

EFFECTS OF NEUROLEPTICS WITH OR WITHOUT ANTI-CHOLINERGICS AMONG SCHIZOPHRENIC PATIENTS OF SOUTH GUJARAT

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ABSTRACT

Objective: Neuroleptics (or anti-psychotics) indicated for the treatment of schizophrenia have significant dose-limiting extra-pyramidal side effects (EPS). Literature suggests limited evidence for the efficacy of anticholinergics in the treatment of neuroleptic-induced EPS. Thus, the present study was conducted to understand the effects of anti-cholinergics on EPS among schizophrenics already on neuroleptics (typical and atypical).

Methods: This prospective, cross-sectional, observational study was conducted at a tertiary care teaching hospital in South Gujarat for 15 months. A total of 200 participants were included based on selection criteria and distributed equally among four groups (A, B, C, and D) of 50 participants each. The collected data were analyzed for sociodemographic profile, current treatment regimen, type of neuroleptic drug, present complaints of EPS, and addition of any anti-cholinergic agent. An abnormal involuntarily movement scale score was used for examining movement disorders in all study participants. Descriptive statistical analysis was done using Microsoft Excel 2019 and IBM SPSS software version 28, and $p < 0.05$ was considered statistically significant.

Results: Hundred patients who were prescribed typical neuroleptics were divided into groups A (with anti-cholinergic) and B (without anti-cholinergic), whereas the remaining 100 patients being prescribed atypical neuroleptics were divided into groups C (with anti-cholinergic) and D (without anti-cholinergic) by simple randomization. The majority of 56% were young adults (18–35 years) with an overall male pre-ponderance (2.14:1). Out of 50 participants in both groups A and B, a higher number of group B participants experienced tremors, rigidity, difficulty in movements, and tardive dyskinesia (TD) (48/50 vs. 30/50, 36/50 vs. 6/50, 24/50 vs. 1/50, 36/50 vs. 19/50) as compared to group A, respectively. Similar results were noted with groups C and D, where a higher number of group D participants experienced tremors, rigidity, difficulty in movements, and tardive dyskinesia (TD) (15/50 vs. 5/50, 11/50 vs. 3/50, 18/50 vs. 2/50, and 16/50 vs. 4/50, respectively). All the results were statistically significant ($p < 0.05$).

Conclusion: There was a significant reduction in EPS among schizophrenia patients who were prescribed atypical over typical neuroleptics. The addition of one anticholinergic to the drug regimen also significantly reduced the frequency of EPS in schizophrenia patients.

Keywords: Anticholinergics, Neuroleptics, Rigidity, Schizophrenia, Tardive dyskinesia, Tremors.

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INTRODUCTION

Schizophrenia is a chronic, incapacitating psychiatric disorder characterized by psychotic as well as negative symptoms [1], with a prevalence of ~0.4% in countries like India [2,3]. The beneficial role of antipsychotic drugs (APDs), also known as neuroleptic drugs, is very well established for acute as well as maintenance therapy of psychotic symptoms of schizophrenia [4].

Typical antipsychotics are also known as first-generation antipsychotics. Some examples of this category of drugs include chlorpromazine, thioridazine, fluphenazine, and haloperidol [5]. Atypical antipsychotics are also known as second-generation antipsychotics. Some of the examples include aripiprazole, quetiapine, olanzapine, and risperidone [6].

Contrary to their beneficial role, typical (first generation) neuroleptics have a significant dose-limiting adverse effect profile too, such as extra-pyramidal side-effects (EPS), along with a narrow therapeutic window. These extra-pyramidal effects include parkinsonism (tremors, rigidity, and hypokinesia), acute muscular dystonia, akathisia, tardive dyskinesia (TD), etc. [7,8] Nonetheless, these risks are minimal or lower with atypical (second generation) neuroleptics.

For this emergence of neuroleptics-induced extrapyramidal side effects (NIES), anti-cholinergic agents were introduced. They played a mixed role showing improvements in a few and complications in the remaining few [9]. There was limited evidence for its efficacy then, thus indicating uncertain functional relevance [10].

The majority of studies are *post hoc* analysis or retrospective studies, leading to a dearth of prospective studies examining the effects of neuroleptics with or without anti-cholinergics for schizophrenia management. Thus, the present study was envisaged to identify the effects of anti-cholinergics on EPS among schizophrenics already on neuroleptics (typical or atypical) at a tertiary care teaching hospital in South Gujarat, India.

METHODS

Ethics and study design

This prospective, cross-sectional, observational study was initiated only after obtaining approval from the Institutional Ethics Committee.

Study site, duration of study, and sample size: It was conducted at the Department of Pharmacology in collaboration with the Department of Psychiatry at a tertiary care teaching hospital in South Gujarat, India,

from January 2021 to March 2022 (15-month duration). A total of 200 study participants fulfilling selection criteria were distributed into four groups (A, B, C, and D) of 50 participants each.

Selection criteria

Those schizophrenia patients aged 18–65 years, visiting the Outpatient Department of Psychiatry, being treated with neuroleptic monotherapy Since at least 3 months with or without anticholinergic drugs and/or adjuvant medication like benzodiazepine by the attending psychiatrist as well as willing to participate were enrolled in the study only after obtaining voluntary written informed consent. Here, those who were prescribed typical neuroleptics with and without an anticholinergic were assigned groups A and B, respectively, using a simple randomization technique. Similarly, groups C and D comprised of study participants prescribed atypical neuroleptics with and without an anticholinergic, respectively, using a simple randomization technique. Those who were prescribed neuroleptic polytherapy and/or other concomitant medications, had a history of alcohol in the past 1 year, or had a history of any other psychotic disease, non-cooperative patients were excluded from the study.

Data collection

The baseline data collected from enrolled participants on a pre-validated case record form by the investigator included socio-demographic profile, current treatment regimen for schizophrenia, type of neuroleptic drug, present complaints with neuroleptic monotherapy, addition of any anti-cholinergic agent, and an abnormal involuntarily movement scale (AIMS) score (for examining movement disorders in all study participants) [11]. AIMS score of two in at least two discrete body areas indicated mild severity whereas an AIMS score of three in at least one body area indicated moderate severity for TD [12]. The AIMS score was calculated by the consulting psychiatrist of the respective patient at the study site.

Statistical considerations

After data entry into Microsoft Excel 2019, the data were analyzed using IBM SPSS software version 28. Univariate descriptive analysis was done using mean, median, frequency, and percentage whereas bivariate analysis was done by cross tabulation, and a Chi-square test was applied to find a significant association ($p < 0.05$) between appropriate variables. The odds ratio was calculated with a 95% confidence interval for risk assessment.

RESULTS

Out of 200 schizophrenia patients, 100 who were prescribed typical neuroleptics were assigned into groups A (with anti-cholinergic) and B (without anti-cholinergic) comprising 50 participants each. The remaining 100 patients were prescribed atypical neuroleptics and were assigned into groups C (with anti-cholinergic) and D (without anti-cholinergic) with 50 participants each.

Socio-demographic profile

In the age range of 18–65 years, the mean and median ages were 35.6 ± 11.3 and 40 years, respectively. The majority of patients (56%) were young adults (18–35 years). The male: female ratio (2.14:1) showed a higher male preponderance with 68.5% males and 31.5% females (Table 1).

The majority of patients (~70%) lived in a nuclear family. Nearly ~23% lived with extended family. (Fig. 1)

Approximately 50% of the study participants were illiterate. The remaining 50% comprised a literate population, out of which only 5% were graduates (Fig. 2).

EPS

Tremors, rigidity, difficulty in movements, and TD

Out of 50 participants in both groups A and B, a higher number of group B participants experienced tremors, rigidity, difficulty in

movements, and TD [~ 48 (96%), 36 (72%), 24 (48%), and 36 (72%)], respectively. In group A, difficulty in movements was noted in only 1/50 (2%) of participants. These results were statistically significant ($p < 0.0001$) (Fig. 3 and Table 2).

Similarly, out of 50 participants in both groups C and D, a higher number of group D participants presented with tremors (15 [30%]), rigidity (11 [22%]), difficulty in movements (18 [36%]), and TD (16 [32%]) as compared to group C (5 [10%], 3 [6%], 2 [4%], and 4 [8%]), respectively (Fig. 4, Table 2).

Thus, out of a total of 200 participants, approximately 50% experienced tremors, whereas ~40% had TD (Table 2).

TD in the haloperidol group

TD was present in 50 (58%) out of total 86 haloperidol users. The majority of patients (36/50 [72%]) among these were not administered an anti-cholinergic agent. In 36 (42%) out of the total

Table 1: Age-wise gender distribution of schizophrenia patients (n=200)

Age groups (years)	Gender distribution				Total (n=200)	
	Males		Females		(n)	(%)
	(n)	(%)	(n)	(%)		
18–35	79	57.7	33	52.4	112	56
36–50	41	29.9	24	38.1	65	32.5
51–60	17	12.4	6	9.5	23	11.5
Total (n=200)	137	68.5	63	31.5	200	
Mean age±standard deviation	35.8±11.4		35.7±11.2		35.6±11.3	
Median age	40					

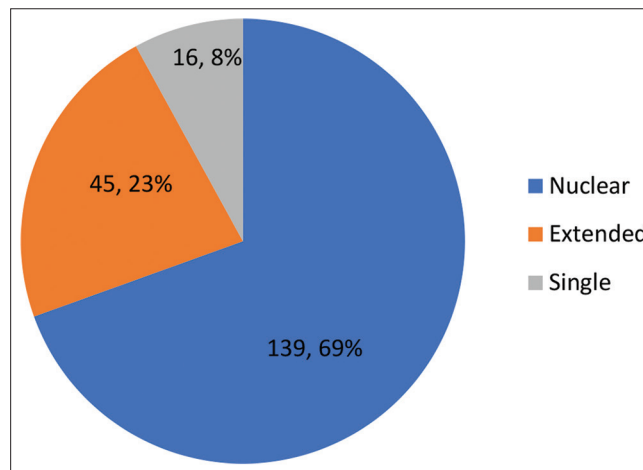


Fig. 1: Family structure of schizophrenia patients (n=200)

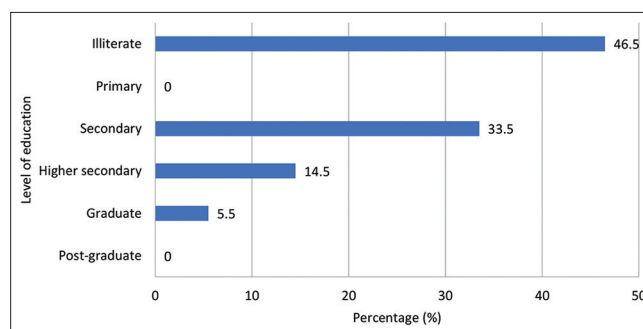


Fig. 2: Level of education among schizophrenia patients (n=200)

86 haloperidol users, TD was absent, and nearly 60% (22/36) of them were administered an anti-cholinergic agent (Table 3).

DISCUSSION

For the past few decades, neuroleptic medications have been extensively prescribed to treat psychiatric illnesses, such as schizophrenia. In spite of early neuroleptics (first-generation/typical anti-psychotics) (chlorpromazine, haloperidol, or fluphenazine) relieving positive symptoms of schizophrenia, they lack effectiveness in treating negative symptoms of schizophrenia and have an adverse effect profile (EPS) too. The novel neuroleptics (second generation/atypical anti-psychotics) (olanzapine, risperidone, and quetiapine) have an improved safety profile, thus becoming the mainstay treatment for schizophrenia. Thus, the development of EPS with the chronic use of typical neuroleptics led to an impaired ability to accomplish daily chores and affected the patient's quality of life as well, if left unattended.

As per reports, the incidence of EPS with typical neuroleptics (5–8%) as compared to atypical ones (2–4%) was significantly higher [13]. Its incidence was higher, particularly with higher-potency

neuroleptics [14]. This suggests that neuroleptic-induced EPS such as movement disorders, drug-induced parkinsonism (tremors and rigidity), TD, etc. can be countered with anti-cholinergics.

In the present study, sociodemographic analysis showed that a larger number of patients were younger adults, along with a male preponderance. This may probably indicate that the 18–35-year-old age group is relatively more vigilant toward the management of illness. Nearly half of the study population was illiterate in the present study. Among the remaining half, only a few had accomplished graduation degree. Luo *et al.* also showed that the majority of his study patients had received only primary education [15]. This indicated that the schizophrenia illness may have had a negative impact on the education status of the patients. Maximum patients of present study had been living as a nuclear family. Literature has suggested that the family history of schizophrenia may be associated with a higher risk of developing schizophrenia as well as mood disorders and delusional disorders [16]. The lack of social interaction and abuse witnessed by the patients during childhood may also have had an impact on the severity of the illness. In addition, the stigma around this psychiatric illness also restricts patients from finding suitable employment and marriage partners, indicating its negative impact socially as well.

In the present study, the EPS profile of all the study participants was analyzed after distributing them into four groups (A, B, C, and D) of 50 participants each where the former two groups (A and B) were receiving typical neuroleptic drugs and the latter two (groups C and D) were receiving atypical neuroleptic drugs. Furthermore, only groups A and C had patients with respective neuroleptics with add-on anticholinergics. During the study duration, neuroleptic drug administration in these study patients led to various EPS which included tremors, rigidity, difficulty in movements, and TD.

The frequency of these EPS varied in all four study groups, depending on the administration of type of neuroleptic with or without anti-cholinergic medication that they had been prescribed by the consulting psychiatrist. The results of the present study showed that the overall frequency of EPS was significantly higher in patients taking typical neuroleptic drugs as compared to atypical neuroleptics. In addition, the frequency of EPS was relatively lower in those being administered an anti-cholinergic drug along with the respective neuroleptic as compared to those not being administered any anti-cholinergic medication. This showed that atypical drugs (second-generation anti-psychotics) were associated with a lower incidence of EPS as compared to typical ones (1st-generation anti-psychotics). Thus, second-generation ant-psychotics do not abolish the EPS but definitely lead to a reduced incidence. In the present study, the addition of an anti-cholinergic drug also reduced the frequency of EPS in schizophrenia patients significantly. This showed that the use of anti-cholinergic drugs had a protective role in preventing EPS in schizophrenia patients being managed with neuroleptics.

These findings support the existing literature which suggests the use of atypical neuroleptics for the management of schizophrenia

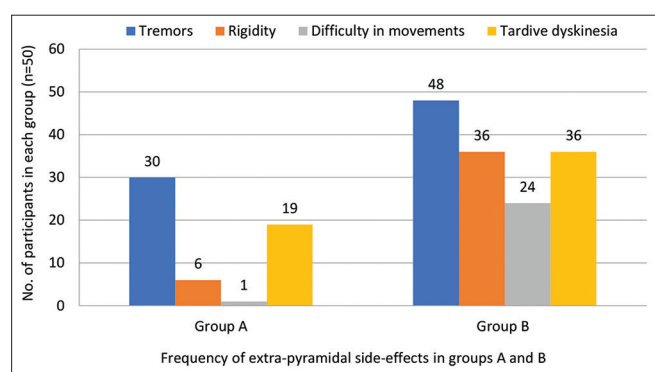


Fig. 3: Frequency of extra-pyramidal side-effects in groups A and B (n=50 in each group)

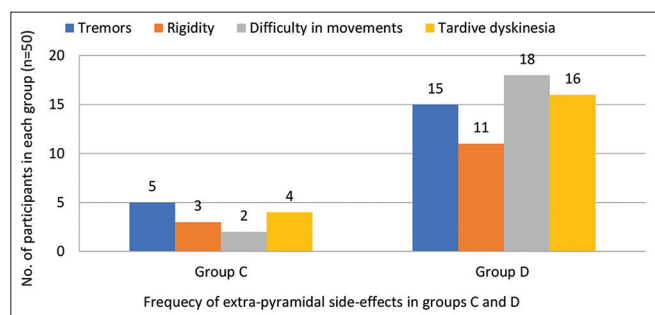


Fig. 4: Frequency of extra-pyramidal side-effects in groups C and D (n=50 in each group)

Table 2: EPS profile in schizophrenia patients (n=200)

Groups (n=50)	Frequency of EPS							
	Tremors (n=50)		Rigidity (n=50)		Difficulty in movements (n=50)		Tardive dyskinesia (n=50)	
	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)	Present n (%)	Absent n (%)
A	30 (60)	20 (40)	6 (12)	44 (88)	1 (2)	49 (98)	19 (38)	31 (62)
B	48 (96)	2 (4)	36 (72)	14 (28)	24 (48)	26 (52)	36 (72)	14 (28)
C	5 (10)	45 (90)	3 (6)	47 (94)	2 (4)	48 (96)	4 (8)	46 (92)
D	15 (30)	35 (70)	11 (22)	39 (78)	5 (10)	45 (90)	16 (32)	34 (68)
	98 (49)	102 (51)	56 (28)	144 (72)	32 (16)	168 (84)	75 (37.5)	125 (62.5)

EPS: Extra-pyramidal side-effects

Table 3: Frequency of tardive dyskinesia in Haloperidol group (n=86)

Anticholinergic drug	Tardive dyskinesia		Total (n=86) n (%)
	Present n (%)	Absent n (%)	
Not administered	36 (72)	14 (39)	50 (58)
Administered	14 (28)	22 (61)	36 (42)
Total (n=86)	50 (58)	36 (42)	86

along with the addition of an anti-cholinergic drug. In the Peluso *et al.* study, many randomized controlled trials showed that first-generation antipsychotics had a higher risk of tremors than a second-generation drug, suggesting that potential tremors from 1st-generation antipsychotics can be effectively managed with adjunctive anticholinergic medication [17]. One such study by Mathews *et al.* also discussed that rigidity can be eliminated with a reduced dose or replaced with a low-potency antipsychotic, and if it does not help, an anticholinergic drug can be added too [18]. Thus, the availability of atypical neuroleptics, which results lesser into EPS and prevents as well as manages EPS, could eliminate this significant clinical problem entirely. In addition, prescribing second-generation neuroleptics along with an anticholinergic may also lead to increased treatment adherence, ultimately improvising treatment outcomes among schizophrenia patients.

In the present study, the association of anticholinergic use with a reduced frequency of TD in haloperidol users was found to be significant. In a Japanese cohort study among haloperidol users (64 mg/day), nearly 40% of the study participants showed signs of TD and parkinsonism each [19]. This is in contrast to the results of the present study since, in our study, anticholinergic drug usage had a protective effect in preventing TD induced by haloperidol. However, Schooler *et al.* had suggested that second-generation APDs-induced fewer EPS than did first-generation antipsychotics, especially haloperidol [20]. This again advocates the fact that potential EPS from first-generation antipsychotics can be effectively managed with adjunctive anticholinergic medication.

CONCLUSION

Among the varied side-effects known with typical neuroleptics in schizophrenia patients, those commonly found and noted were tremors, rigidity, difficulty in movements, and TD. There was a significant reduction in EPSS among schizophrenia patients who were prescribed atypical neuroleptics as compared to typical neuroleptics. Similarly, those also prescribed an anticholinergic agent with a typical or atypical neuroleptic drug had a reduced frequency of EPS versus those being administered only a neuroleptic agent (no anticholinergic). Thus, the present study outlines the primary effects and observations to summarize the current knowledge on the occurrence and risk of EPS with neuroleptic drugs.

Strengths and limitations

Neuroleptic monotherapy helped in understanding the role of neuroleptic agents (with and without anti-cholinergics) in the EPS profile of schizophrenia patients. It also helped in the generation of data for reference by patients visiting the study site for schizophrenia treatment. This shall also guide to evaluate the impact of neuroleptic agents (monotherapy versus polytherapy) among schizophrenia patients for a longer duration. However, the effectiveness of chronic use of anticholinergics in neuroleptic-induced TD needs to be evaluated in further studies.

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CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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AUTHOR CONTRIBUTIONS

Conceptualization: Dr. Pradipsinh Sodha, Dr. Preeti Yadav, Data curation: Dr. Pradipsinh Sodha, Dr. Kajal Chaudhari, Dr. Tushar Talavia, Formal analysis: Dr. Pradipsinh Sodha, Dr. Haiya Sheth, Dr. Hita Rana, Funding acquisition: None. Methodology: Dr. Pradipsinh Sodha, Dr. Mayur Chaudhari, Project administration: Dr. Pradipsinh Sodha, Dr. Kajal Chaudhari, Dr. Tushar Talavia, Visualization: Dr. Pradipsinh Sodha, Dr. Preeti Yadav, Dr. Mayur Chaudhari, Writing-original draft: Dr. Pradipsinh Sodha, Dr. Hita Rana, Writing-review and editing: Dr. Haiya Sheth, Dr. Preeti Yadav, Dr. Mayur Chaudhari

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