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SLEEP DISORDERS AND COGNITIVE FUNCTIONING IN PATIENTS WITH ASTHMA

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ABSTRACT

Sleep disturbances are found to be quite prevalent in asthma patients. However, information about the prevalence of sleep disorders and their association with cognitive impairment and disease severity in asthma patients is lacking. This cross-sectional study was done to find out the frequency of sleep disorders and investigate the relationship between sleep and cognitive functioning in patients with mild, moderate and severe asthma. A convenience sample of 150 physician diagnosed asthma patients with age range between 30 - 70 years was chosen from two pulmonary clinics of Lahore, Pakistan. Sleep disorders scale, cognitive functioning scale and a demographic sheet were used for collecting data from the patients. The frequency of sleep disorders was found to be 38% in this study. Patients having severe asthma had worse cognitive functioning and sleep as compared to the ones with mild or moderate asthma. Multiple hierarchical analysis indicated sleep disorders and severe stage asthma to be significant predictors of deteriorated cognitive functioning and significantly increased the model's predictive power ($\Delta R^2 = .42$). Severe asthma ($p < .05$), SRBD ($p < .05$), hypersomnia ($p < .01$), nightmare disorder ($p < .01$), RBD ($p < .01$), and general sleep problems ($p < .001$) emerged as strong predictors of declined cognitive function in the patients. This study highlights the significance of identifying and treating sleep disorders timely in adult asthma patients as a strategy to prevent cognitive decline and enhance the wellbeing of the patient.

INTRODUCTION

Asthma is a chronic and potentially serious lung disease which puts substantial burden on the patients as well as their caregivers. It is estimated to affect 339

million people worldwide and is ranked 16th globally among the leading causes of years lived with disability. It is a disease of the airways which allow air to get in and out of the lungs. It causes inflammation and narrowing of airways, which become even more swollen when an asthma trigger is encountered. The inflammation tightens the muscles around the airways causing a reduction in the airflow. Coughing, wheezing, shortness of breath, and chest tightness are reported to be most common symptoms of asthma (1).

Both sleep disturbances and cognitive impairment are found frequently in asthma patients. Previous research has revealed an association between cognitive impairment and asthma (Irani, Barbone, Beausoleil, & Gerald, 2017) as well as cognitive impairment and sleep disturbances. Despite this information, the association between sleep disorders and cognitive functioning in asthma has not been assessed rigorously. Asthma patients often report various sleep problems and deteriorated sleep quality. Problems like difficulty in initiating and maintaining sleep, fragmented sleep, early morning awakenings, and excessive daytime sleepiness (EDS) are issues which are commonly reported, but often remain unaddressed. These problems not only disrupt the patient's nocturnal sleep but also cause consequences like work performance issues, poor asthma control, declined cognitive functioning, and reduced quality of life (QoL) (Darchia et al., 2018). Research has indicated that sleep disturbances are more common in individuals with asthma as compared to ones without a bronchial disease (Braido, 2020; Brumpton, 2017). There could be several causes for this including the use of theophylline, oral corticosteroids, and long-acting beta-agonist (Cukic, Lovre, Dragisic, 2011). However, this connection between sleep problems and asthma goes both ways. On one hand, asthma has been observed to affect nocturnal sleep, and on the second, sleep issues have been found to aggravate asthma control and symptoms. Obstructive sleep apnea (OSA), for example, is a disorder of sleep which increases inflammation in the bronchial air tubes that could both cause or aggravate asthma symptoms. Patients with asthma have more chances of developing a sleep disorder as compared to ones without asthma (Dixit, 2018). This link is presumed to be bidirectional and more research studies need to be carried out to explore this connection between sleep and asthma.

Chronic respiratory diseases like COPD and asthma are well known to put the patients at risk for accelerated cognitive deterioration citing mechanisms such as effects of medications, systemic inflammation, and sleep disturbances (Ray et al., 2015; Rusanen et al., 2013). A meta-analytic review found that cognitive deficits associated with asthma were global with strongest impact on broader dimensions like executive functioning and academic achievement, but with additional effects on attention, memory, learning, language, speed processing, and, visio-spatial functioning. Asthma severity was a key moderator of impairment and severe asthma was associated with most of the cognitive deficits (Darchia, 2018). Cognitive impairment in asthma usually occurs as a direct result of respiratory limitations like hypoxemia or due to other risk factors frequently linked with lung diseases such as smoking, hypertension, or sleep disturbances (Peng et al., 2015).

Deteriorated sleep quality is often seen to be an early indicator of declined cognitive functioning. In addition to poor sleep quality, EDS is considered to be one of the initial markers of cognitive impairment as well as dementia onset. Nonetheless, EDS and poor sleep are reversible risk factors of cognitive decline and attention to early diagnosis and treatment with reference to cognitive functioning could prevent the catastrophic consequences of sleep disorders (Potvin et al., 2012). Timely diagnosis of sleep disorders could serve various purposes including proper treatment and management which could save the individual from any other health complications.

Recent studies conducted with both objective as well as self-reported sleep measures have supported sleep disturbances and disorders as a risk factor for cognitive deterioration and Alzheimer's disease (AD). Sleep problems like difficulty in initiating sleep, EDS, poor sleep quality and sleep disordered breathing were observed to increase accumulation of cerebral amyloid- β ($A\beta$) in normal elderly people (Holth et al., 2019). OSA was found to be associated with neuronal injury biomarkers of AD i.e., higher levels of tau. OSA was also found to be associated with neuronal injury biomarkers of AD i.e., higher levels of tau (Xu, Tan, Zou, Cao, & Tan, 2020). These findings are of significance as 25-40 % of patients having AD tend to complain of sleep-wake disturbances. Also, what is of significance is the finding that disturbances in the sleep wake patterns in these patients appeared several years prior to the appearance of cognitive deficits. Abnormalities in sleep wake patterns were actually predictive of cognitive decline in these patients and this finding makes it imperative to conduct studies which could explore this link between cognitive functioning and sleep further (Holth, Patel, & Holtzman, 2017).

According to a recent finding, middle aged and older adults with insomnia disorder experienced poorer memory performance and worse health outcomes than the ones having a few symptoms of insomnia only or the ones without any sleep complaints (Cross et al., 2019). Preclinical studies have also suggested a causal association between untreated OSA and initiation of neurodegenerative processes. Studies have shown that OSA might be a reversible cause of dementia and cognitive impairment, and treating OSA in the earlier stages of dementia, when individuals are still quite independent might slow down cognitive decline (Emamian et al., 2016).

Sleep disorders are prevalent in general as well as in patient population globally and in Pakistan (Malik & Muazzam, 2018). Disorders of sleep and cognitive impairment are common comorbid conditions in asthma and lead to worse asthma control and other health complications. However, an insufficient number of studies have explored this relationship. There are more studies required in this area of research which could enrich the understanding and knowledge of the interrelationship among asthma, sleep, and cognitive functioning. Therefore, the current study was designed and carried out to examine the association between sleep disorders and cognitive functioning in patients having mild, moderate and severe asthma. Based on prior literature, it was hypothesized that patients with sleep disorders have poor cognitive functioning than patients without sleep disorders. Another hypothesis was that

asthma patients at severe stage of disease have poor cognitive functioning than the ones at mild or moderate stages.

METHOD

It was a cross-sectional study conducted from April 2018 to July 2018. The participants were 150 patients (male=84) of asthma with age range from 30 - 70 years ($M= 51.41$, $SD= 9.46$) selected through convenience sampling technique from two pulmonary clinics of Lahore. Individuals who were diagnosed as having asthma by a pulmonologist were included in the study. The patients were separated into mild (18%), moderate (46%) and severe (36%) category of asthma by the pulmonologist. The patients who had any comorbid terminal disease, psychiatric disorder and/or a cognitive impairment disorder which could had a confounding impact on sleep and cognitive functioning were excluded from the study.

Sleep disorders scale (Malik & Muazzam, 2017) which consists of 47 items and assesses eleven sleep disorders according to the DSM-5 criteria was used to assess sleep. Participants assess each statement on a five-point likert scale which range from always, 3-5 times in a week, 1-2 times in a week, sometimes in a month and never. The recall period is past 3 months and the alpha reliability of SDS is high (.93) which is excellent.

The Medical outcomes study cognitive functioning scale- revised (MOS Cog-R) consisting of six items was employed to measure various domains of cognitive functioning like concentration, attention, memory, confusion, reasoning and psychomotor. It is a self-reported scale intended for adults with four weeks recall period (Yarlas, White, & Bjorner, 2013). Each statement is rated on a five-point scale and the responses range from 'all of the time' to 'none of the time'. The scale has high internal consistency reliability (0.90).

The severity of asthma was assessed through symptoms and peak expiratory flow ratio (PEFR) and the patients were classified as belonging to mild, moderate and severe category of the disease (three levels of asthma control). The tests of disease severity were conducted by the pulmonologist and this information was obtained from the medical record form of the patients after obtaining their permission.

The approval of the study was obtained from the departmental research ethical committee and board of studies. Permission was also taken from the relevant authorities at the clinics from which data was collected. Informed consent was obtained from the study participants after debriefing them about the objectives of the study.

RESULTS

Table 1 indicates the frequency and percentages of each sleep disorder in asthma patients divided according to severity of asthma, i.e., mild, moderate, and severe. Sleep disorders were prevalent in 38% of the patients. The highest percentages were observed for hypersomnia (12%), RLS (12%) and insomnia (8.7%) in the current sample. The frequency of general sleep problems was found to be considerably high and 21% patients reported disturbed sleep.

Table 1: Frequencies and percentage of sleep disorders in asthma patients

Variables	Asthma (n = 150)			
	Total(n=150) f (%)	Mild (n=27) f (%)	Moderate (n=69) f (%)	Severe (n=54) f (%)
Sleep disorders	57 (38)	2 (7)	27 (39)	28 (52)
Insomnia	13 (8.7)	2 (7)	7 (10)	4 (7.4)
Hypersomnolence disorder	18 (12)	–	6 (8.7)	12 (22)
Narcolepsy	6 (4)	–	3 (4.3)	3 (5.6)
Sleep-related breathing disorder	10 (6.7)	–	1 (1.4)	9 (16.7)
NREM sleep arousal disorders	-	–	-	–
Nightmare disorder	3 (2)	–	1 (1.4)	2 (3.7)
REM sleep behavior disorder	2 (1.3)	–	–	2 (3.7)
Restless legs syndrome	18 (12)	1 (4)	9 (13)	8 (15)
General sleep problems	32 (21)	1 (4)	14 (20)	17 (31)

One-way Anova (Table 2) was run to see the differences in patients having mild, moderate, or severe asthma on sleep and cognitive functioning. The findings indicated better sleep and cognitive functioning for patients with mild asthma as compared to patients with moderate ($p < .05$) and severe asthma ($p < .05$). Asthma severity had a large effect on sleep and a medium effect on cognitive functioning as indicated by effect size.

Table 2. Effects Of Mild, Moderate, And Severe Asthma Stages on Cognitive Functioning and Sleep (N=150)

Variables	Mild (n=27)		Moderate (n=69)		Severe (n=54)		F	p- value	η^2
	M	SD	M	SD	M	SD			
Sleep Disorders	23.52	13.33	38.89	16.10	43.89	16.49	14.37	.000**	.20
Cognitive Functioning	25.60	3.38	22.87	5.05	22.04	6.64	3.68	.03*	.05

** $p < .001$; * $p < .05$

Table 3 indicates the results of hierarchical regression analyses performed to determine the variables predicting cognitive functioning in asthma patients. The first model consisted of sample's demographics which explained 10% of the variance in cognitive functioning ($p < .01$) and the result revealed that being married was a significant predictor of better cognitive functioning in the patients as compared to single, widowed or divorced patients. The stages of asthma were

added in model 2 with the moderate stage as the base, and this model accounted for 20% variance in cognitive functioning ($p < .001$). Severe asthma was a significant predictor of deteriorated cognitive functioning ($p < .01$). The subscales of sleep disorders scale were added in last model which added to the predictive power of the model and accounted for 62% variance ($p < .001$) indicating severe asthma ($p < .05$), hypersomnia ($p < .01$), SRBD ($p < .05$), RBD ($p < .01$), and general sleep problems ($p < .001$) as strong predictors of declined cognitive function in patients.

Table 3. Summary Of Hierarchical Regression Analysis for Predictors of Cognitive Functioning in Asthma Patients (N=150)

Variable	Model 1		Model 2		Model 3	
	SE B	B	SE B	B	SE B	B
Gender	1.07	.13	1.04	.09	.78	.09
Age	.05	-.07	.05	-.03	.04	.13
Marital status	.78	-.24**	.76	.19*	.56	-.12
Duration of asthma			.10	-.11	.07	-.05
Mild stage (base: moderate)			1.47	.09	1.10	-.08
Severe stage(base. Moderate)			1.07	-.25**	.83	-.13*
Insomnia					.09	.04
Hypersomnolence					.09	-.20**
Narcolepsy					.12	-.10
SRBD					.11	-.15*
NREM arousal					.23	-.02
Nightmare disorder					.14	-.14*
RBD					.56	-.13*
RLS					.09	-.07
General sleep problems					.09	-.46***
R		.31**		.45***		.79***
R ²		.10		.20		.62
ΔR ²				.10		.42
F		3.95		5.02		11.77

Note. *** $p < .001$; ** $p < .01$; * $p < .05$; Gender:1=male,2=female; SRBD = Sleep-related breathing disorder; NREM = Non-REM sleep arousal disorders; RBD: REM sleep behavior disorder; RLS: Restless legs syndrome;

DISCUSSION

In Pakistan, there is generally low awareness among the general public related to disorders of sleep and their negative impact on health. No large-scale studies have been conducted here on prevalence of sleep disorders and their healthcare burden and hence, there is lack of statistical data despite the evidence of their high presence in both patient and general population (Malik & Muazzam, 2018). Sleep disorders were found in 38% of the asthma patients in the current study and it was quite surprising that the majority of the patients were unaware of the sleep disorder and considered their sleep issues to be a consequence of asthma and medications. There were higher percentages for presence of hypersomnia, RLS, SRBD and insomnia specifically in the moderate and severe asthma

stages. In addition to these specific disorders, a number of patients reported general sleep problems (21%) which were related to quality and quantity of their sleep, and its adverse impact on their mood and daytime functioning. The prevalence of sleep disorders and problems in such a considerable number in asthma patients is a new finding in Pakistan because of lack of information and research data on sleep disorders here. However, studies conducted elsewhere in the world have reported similar findings (Gungen, 2018; Luyster, 2016). EDS has also been found to be a frequently occurring complaint of asthmatics. It could be a comorbid condition or indicative of another disorder like OSA. A recent study found 24% of the asthma patients to have comorbid OSA (Shaker, 2017). A number of other studies have also found OSA to frequently coexist with asthma particularly with severe asthma and have adverse impact on the clinical outcomes (Davies, Bishopp, Wharton, Turner, & Mansur, 2019; Teodorescu, 2015). Such findings support the results of the current study. Likewise, RLS has been found to be present more frequently in asthmatics than in healthy adults. A recent study indicated that RLS frequency increased with a decrease in asthma control and suggested to evaluate asthma patients for the presence of RLS in order to improve their QoL (Gungen, 2018). In another study, 263 asthma patients (37%) were identified with insomnia. The ones with insomnia had deteriorated QoL, higher levels of anxiety and depression symptoms, and 2.3-fold higher possibility of poor asthma control as compared to ones without insomnia (Luyster, 2016).

The results of the current study indicated strong impact of asthma severity and sleep on cognitive functioning specifically amongst the vulnerable group having severe asthma. These results were in line with many other studies which have indicated severity of asthma to have negative consequences on cognitive functioning in patients (Irani, 2017; Esmael & Aly, 2019).

Prospective studies have also suggested that insomnia, OSA, changes in sleep duration, and REM behavior disorder significantly increase the risk of cognitive disorders among adults (Holth, 2019). Hypersomnolence disorder characterized by EDS was one of the significant predictors of cognitive decline in this study. Similar results have been indicated by other studies which found EDS and sleeping duration of more than 10 hours to be associated with deteriorated cognition causing impairment in attention, memory and orientation (Tsapanou, 2016; Xu, 2020).

SRBD specifically OSA is one of the disorders which came out to be a significant predictor of cognitive decline in the current study. This is in line with previous studies and OSA has been linked with cognitive decline and development of dementia overtime OSA patients often report declined performance in cognitive domains related to attention, memory, vigilance, perception, and executive functions. Problems like forgetfulness, concentration difficulties, trouble in decision making, and falling asleep during important tasks specifically while driving could have extremely adverse consequences on patients' lives if OSA is not treated timely (Stranks & Crowe, 2016). Continuous positive airway pressure (CPAP) treatment of OSA has also been found to be quite effective in improving mood, sleep and cognitive processing specifically in patients with AD (Emamian, 2016).

RBD was another sleep disorder which predicted declined cognition among asthma patients in the study. RBD has not been studied and assessed commonly in chronic diseases. Most of the studies on RBD are conducted on Parkinson's disease patients. It has not been researched upon much in Pakistan with this reference specifically. RBD has been found to be a strong predictor of cognitive decline in previous studies (Xu, 2020) but there is need to investigate this relationship extensively in asthma patients or in patients with chronic diseases. Nightmare disorder, though was present in a very small number in the current study sample but it contributed significantly towards cognitive functioning in asthma patients. There is previously evidence present for similar results and existing literature has indicated nightmare disorder to be a potential cause of mood swings, impaired interpersonal and social functioning and declined cognitive functioning. Individuals having nightmare disorder not only experience unpleasant nightmare imagery causing distress but also report impaired concentration, perception, and attention (Morgenthaler, 2018).

It is supported through findings of current as well as previous studies that a number of sleep parameters and disorders contribute towards risk of cognitive decline and disorders in normal adults. Evaluating cognitive functioning of adults having sleep disorders could help to timely identify and treat potentially reversible form of cognitive damage (Emamian, 2016).

CONCLUSION

Sleep disorders are prevalent in patients having asthma and this study emphasizes the need to thoroughly assess patients for the presence of sleep disorders in order to improve patient management. Sleep disorders are a contributing factor in cognitive decline and timely diagnosis and treatment of sleep problems and disorders could benefit cognition and lower the risk of complications to enhance the patients' quality of life.

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