A comparative study of positive and negative symptoms in patients of schizophrenia with and without nicotine use

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ABSTRACT
Background: Schizophrenia is a chronic debilitating illness characterized by delusions, hallucinations, disorganized speech, grossly disorganized behavior/catatonic symptoms and negative symptoms. Etiologically, Genetic factors, biochemical factors, neuro-pathological factors and environmental factors are important. Incidence of substance use is higher in patients suffering from psychotic conditions than in general population. Nicotine is the most common substance that is consumed by patients of schizophrenia. There is increased incidence of smoking in patients suffering from positive symptoms of schizophrenia to reduce the distress caused by delusions and hallucinations as per the well documented 'Self-medication' hypothesis in schizophrenia. **Aims and Objective:** This study aims to focus on the correlation of symptomatology of schizophrenia in patients who use nicotine against those who don't. **Materials and Method:**A cross-sectional observational study. 60 patients of schizophrenia who consented for the study were selected according to the inclusion and exclusion criteria using consecutive sampling method. **Results:** Mean age for case group was 42.20; while for the control group it was 38.53 Most of the subjects were in middle socio-economic status, i.e. 50% and 73.3% respectively. 70% of patients amongst nicotine users and 76.7% of patients amongst non-nicotine users were from an urban habitat. 76.6% studied beyond secondary; while in the control group, 83.4% studied beyond secondary. 50% patients amongst case group and 56.7% amongst control group were regular and compliant with medicines for schizophrenia. While 40% amongst cases were irregular and 20% amongst controls were irregular with their medications. **Conclusion:** The study found nicotine use was more commonly associated with irregular medication compliance in patients of schizophrenia. Use of nicotine was significantly associated with improvement in attention scores compared to other negative symptoms.
Keywords: Schizophrenia; Positive and negative symptoms; Nicotine; Attention scores.

INTRODUCTION
Schizophrenia is a chronic debilitating illness characterized by delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized behavior/catatonic symptoms andnegative symptoms. Two of these five symptoms are required for its diagnosis and at least one symptom must be one of the first three (delusions,

hallucinations, disorganized speech). Incidence of the disease is 1% amongst general population.[1]

Etiologically, various factors are involved which include: (a) Genetic factors and predisposition due to family history of the illness (b) Biochemical factors comprising of abnormalities of neurotransmitters, majorly Dopamine, Serotonin and Nor-epinephrine (c) Neuro-pathological factors like structural neuroanatomical abnormalities in certain areas of brain along with functioning of certain neural pathways like meso-limbic and meso-cortical pathways in brain (d) Environmental factors like various viral infections in early life, antenatal infections in mother.The relationship between substance use and psychosis is well known.[1]Consumption of few substances can produce schizophrenia and similar psychosis which may eventually increase the likelihood of a person to develop schizophrenia in future.[2]

Although some substances increase the likelihood of developing psychotic conditions, it has also been noted that incidence of substance use is higher in patients suffering from psychotic conditions than in general population.[3]Many patients consume substances before the onset of schizophrenia whilst some may initiate the consumption after the onset of psychotic spectrum disorder. Some patients consume substances during psychosis as a part of psychotic behavior. For e.g. in manic patients, consumption of alcohol or other substances may increase as a part of their psychotic behavior.

Patients may consume various substances during the course of illness but nicotine is the most common substance that is consumed by patients of schizophrenia.[4] Nicotine may be consumed orally in the form of tobacco, particularly common in Asian patients or may be consumed by inhalational mode through smoking cigarettes.[5] Patients may have increased consumption of nicotine as a part of disorganized behavior in the mental illness or some patients also smoke to relieve the distress due to psychotic symptoms. It has been noted that there is increased incidence of smoking in patients suffering from positive symptoms of schizophrenia to reduce the distress caused by delusions and hallucinations as per the well documented 'Self-medication' hypothesis in schizophrenia.[6]

Nicotine is the commonest substance consumed in psychotic disorders.[4]The self-medication hypothesis can be described as being composed of several principles like (a) Diagnosed or undiagnosed psychotic disorders precede initiation of substances; (b) Mentally ill patients are more likely to consume psychoactive substances than general population; (c) Due to the symptomatic relief from anxiety, the mentally ill patients are led to excessive use of substances.[6] Some studies suggest that patients suffering from schizophrenia also initiate the use of nicotine after the initiation of symptoms or may increase the consumption of the same through various forms to relieve the discomfort or the ill effects caused by the medications or the anti-psychotic agents used in schizophrenia.[7] If these assumptions are to be held true then there are few questions which arise like;A) What are the patterns of initiationof nicotine use in patients of schizophrenia and its implications on the symptomatology? B) Whether nicotine use helps with distress caused by positive symptoms or negative symptoms? C) How does the severity of nicotine use affect the clinical course and symptomatologyofschizophrenia?Hence to address these gray areas, a detailed research about the symptomatology and its association with use of nicotine would help in giving a better perspective.

This study aims to focus on the correlation of symptomatology of schizophrenia in patients who use nicotine against those who don't. The study also aims at determining various other factors like socio-demographic profile, initiation of nicotine use and its effect on medication compliance, pattern of presentation, the severity of nicotine use in patients,the type of treatment received by the patients thus trying to address the aforementioned cause.

AIM AND OBJECTIVES

To Compare the Severity of Positive and Negative Symptoms in Patients of Schizophrenia with and without Nicotine use.

MATERIAL AND METHODS

A cross-sectionalobservationalstudy.The study was carried out at Government Medical College and hospital, Aurangabad, Maharashtra. The study was carried out after due approval by the Institutional ethical committee.60 patients of schizophrenia who consented for the study were selected according to the inclusion and exclusion criteria using consecutive sampling method. An information sheet (annexure) regarding the illness and the purpose of the study was provided to the patient. A written informed consent was taken from the subjects before commencing the study.Informed consent was obtained in the mother tongue. For illiterate patients the contents were read out and then written consent was obtained. Only those patients who consented to participate in the study and were cooperative for interview were recruited.

CLINICAL INSTRUMENTS PROPOSED FOR THE STUDY:

1. **SOCIO-DEMOGRAPHIC AND CLINICAL DATA SHEET**

   The data sheet would record the socio-demographic and clinical details of each patient, including family history, duration of illness, and various other factors associated with nicotine use.

2. **DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA AS PER DSM 5 CRITERIA[8]**

   Patients were diagnosed as Schizophrenia according to DSM 5 criteria; which is as follows;

A. Two(ormore)ofthefollowing,eachpresentforasignificantportionoftimeduringa1-monthperiod(orlessifsuccessfullytreated).At leastoneofthesemustbe 1,2 or3:

   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g.frequentderailmentor incoherence).
   4. Grosslydisorganizedorcatatonicbehavior.
   5. Negative symptoms (i.e. diminishedemotionalexpressionoravolition).

B. Forasignificantportionofthetimesincetheonsetofdisturbance,leveloffunctioninginoneormoremajorareas,suchaswork,interpersonalrelations,orself-care,ismarkedlybelowthelevelachievedpriortotheonset(orwhentheonsetisinchildhoodoradolescence,thereisfailuretoachieveexpectedlevelofinterpersonal,academic,oroccupationalfunctioning).

C. Continuoussignsofdisturbancepersistforatleast6months.This6-monthperiodmustinclude atleast1monthofsymptoms(orlessifsuccessfullytreated)thatmeetcriterionA(i.e.activephasesymptoms)andmayincludeperiodsof prodromal orresidualsymptoms.Duringtheseprodromalorresidualperiods,thesignsofdisturbancemay bemanifestedbyonlynegativesymptomsorbytwoormoresymptomslistedinCriterionApresentinanattenuatedform(e.g.odd beliefs,unusualperceptualexperiences).

D. Schizoaffectivedisorderanddepressiveorbipolardisorderwithpsychoticfeatureshavebeenruledoutbecauseeither1)nomajordepressiveormanic episodeshaveoccurredconcurrentlywiththeactive-phasesymptoms,or2)ifmoodsymptomshaveoccurreduringactive-phasesymptoms,theyhavebeenpresentforaminorityofthetotaldurationoftheactiveandresidualperiodsoftheillness.

E. Thedisturbanceisnotattributabletophysiologicaleffectsofasubstance(e.g.adrugofabuse,am

edication)oranother medical condition.

F.   Ifthereisahistoryofautismspectrumdisorderoracommunicationdisorderofchildhoodonset,theadditionaldiagnosisofschizophreniaismadeonlyifprominentdelusionsorhallucinations,inadditiontotheotherrequiredsymptomsofschizophrenia,arealsopresentforatleast1month(orlessifsuccessfullytreated).

3.   SCALE FOR ASSESSMENT OF POSITIVE SYMPTOMS (SAPS)[9]

The scale for assessment of positive symptoms (SAPS) contains 34 items divided into 5 domains i.e. Hallucinations, Delusions, Bizarre behavior, Positive formal thought disorder and inappropriate affect. Items in both the scales are scored between 0 (none) and 5 (severe).

4.   SCALE FOR ASSESSMENT OF NEGATIVE SYMPTOMS (SANS) [10]

The SANS contains 25 items divided into 5 domains i.e. Affective flattening or blunting, Alogia, Avolition-Apathy, Anhedonia-Asociality and Attention. Similar to SAPS, items in both the scales are scored between 0 (none) and 5 (severe).

5. SCALES FOR NICOTINE DEPENDENCE

a) Fagerstrom's test for nicotine dependence (FTND)[11]

The FTND is a short scale comprising of 6 items which quantify nicotine dependence. The smoking rate and the time lag between wakingand the first cigarette is being scored 0 to 3.If the patient smokes fewercigarette per day and if he takes a longer time for his first cigarette of theday he gets a lower score.The other 4 variables which are rated in adichotomous manner are smoking even while he is ill, havingdifficulty in refraining from smoking in places where it is forbidden,smoking cigarettes more heavily especially in the mornings and havingdifficulty in giving up the day's first cigarette. These variables are scoredas yes (1) or no (0). The overall scores for severity of dependence: 0–2: very low dependence, 3–4: low dependence, 5: moderate dependence,6–7: high dependence, 8–10: very high dependence.

b) TheFagerstorm'sTestforNicotineDependence-SmokelessTobacco(FTND-ST) [12]

It is similar to the FTND scale and this scale measures the severity of using smokeless tobacco by estimating the number of pouches/tins or cans used instead of the number of cigarettes smoked. It is scored in the same manner as FTND.

DATA ANALYSIS

The data was entered in Microsoft excel 2010 and analyzed using SPSS version 20.0. Centraltendenciesandthedispersionofthevariableswerestudiedusingdescriptivestatisticalmethodssuchasmean,standarddeviation.

TheCasegroup(Nicotineusers)andcontrolgroup(Nicotinenonusers)werematchedwithrespectto theirdemographic parameters toidentifytheconfoundingvariables. Qualitative data was represented in the form of frequency and percentage; while quantitative data with mean and standard deviation. The association between the two qualitative data was calculated using 'Chi-square' test or 'Fischer's exact test' (whichever appropriate). The comparison of quantitative data between the two groups was done using 'unpaired t test'. Mann-Whitney 'U' test was used to find out the correlation (p-value) between severity of nicotine use and positive and negative symptoms of schizophrenia; results for this analysis were interpreted in   form   of   Median   and   Inter-Quartile   Range   (IQR).   Thep-valueslessthan0.05(p<0.05)weretreatedassignificantintwotailcondition.

OBSERVATIONS AND RESULTS

Table 1: Sociodemographic parameters of study population

			Nicotine Use		P-value
			Yes	**No**	
Mean Age			**42.20**	**38.53**	0.274
Marital Status	**Married**	%	53.3	53.3	0.1000
	Divorced	%	30.0	10.0	0.106
	Single	%	16.7	36.7	0.079
Socioeconomic status	**low**	%	33	20	.242
	Middle	%	50	73.3	.063
	High	%	16.7	6.7	.423
Habitat	**Urban**	%	70	76	0.559
	Rural	%	30	23.3	
Education	**Uneducated**	%	16.7	3.3	0.194
	Primary	%	6.7	13.3	0.671
	Secondary	%	23.3	40	0.165
	Graduate	%	53.3	36.7	0.194
	Postgraduate	%	0	6.7	
Occupational status	**Employed**	%	33.3	30	0.781
	Not employed	%	66.7	70	
Family history of Psychosis	**Yes**	%	43.3	26.7	0.176
	No	%	56.7	73.3	
Age of onset of illness	**10-20**	%	20	23.3	0.754
	21-30	%	46.7	60	0.306
	More than 30	%	33.3	16.7	0.136
Duration of Illness in Years	**2-4**	%	10	23.3	0.298
	4-6	%	0	20	0.024
	6-8	%	16.7	10	0.706
	8-10	%	20	10	0.471
	More than 10	%	53.3	36.7	0.194

Table 2: Duration of Nicotine Use before and after the onset of illness

Duration of nicotine use before onset of illness	**Frequency**	**Percent**
Never used	13	43.3
1 year – 5 years	13	43.3
5 years – 10 years	3	10.0
More than 10 years	1	3.3
Total	30	100.0
Duration of nicotine use after onset of illness	**Frequency**	**Percent**
1 year – 5 years	6	20.0
5 years – 10 years	7	23.3
More than 10 years	17	56.6

Table 3: Form of Nicotine consumed

Form of nicotine consumed	**Frequency**	**Percent**
Smokeless	10	33.3

Smoking	20	66.7
Total	30	100.0

Table 4: Pattern of Nicotine consumed

Pattern of Nicotine use	Frequency	Percent
Dependent	23	76.7
Non Dependent	7	23.3
Total	30	100.0

Among demographics parameters that ismean age, marital status,socio economic status, habitat, education,occupational status, positive family history for psychosis, age of onset of illness, duration of illness, the form of nicotine consumed there was no statistically significant difference between the two groups.

Nicotine dependence as per DSM 5 [64] criteria was established in 76.7% of patients.23.3% had attempts at abstaining while 26.7% patients sought treatment for nicotine dependence.Medication compliance was regular in 50.0% of cases and 56.7% of controls. p-value for this group was 0.60, while it was irregular in 40.0% of cases and 20.0% of controls with a p-value of 0.158 thus there was no statistically significant difference between the two groups.

Also 10.0% patients were off medications amongst cases while 13.3% were off medications amongst controls. 10.0% of non-nicotine users had not received any medications prior to current consultation.

Table5:SAPS scores amongst cases and controls

	Nicotine Use	n	Mean	SD	p value
Hallucination score	Yes	30	3.87	4.041	.448
	No	30	4.70	4.403	
Delusion score	Yes	30	8.10	5.435	.854
	No	30	7.83	5.712	
Bizarre behavior score	Yes	30	3.53	3.785	.281
	No	30	4.67	4.262	
Positive Formal thought disorder score	Yes	30	6.07	5.166	1.000
	No	30	6.07	5.291	
SAPS Gross score	Yes	30	21.57	16.671	0.667
	No	30	23.53	18.554	

The following table shows comparison of SAPS score and its components amongst nicotine users and non-nicotine users.

Analysis of hallucination score, Delusion score, Bizarre behavior score, Positive formal thought disorder score and the gross SAPS scores between the groups,there was no statistical significance difference in the SAPS scores of the two groups.

Table 6: SANS scores amongst cases and controls

	Nicotine Use	n	Mean	Standard Deviation	p value
Affective fattening score	Yes	30	8.23	3.739	.457
	No	30	9.17	5.718	
Alogia score	Yes	30	3.63	3.577	.357
	No	30	4.53	3.928	
Avolition-Apathy	Yes	30	4.60	3.440	.125

score	No	30	6.03	3.681	
Anhedonia-Asociality score	Yes	30	8.03	3.873	.863
	No	30	7.83	4.976	
Attention score	Yes	30	5.00	1.640	0.0001 s
	No	30	7.27	2.753	
SANS Gross score	Yes	30	29.50	11.506	0.156
	No	30	34.83	16.719	

The following table shows comparison of SANS scores and its components amongst the two groups.Amongst the sub-categories of SANS, comparing the affective flattening score, Alogiascore,Avolition-Apathy score, Anhedonia-Asociality score and gross SANS score there was no statistically significant difference amongst two groups

While in the attention scores of the two groups, amongst cases, mean score was 5.0 and standard deviation was 1.640; while amongst controls, mean score was 7.27 and standard deviation was 2.753. p-valuefor this group was 0.0001 which meant there was statistically significant difference in attention scores between the two groups.

Table 7: FTND and SAPS scores amongst cases

	FTND SCORE		
Median SAPS Score (Inter-Quartile range)	**0-5 (n- 19)**	**6-10 (n-11)**	**Mann-Whitney Test p-value**
Hallucinations n (IQR)	4 (0-4.5)	4 (0-6.5)	0.641
Delusion n (IQR)	4 (3.5-12)	10 (6-14)	0.063
Bizarre Behavior n (IQR)	0 (0-6)	4 (1-8.5)	0.19
Positive Formal Thought Disorder n (IQR)	4 (0-8)	6 (4-12)	0.09
Median Gross SAPS Score n (IQR)	12 (7-28.5)	27 (12.5-37.5)	0.10

Following table shows analysis between FTND scores with categories of SAPS.

To conclude, although delusion score and gross SAPS score were higher in the group with increased nicotine use (FTND 6-10), there was no statistically significant difference between any of the sub-categories of SAPS scores and severity of nicotine use.

Table 8:FTND and SANS scores amongst cases

	FTND SCORE		
Median SANS Score (Inter Quartile Range)	**0-5 (n- 19)**	**6-10 (n-11)**	**Mann-Whitney Test p-value**
Affective Flattening n (IQR)	9 (6-10)	9 (6-12)	0.800
Alogia n (IQR)	3 (0-4)	4 (3-7)	0.158
Avolition-Apathy	4	4	0.97

	(1.5-6)	(3-6.5)	
Anhedonia-Asociality n (IQR)	8 (5-12)	8 (7-12)	0.47
Attention n (IQR)	4 (4-6)	5 (4-6.5)	0.31
Median Gross SANS Score n (IQR)	29 (22.5-33.5)	34 (25.5-39)	0.25

Following table shows the analysis of FTND scores in comparison with categories of SANS. To conclude, although median gross SANS score was higher in the group with increased nicotine use (FTND 6-10), there was no statistically significant difference in any of the sub-categories of the SANS scores and severity of nicotine use.

DISCUSSION

Present study showed that presence or absence of nicotine use did not show any significant correlation with positive symptoms of schizophrenia.On the other hand, comparing the negative symptoms amongst both the groups, attention score of patients with schizophrenia with nicotine use was significantly lower (p-0.0001) as compared to those without nicotine use. When severity of nicotine use amongst cases was compared with positive and negative symptoms, in those with more severe use of nicotine (FTND 6-10), median delusion scores and median gross SAPS scores were higher.

Amongst demographic profiles and other variants, divorce rates were higherin patients with nicotine use. Positive family history of psychosis was higher in the nicotine users. Nicotine use was more common in longer duration of illness. Patients with irregular medication compliance were higher in those with co-morbid nicotine use.

In socio demographic profile of our study, the mean age in the case group was 42.2 years while that in the controls was 38.53. Most of the subjects were in middle socio-economic status, i.e. 50% and 73.3% respectively.70% of patients amongst nicotine users and 76.7% of patients amongst non-nicotine users were from an urban habitat. 76.6% studied beyond secondary; while in the control group, 83.4% studied beyond secondary.When the cases and controls were matched with respect to above variables we found that there is no statistically significant difference amongst these variables (p>0.05).

But it was highlighted that nicotine users amongst schizophrenia patients were three times more likely to be divorced compared to non-nicotine users. The findings were supported by Tang YL et al., which showed that divorce rates were higher in patients of schizophrenia with co-morbid nicotine use. Percentage of actively employed subjects was much lower (31.7%) in both the groups in total. Compared to another study done by Chandra et al. which showed that only 45% of the patients were actively involved in an outdoor occupation; which is comparable to the findings of the present study.[13]

In the present study, amongst cases, 43.3% had a positive family history of psychosis; while in controls, it is 26.7%. Aichet al., also demonstrated that comorbid substance use was significantly associated with a positive family history of schizophrenia[14]. Amongst cases, 53.3% patients and in controls 36.7% patients had more than 10 years of duration of illness. Similarly in a study by Dickerson et al. showed that current nicotine use amongst the patients of schizophrenia was significantly associated with a longer duration of psychiatric illness.[15]

Present study showed that 50% patients amongst case group and 56.7% amongst control group were regular and compliant with medicines for schizophrenia. While 40% amongst cases were irregular and 20% amongst controls were irregular with their medications.Thus, it

shows that schizophrenia patients with nicotine use are generally less likely to be compliant with treatment. One such study by Diane M Herbecketal, concluded that medication compliance issues were higher(48.8%) in patients of schizophrenia with comorbid substance use.[16]

COMPARISON OF SAPS AND SANS AMONGST CASES AND CONTROLS

In the present study, the analysis of SAPS score has not showed statistically significant variation amongst different mean score in cases and controls.

Coming to analysis of SANS scores amongst cases and controls, Mean Attention score was the only statistically significant (p-0.0001) clinical parameter; in cases it was 5.00 while in controls it was 7.27. Mean gross SANS scorefor case group was 29.50 while for controls it was 34.83. Thus, present study implies that mean attention score was significantly lower amongst cases as compared to controls. None of the other parameters of SANS showed any significant correlation.

One such study by ALP Ucoket al. states that there was significant correlation in SAPS score with nicotine use only in acute episodes of schizophrenia, when SAPS scores were much higher in nicotine users.[17] Another study in Indian population by Vatsset al. concluded that there was no statistically significant difference in terms of SAPS and SANS scores in patients of schizophrenia with and without nicotine use.[18] Further the finding that selective attentional improvement with the use of nicotine in patients of schizophrenia has also been replicated in the work done by Beck et al.[19] Another possible explanation for this is many negative symptoms in schizophrenia can be attributed to the use of first generation anti-psychotics;[20]while it is concluded in some of the work done in this aspect by Goff et al. that smoking was associated with reduction in extra-pyramidal syndrome and drug induced contributions to negative symptoms.[21]

CORRELATION OF SAPS AND SANS WITH FTND SCORES AMONGST CASES

The present study showed that, in subjects who used nicotine in higher amount (FTND 6-10), median delusion scores and median gross SAPS scores and median gross SANS score were higher (10, 27 and 34 respectively) as compared to (4,12 and 29 respectively) in those with lower scores on FTND (0 to 5). However findings were statistically insignificant, scores amongst other sub-categories of SAPS and SANS were comparable to each other with respect to severity of nicotine use. Possible reason for higher delusion score and gross SAPS scores amongst heavy users of nicotine could be that nicotine can help in reducing the anxiety associated with delusions.[6]The present study was supported by a study by Kumari V and Postma P[82]and Ziedonis et al.[22]

Thus to conclude, in the present study, subjects using higher amounts of nicotine had higher median delusion score and gross SAPS score on Positive symptom scale (SAPS).

CONCLUSIONS

Divorce rates were higher amongst patients of schizophrenia with comorbid nicotine use.The tendency to use nicotine amongst patients of schizophrenia was higher in patients with positive family history of psychosis.Nicotine use was more common in patients of schizophrenia with longer duration of illness.Nicotine use was more commonly associated with irregular medication compliance in patients of schizophrenia.Use of nicotine was significantly associated with improvement in attention scores compared to other negative symptoms.Although there was no significant association between positive symptoms of schizophrenia and presence or absence of nicotine use; however, amongst the patients withnicotine use, higher delusional score was associated with heavier nicotine use.

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