two times; however, this was not statistically significant. OSA increased the likelihood of MetS in subjects exposed to SGA by seven times and this was highly significant.

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