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Original Article

Risk of Respiratory Diseases with Use of Psychotropic Drugs: Results of a Community-based Cross-sectional Study from South India

Abhirami Eby*, Raman Dang, Elsa Jacob

Department of Pharmacy Practice, Krupanidhi College of Pharmacy, Bangalore, Karnataka, INDIA.

ABSTRACT

Background: The study evaluated the effect of various psychotropics on pulmonary function to identify the psychotropic drug class most commonly associated with risk of respiratory disorders. Since psychotropic medications have safety concerns for usage in general population, their use in people with Coronavirus Disease (COVID-19) is considered challenging. The study may also serve to draw evidence-based practical recommendations for the treatment of people with COVID-19. **Materials and Methods:** A 10-item containing questionnaire was designed to capture clinical information regarding psychotropic use and respiratory disorders. Internal consistency and reproducibility were determined using Cronbach's alpha and intra-class correlation coefficient respectively. A validated questionnaire was administered to patients or caregivers at a community pharmacy setup and data was collected through electronic data capture. All captured data were summarized descriptively and statistically analyzed using R Studio 4.0. **Results:** Cronbach's alpha and intra-class correlation coefficient values were found to be 0.92 and 0.85 respectively. In a sample of 198 patients, benzodiazepines were the commonly used medication (43.9%) followed by selective serotonin reuptake inhibitors (21.2%), anti-psychotics (15.1%), mood stabilizers (7.6%) and others (12.2%). A statistically significant association was observed between benzodiazepine, second-generation antipsychotics, and respiratory disorders (OR 1.56 [1.1 – 2.3, p<0.1]). However, the use of first-generation antipsychotics was found to be less associated with respiratory infections. **Conclusion:** Benzodiazepine and second-generation antipsychotics were found to be significantly associated with respiratory disorders. Hence patients on psychotropics should be monitored for respiratory symptoms and the choice of anti-psychotic medications should be on existing clinical evidence. The psychotropics which were found to be safer through the study can be chosen to improve the quality of psychiatric care in COVID-19 patients, also promoting an optimal management of psychiatric conditions without worsening the medical condition due to COVID-19.

Keywords: Psychotropic, Anti-psychotics, Respiratory disorder, Pneumonia, COVID-19.

Correspondence:
Dr. Abhirami Eby
Department of Pharmacy Practice,
Krupanidhi College of Pharmacy,
Bangalore-560035, Karnataka, INDIA.
Email: abhiramieby@gmail.com

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INTRODUCTION

Psychiatric disorder is defined as psychological or behavioral syndrome or pattern that occurs in an individual the consequences of which are clinically significant distress or disability as per Diagnostic and Statistical Manual of Mental Disorder (DSM) V criteria.[1] Standardized classification systems have attempted to provide an adequate definition for mental illness, with the International Statistical Classification of Diseases and Related Health Problems (10th revision; World Health Organization, 2010) and the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013).[2]

Depression, schizophrenia, Attention Deficit Hyperactivity Disorder (ADHD), autism, and Obsessive-Compulsive Disorder (OCD) are among the psychiatric disorders. Psychotherapy along with administration of appropriate medications is most effective in the treatment of these mental disorders.[3] Moreover, as per the standard classification system, Attention-Deficit Hyperactivity Disorder (ADHD) and anxiety disorders in childhood belong to the class of mental, behavioral, and developmental disorders in childhood whereas delirium, dementia, amnestic, and other cognitive disorders belong to neurocognitive disorder class.[4,5] Delusional disorders are common among schizophrenia spectrum disorders and other associated psychotic disorders.[6] Major depressive disorder is a type of mood disorder as per various studies conducted.[7]

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It is found that seventy-seven percent of the mental disorders use psychotropic medications in the treatment. The most common psychotropic drug classes include antipsychotics, antidepressants, anti-anxiety agents, Benzodiazepines (BZD), stimulants and mood stabilisers.[8]

Among the various antipsychotics prescribed, both First Generation Antipsychotics (FGA) and Second Generation Antipsychotics (SGA) show Dopamine D2 Receptor (D2R) blockade. However, SGA shows predominant 5-Hydroxy-Tryptamine-2A (5-HT2A) receptor blockade as well.[9,10] Antidepressants such as sertraline are Selective Serotonin Reuptake Inhibitors (SSRI)[11] whereas Desvenlafaxine, Venlafaxine etc., are Selective Norepinephrine Reuptake Inhibitors (SNRI).[12] There are antidepressants which shows Monoamine Oxidase A (MAO_A) and Monoamine Oxidase B (MAO_B) inhibition.[13] In addition to this, they may also show postsynaptic alpha cholinergic 1 and alpha cholinergic 2 (α1 and α2) inhibition, muscarinic Acetylcholine Receptor (mAChR) blockade and Histamine H1 receptor blockade.[14,15] Anti-anxiety agents such as Clonazepam, Diazepam, Lorazepam are $GABA_A$ receptor modulators.[16,17] Psychotropic drugs such as mood stabilizers act by GABAergic and glutamatergic modulation.[18] CNS stimulants show Vesicular Monoamine Transporter 2 (VMAT2) Inhibition,[19] MAO inhibition[20] and Trace Amine-Associated Receptor 1 ($TAAR_1$) Modulation.[21]

Certain psychotropic drug class use has reported safety risks associated with respiratory functioning.[22] Antipsychotic exposure, especially second generation antipsychotics, is associated with an increased risk of pneumonia.[23,24] Our previously published article on the systematic review and meta-analysis studying the effect of antipsychotics on respiratory function provide the evidence that FGAs are particularly associated with a lower risk for pneumonia compared to exposure to other psychotropics drugs, whereas SGAs are more significantly associated with the development of pneumonia.[25] Studies have reported the increased risk of respiratory illness, including pneumonia and respiratory failure following Benzodiazepine (BZD) usage. The current and recent past use of BZD is related to a higher chance of pneumonia occurrence.[26-28] It is also found to be associated with an increased risk of respiratory failure in patients with Chronic Obstructive Pulmonary Disorder (COPD), Obstructive Sleep Apnea (OSA).[29,30] However, the risk outcomes associated with antidepressant use is found to be discrepant. Studies have reported a higher risk of respiratory related morbidity and mortality and hospitalization for pneumonia following the use of serotonergic anti-depressants[31,32] however, a study by Hennessy. S *et al.* has refuted this hypothesis.[33] Mood stabilizers are not found to be related to increased pneumonia risk following usage.[34] Prescribed opioids, especially immunosuppressive opioids are associated with increased pneumonia risk.[35,36]

The plausible mechanisms associated with psychotropic drug usage and risk of respiratory illness has been hypothesized. The use of FGA is associated with higher risk of pneumonia which may be attributed to the risk of the occurrence of Extrapyramidal Symptoms (EPS) such as akinesia. However, the risk of EPS is negligible at lower doses and with the use of SGA which suggests the presence of another mechanism. Anticholinergic action of the drug molecule resulting in dry mouth and altered oropharangeal bolus transport, H-1 receptor blockage resulting in sedation can cause swallowing problems which may predispose aspiration pneumonia.[37] Benzodiazepines (BZD) increase the risk of pneumonia by its activation of inhibitory $GABA_A$ predisposing infections including pneumonia.[27] The sedation induced by the BZD doubles the risk of pneumonia associated with its use.[38] SSRI and SNRI use is related to side-effects such as fatigue, sleepiness along with other reported effects including nausea and vomiting which can predispose acute respiratory exacerbation in the patients. The elevated serotonin levels caused by the drugs result in airway inflammation and plugging due to the altered removal of dead cells, which increases the chances of pneumonia occurrence.[31,39] The mechanism behind the opioid use and pneumonia is attributed to its immunosuppressive property along with the sedative action which lowers the infection threshold and increases the possibility of aspiration pneumonia.[40,41]

MATERIALS AND METHODS

We conducted a cross-sectional study to assess the association between psychotropic drug usage and the risk of respiratory disorders in patients with psychiatric disturbances.

Ethical approval

The study protocol was reviewed and accorded permission by the independent ethics committee vide IEC/KCP/2020/01.

A prospective, cross-sectional, community-based study was conducted for a period of eight months from August 2020 to February 2021 in pre-identified community pharmacies of South India. The study population included patients, first degree relatives of patients who had a valid prescription for psychotropic medication or had a history of psychotropic drug administration in the past.

Study criteria

Inclusion criteria

Patients, first degree relatives, spouse of the patients with a prescription of psychotropic drugs.

Patients with a previous history of psychiatric disturbance and history of psychotropic medication use in the past.

Exclusion criteria

Any participant other than patient themselves, first degree relatives or spouse.

Example: Friends, colleagues

Table 1: Mean score, Cronbach's alpha, and Intra-class correlation coefficient of knowledge section.

Sl. No.	Items	Cronbach's alpha coefficient (*n*=22)	Intra-class correlation coefficient (*n*=22)
Q1	Describe your relationship with the patient.	0.98	0.94
Q2	Since how long has the patient been taking this medication (years).	0.98	0.96
Q3	Do you know the name of the psychotropic medication which the patient is being administered?	0.97	0.86
Q4	If yes, pick the psychotropic medication which the patient is administering.	0.94	0.85
Q5	Has the patient experienced any kind of respiratory illness following the use of psychotropic medication?	0.97	0.95
Q6	If yes, what kind of a respiratory illness?	0.95	0.92
Q7	Describe the type of respiratory illness.	0.88	0.94
Q8	Does the patient have any co-morbidities?	0.90	0.84
Q9	If yes, which co-morbid condition does the patient have?	0.92	0.86
Q10	Has the patient tested COVID-19 positive during the course of psychotropic therapy?	0.85	0.91

Any subject unwilling to participate or disclose information for the study.

Study instruments used

Validated questionnaire containing 10 items designed to capture clinical information regarding psychotropic drug use and respiratory disorders.

The validated questionnaire was administered and data was collected through electronic data capture.

All data captured were summarized descriptively and statistically analyzed using R Studio 4.0.

Study procedure

A retrospective, cross-sectional study was conducted in pre-identified community pharmacies in South India.

The study was begun following the study protocol approval by the independent ethical committee at Krupanidhi College of Pharmacy.

The sample size was calculated using the sample size calculation formula for cross-sectional study. Thus, a sample size of 198 was calculated using the formula, based on prevalence of the disease.

Sample size calculation formula

$$\text{Sample size} = \frac{z^2 \times p(1-p)}{d^2}$$

Where, z = z – score.

p = Estimated prevalence of an indicator.

d = Margin of Error.

Validation of the questionnaire

Initially, data was captured from 10% (*n*=22) of total population calculated (*n*=198).

The data collected was assessed and the internal consistency and reproducibility were determined using Cronbach's alpha and Intra-class Correlation Coefficient (ICC) respectively.

After a period of 14 days, the questionnaire was administered to the same set of population (*n*=22) and data was collected to validate the questionnaire by assessing their internal consistency and reproducibility.

The Cronbach's alpha and ICC values were found to be 0.92 and 0.85 respectively, thus validating the questionnaire (Table 1).

The validated questionnaire was administered to the patients or caregivers at the community pharmacy setup.

Data was collected through electronic data capture.

All the captured data were summarized descriptively and statistically analyzed using R Studio 4.0.

Analysis of data

The questionnaire was evaluated by scoring the subject responses to each question to assess the occurrence of respiratory disorders during the course of psychotropic drug therapy.

The data obtained from the subjects were analyzed in two ways. A basic descriptive analysis was performed using Graph Pad-Prism and the statistical analysis was performed using R Studio 4.0.

The association between exposure to different psychotropic drug classes and respiratory disorders was evaluated using Odds ratio.

Table 2: **Demographics.**

Sl. No.	Parameter	Category	Number (%)
1	Age (Years)	19-40 41-60 >60	51 (25.76) 23 (11.62) 124 (62.63)
2	Gender	Male Female Other	127 (64.14) 67 (33.84) 4 (2.02)
3	Relationship with the patient	Patient himself/herself First degree relative Grandparents Spouse.	137 (69.19) 53 (26.77) 6 (3.04) 2 (1.01)

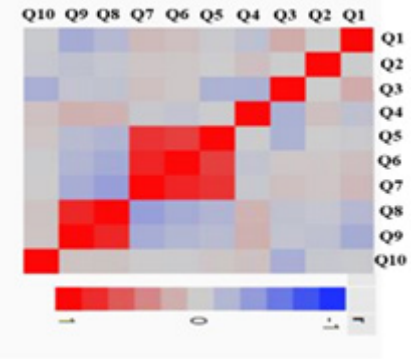


Figure 1: Internal consistency of questions.

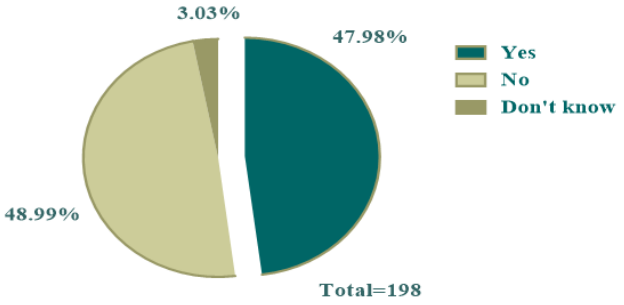


Figure 4: Distribution of incidence of respiratory illness during the course of psychotropic drug therapy.

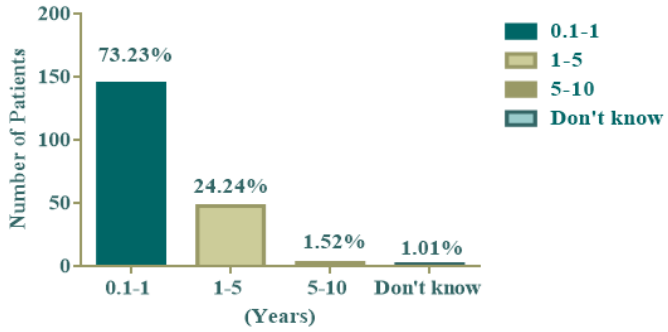


Figure 2: Duration of psychotropic drug therapy.

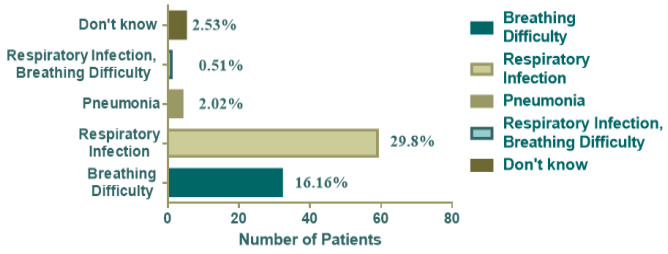


Figure 5: Respiratory illness reported by the subjects during the course of psychotropic drug therapy.

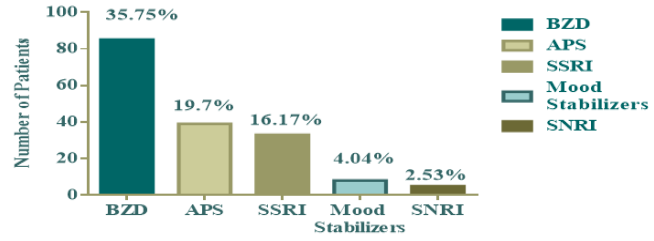


Figure 3: Distribution of different psychotropic drug class.

BZD= Benzodiazepine; APS= Antipsychotics; SSRI= Selective Serotonin Reuptake Inhibitors; SNRI= Selective Norepinephrine Reuptake Inhibitors.

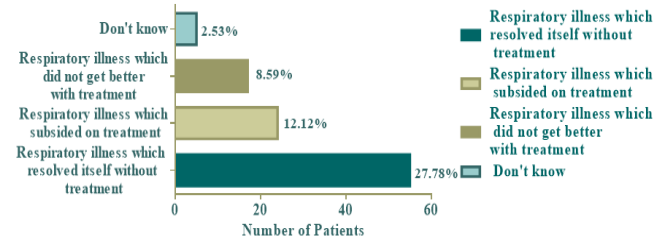


Figure 6: Distribution of the kind of respiratory illness during the course of psychotropic drug therapy.

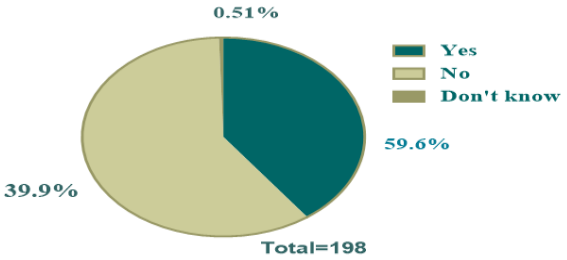


Figure 7: Distribution of response to the presence of comorbid conditions.

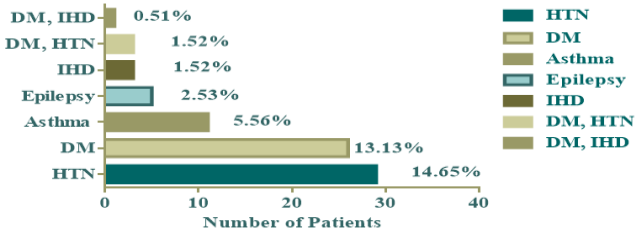


Figure 8: Distribution of comorbidities. DM=Diabetes Mellitus; HTN=Hypertension; IHD=Ischemic Heart Disease.

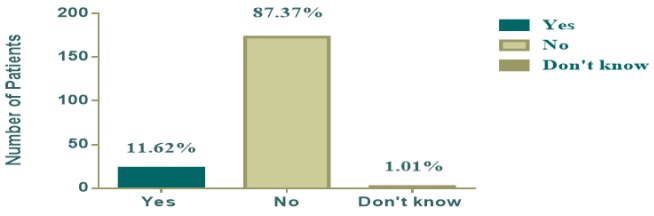


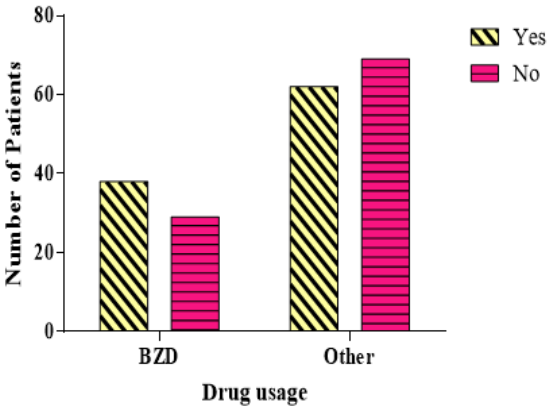
Figure 9: Distribution of COVID-19 in patients during the course of psychotropic drug therapy.

RESULTS

A cross-sectional study was conducted in a community-pharmacy setup with 206 participants using a validated questionnaire, of which 198 subject data was included for the study based on the inclusion and exclusion criteria and sample size calculated.

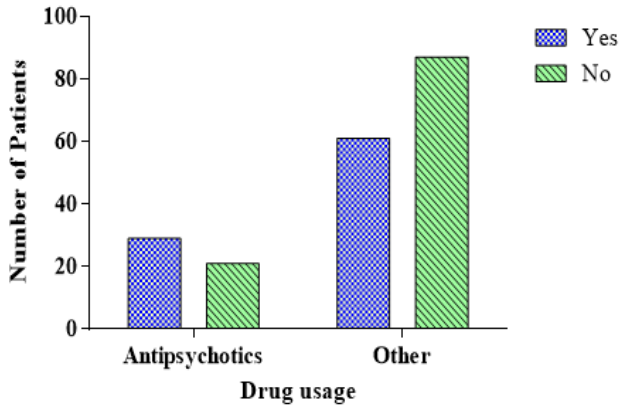
Questionnaire validation

Data from an initial sample (n=22) was captured and assessed for their internal consistency and reproducibility using Cronbach's alpha and Intra-class Correlation Coefficient (ICC) respectively. Cronbach's alpha is the measure of how closely related a set of items are as a group. As the average inter-item correlation increases, Cronbach's alpha also increases. A value of 0.8 and above is considered acceptable. ICC is a measure of how strongly the items in a group resemble each other. ICC value of 0.75 and above is considered good, and above 0.9 is excellent. Cronbach's alpha and ICC values was calculated for the 10 items in the domain with a sample size of 22 subjects (Table 1). Cronbach's value and



OR –1.458 [0.8061 – 2.638], P Value = 0.23

Figure 10: Risk of respiratory disorder in Benzodiazepine use and no use versus other psychotropic drugs.



OR - 1.97 [1.023-3.77], P Value <0.05

Figure 11: Risk of respiratory disorder in antipsychotic use and no use versus other psychotropic drugs.

ICC was 0.92 and 0.85 respectively. The internal consistency of each item in the questionnaire is given (Figure 1).

The distribution of age, gender, and relationship with the patient was analyzed and reported for all the subjects (n=198) (Table 2). Among 198 patients, the majority were male [127 (64.14)]. The majority of the respondents were from the age group > 60 years [124 (62.3)]. The patient himself/ herself was a major part of the respondents of the study [137 (69.19)].

Distribution of the duration of psychotropic therapy

The study showed that the majority of the subjects had a psychotropic drug use duration lesser than a year 145 (73.23),

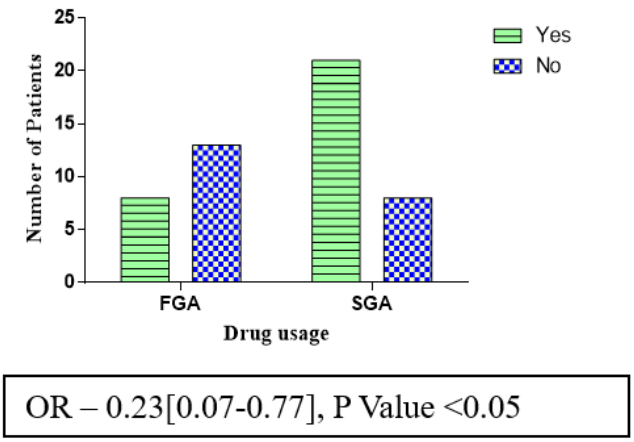


Figure 12: Risk of respiratory disorder in FGA use and no use versus SGA.

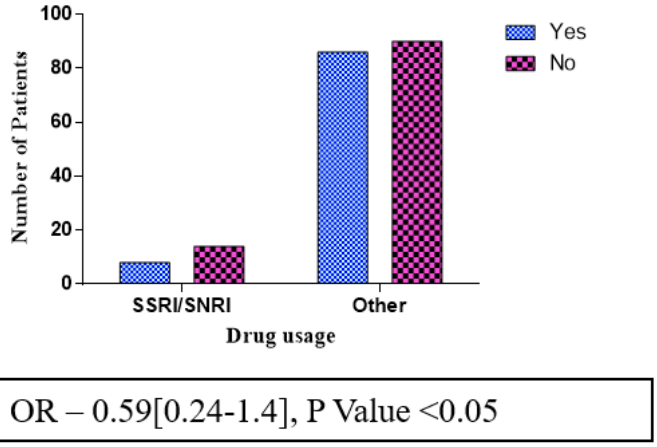


Figure 13: Risk of respiratory disorder in SSRI/SNRI use and no use versus other.

followed by a duration of 1-5 years 48 (24.24) and 5- 10 years 3 (1.52) (Figure 2).

Distribution of the psychotropic drug class used

Among the psychotropic drugs used, benzodiazepines were most commonly used 85 (35.75), followed by antipsychotics 39 (19.7) of which 33 (84.61) were SGA users and 6 (15.4) were FGA users, SSRI users 33 (16.17), mood stabilizers users 8 (4.04) and SNRI users 5 (2.53) (Figure 3).

Distribution of incidence of respiratory disorders in subjects during the course of psychotropic drug therapy

Of 198 patients under study, 95(47.98) experienced respiratory disorders during the course of the therapy, however 97(48.99) did not report any respiratory illness (Figure 4).

Distribution of type of respiratory disorder during the course of psychotropic drug therapy

It was observed that 59 (29.8) of 198 participants experienced respiratory infection,[33] (16.16) experienced breathing difficulty and 4 (2.02) experienced pneumonia during the course of psychotropic drug therapy (Figure 5).

Distribution of the kind of respiratory illness during the course of psychotropic drug therapy

Majority of the population reported a respiratory illness which resolved itself without treatment 55 (27.78%), 24 (12.12%) had a respiratory illness which subsided on treatment, 17 (8.59%) reported respiratory illness which did not get better with treatment (Figure 6).

Distribution of comorbid conditions in patient population

79 (39.9) of the participants had comorbid condition out of a total of 198 participants (Figure 7). Majority of the population had hypertension 29 (14.69), followed by Diabetes mellitus in 26 (13.13) participants, asthma in 11 (5.56) participants, Epilepsy in 5 (2.53), Diabetes and hypertension in 5 (2.53), ischemic heart disease in 3 (1.52) and Diabetes and Ischemic Heart Disease in 1 (0.52) participant (Figure 8).

Distribution of number of patients COVID positive during the course of psychotropic drug therapy

Of the total population of 198 patients exposed to psychotropic drug therapy, 23 (11.62) patients were tested COVID positive during the course of the therapy. However, 173 (87.37) were not tested positive (Figure 9).

Association between Individual Drug Class Usage and Risk of Respiratory Disorder

All the captured data was statistically analyzed and the association was expressed as Odds ratio. Statistically significant association was observed between benzodiazepine (OR 1.46, 95% CI 0.81-2.64, *p* value 0.2) (Figure 10), antipsychotics (OR 1.97, 95% CI 0.81-2.64, *p* value <0.05) (Figure 11) use and risk of respiratory disorders. SGA was associated with increased risk of respiratory disorder compared to FGA (OR 0.23, 95% CI 0.07-0.77, *p* value <0.05) (Figure 12). SSRI/SNRI (OR 0.59, 95% CI 0.24-1.4, *p* Value <0.05) was associated with decreased risk of respiratory disorder compared to other psychotropic drug use (Figure 13).

DISCUSSION

Anxiety, bipolar disorder, dysthymia, severe depression, and schizophrenia are just a few of the psychiatric illnesses for which psychotropic medicines are often prescribed.[42] Despite the wide spectrum of adverse effects on various organ systems, respiratory issues produced by psychiatric medicines is the major area of concern in the present situation of SARS-CoV-2 epidemic.[43] Several studies have reported the occurrence of respiratory disorders following the usage of different psychotropic drug class. Our cross-sectional study has found a significant association between use of psychotropic drug class and occurrence of respiratory illness. 47.98% of the population has reported a respiratory illness during the course of the psychotropic drug therapy. Benzodiazepine (OR: 1.458 [0.8061 – 2.638], *p* Value = 0.23) and antipsychotic (OR - 1.97 [1.023-3.77], *p* Value <0.05) usage was found to be associated with a higher risk of respiratory disorders on comparison with other psychotropic drug usage which are on par with studies Obiora *et al.*, Yang *et al.* 2013, Wang M.T *et al.* 2017 which has reported and increased pneumonia risk. However serotonergic antidepressant users had a lower risk of respiratory illness following its use (OR – 0.59 [0.24-1.4], *p* Value <0.05) the results of which are comparable to the results of Hennessy S *et al.* 2007. The risk of respiratory illness following the use of SGA was found to be higher than FGA (OR – 0.23 [0.07-0.77], *p* Value <0.05) which is comparable to the results of the studies Knol *et al.* 2008. Our study is the first cross-sectional study conducted on the evaluation psychotropic drug usage and effect on respiratory function and to report the reduced risk associated with the use of FGA compared to SGA use.

LIMITATIONS

The cross-sectional study design made it difficult to ascertain the temporal relationship between the prescription of various psychotropic drugs and the onset of respiratory diseases. As a result of the cross-sectional nature of this study, it is difficult to determine whether these conditions are caused by psychotropics itself or by other risk factors that are commonly observed in psychiatric patients, such as poor overall physical health, unhealthy lifestyle, inadequate health care, and so on. As the sample was obtained only from psychiatric patients, we cannot assume that our control group is representative of the general population. Nonetheless, there is no evidence that individuals taking psychiatric medications have a higher risk of respiratory infection than the general population, based on our experience.

Most of the patients in our sample were significantly older (>60 years). Our findings, however, were unaffected by age. Whereas, lack of information about specific respiratory diseases, such as pneumonia and other significant clinical variables, such as the severity of the respiratory illness limits our findings. Our cross-sectional study design makes it difficult to determine the relative degree of risk associated with each type of psychotropic medication. Also, it's important to keep in mind that patients may also have been shifted from a previous antipsychotic to another psychotropic medication preferably as a result of obesity or metabolic problems. Although we can't completely rule out this potentially confounding variable which we tried to manage and it had no significant impact on the results. Furthermore, due to lack of non-treated patients in our sample, we were unable to compute the Relative Risk of developing respiratory illnesses in psychotropic-treated patients compared to those who did not take any psychotropics.

CONCLUSION

History of benzodiazepine and second-generation antipsychotic usage were found to be significantly associated with respiratory disorders including pneumonia and acute respiratory distress. Exposure to psychotropic medications is associated with the development of pneumonia and other respiratory illnesses. Our study provides evidence on developing various respiratory disorders in terms of pneumonia, respiratory infections etc., in patients during the course of psychotropic medication.

ACKNOWLEDGEMENT

We are extremely delighted to appreciate all individual subjects who have taken their time out to participate in the study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

5-HT2A: 5-Hydroxy-Tryptamine 2A Receptor; **ADHD:** Attention-Deficit Hyperactivity Disorder; **BZD:** Benzodiazepines; **CNS:** Central Nervous System; **COPD:** Chronic Obstructive Pulmonary Disease; **COVID-19:** Coronavirus Disease-19; **D2R:** Dopamine D2 Receptor; **DSM:** Diagnostic and Statistical Manual of Mental Disorder; **EPS:** Extra Pyramidal Symptoms; **FGA:** First Generation Antipsychotics; **GABA A:** Gamma Amino Butyric Acid A Receptor; **H1:** Histamine H1 Receptor; **ICC:** Intraclass Correlation Coefficient; **mAChR:** Muscarinic Acetyl Choline Receptor; **MAO A:** Monoamine Oxidase A; **MAO B:** Monoamine Oxidase B; **OR:** Odds Ratio; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus-2; **SGA:** Second Generation Antipsychotics; **SNRI:** Selective Norepinephrine Re-uptake Inhibitor/Inhibition; **SSRI:** Selective Serotonin Re-uptake Inhibitor/Inhibition; **TAAR 1:** Trace Amine-Associated Receptor 1; **VMAT2:** Vesicular Monoamine Transporter 2; **α1:** Post synaptic alpha cholinergic 1; **α2:** Post synaptic alpha cholinergic 2.

SUMMARY

Our study provides evidence on the risk of development of pneumonia associated with the use of psychotropics. Moreover, it gives an idea about association between individual drug class usage and the risk of respiratory disorder. Thus, our study hypothesizes the significant association between the use of psychotropics such as benzodiazepines, antipsychotics etc. and the risk of development of respiratory illness. Thus, clinicians need to be vigilant about the respiratory outcomes which can occur while prescribing psychotropic medication in patients underlying treatment of psychosis and should consider routine investigation of the respiratory profiles as well. The study also implies the clinician to devise the safest treatment regimens for psychiatric disorders in patients with underlying respiratory comorbidities.

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