Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2018/175

Original Article

Evaluation of Subject Response to Antipsychotics - Subjective Aspect and Related Clinical Correlates

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Abstract

Aim: The aim of this study is to assess the subjective response to antipsychotics in patients with schizophrenia and to assess the related factors such as psychopathology, side effects, insight, and treatment variables.

Methodology: A total of 60 patients with schizophrenia were randomized to treatment with risperidone (n-30) or haloperidol (*n* = 30) daily. Efficacy was assessed by the improvement of psychotic symptoms, measured on the positive and negative syndrome scale. The safety and tolerability were evaluated with the extrapyramidal symptom rating scale, the UKU side effect rating scale, and Insight and Treatment Attitude Questionnaire.

Results: Comparing haloperidol group and risperidone group for variables such as sex, age, duration of treatment, literacy level, and drug-free duration before admission was not statistically significant. Hence, both groups are comparable. Haloperidol group had the number of dysphoric patients (21), and risperidone group had only 8 patients who had dysphoria (Chi-square $P < 0.01$). In psychopathology, subjective response was more dysphoric when paranoid scores were high (significant two-tailed −0.00). In the final assessment total, psychopathology scores were high if dysphoria is high and if psychopathology scores were low and the dysphoria is also low (significant two-tailed −0.00). Dysphoria scores are high if insight is low, and dysphoria scores are low if insight is good. Dysphoria scores increase with increasing side effects and decrease with decreasing insight (significant two-tailed −0.00).

Conclusion: Subjective response to risperidone is better than haloperidol. If there is the initial dysphoric response, the treatment response is reduced with low insight and high psychopathology in the dysphoric group.

Key words: Antipsychotic therapy, Insight, Schizophrenia

INTRODUCTION

Schizophrenia has consistently attracted the attention of psychiatrists and neurologists throughout the history of the disorder because of the magnitude of its clinical problem. With improved drug treatments, the area that evinces interest in schizophrenia factors affects the outcome of treatment and relapse. With the introduction of chlorpromazine and haloperidol, there came a revolution in the treatment of patients with schizophrenia. With the introduction of more and more newer antipsychotics, the trend is more toward subjective tolerability and quality of life with antipsychotics.

Access this article online

www.ijss-sn.com

Month of Submission : 04-2018
Month of Peer Review : 05-2018
Month of Acceptance : 06-2018
Month of Publishing : 06-2018

The relevance of subjective response to medications was raised by Sarwer–Foner in the early 1960s itself (George Awad – 1993). The psychological and psychodynamic issues in influencing drug response are gaining interest recently. The effect of subjective response originated when patients receiving antipsychotics complained that medications are worsening their condition even clinically their symptoms reduced. Later, it was found that patients receiving neuroleptics with the complaints of dysphoria when followed up showed that they had a less favorable outcome

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to treatment than the group of patients without dysphoria.[1-5]

Further studies proved that the side effects did not influence the subjective response. The severity of psychopathology had the varied influence on the subjective response. Paranoid states, depression, and negative symptoms also influenced the subjective response to antipsychotics.[6] SPET and PET studies have proved that patients who experience dysphoria had increased binding of dopamine receptors (D2) in the nigrostriatal region.[7] It implies that patient with lower dopamine activities is likely to develop dysphoria. For these reasons, the newer antipsychotics are tolerated better, and patients express favorable subjective response.

The implications to the clinicians are that patients who develop dysphoria to a drug consider changing the drug or the drug dosage should be reduced. Days have changed from isolation and chaining of mentally ill to optimizing the objective and subjective improvement, thereby the quality of life. We ask patients with schizophrenia many questions, but we never ask them whether the medication produces any unpleasant response in them. With the identification of the subjective state, the pharmacotherapy in schizophrenia sees that a new world is exploding in the factors influencing compliance to therapy.

Aim

The aim of this study is to assess the subjective response to antipsychotics in patients with schizophrenia and to assess related factors such as psychopathology, side effects, insight, and treatment variables.

METHODOLOGY

This prospective observational study was conducted in the Department of Psychiatric. A total of 60 consecutive patients with a diagnosis of schizophrenia were screened from the patients getting admitted as inpatients. They were selected based on inclusion and exclusion criteria. Written consent was obtained from the patients and relatives for this study. All subjects gave written consent to participate in the study. Cases were diagnosed as schizophrenia by the investigator based on ICD-10 criteria. All consecutive patients who satisfied the inclusion and exclusion criteria were enrolled into the study. The investigator was blind to the antipsychotic drug used. The treating clinician gave the prescription. Of these 60 patients who gave consent, 6 patients withdrew within a week due to personal reasons and requested to be discharged. Patients were given either haloperidol or risperidone. Odd-numbered patients received haloperidol and even-numbered patients received risperidone. The first assessment was done on the 1st day, and final evaluation was done on the 14th day. In few patients, it was done few days before itself as they requested to be discharged. Patients were maintained on one antipsychotic, and other oral medications were not given. Anticholinergics were started whenever indicated. Injection lorazepam was used in agitated patients. The antipsychotic dosage was not fixed, and it was titrated based on the daily clinical evaluation. ECT was not given.

Inclusion Criteria

The following criteria were included in the study:

1. Patients with a diagnosis of schizophrenia based on ICD-10 criteria.
2. Patients who were drug free for 4 weeks or drug naïve.
3. Age between 15 and 45 years.
4. Giving consent for the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. Comorbid substance abuse amounting to dependence
2. Significant medical and neurological illness
3. Comorbid psychiatric disorders.

The tests were administered by a single rater, and approximate duration for administering all the tests for an individual is 1–1 ½ h and was conducted in a single session. The second assessment was done on 14th day after starting treatment.

Instruments Used

1. Semi-structured pro forma for sociodemographic details and illness details.
2. PANSS - positive and negative syndrome scale
3. DAI - drug attitude inventory
4. The UKU side effect rating scale
5. ITAQ - insight and treatment attitude questionnaire.

RESULTS AND DISCUSSION

Of the 60 patients who gave consent, 6 patients withdrew within few days and requested to be discharged for personal reasons. Hence, the final sample size was 54, i.e., 27 in haloperidol group and 27 in risperidone group.

Chi-square test was used to find the significant difference between haloperidol and risperidone and found not statistically significant for variables - sex, age, duration of illness, previous treatment, literacy level, drug free duration before the study. Hence, the cases in both the groups are comparable.

Of the patients receiving haloperidol, one patient opted to get discharged early due to these reasons. Five patients (18.5%) in haloperidol group and three patients in risperidone (11.11%) group wanted to get discharged

on the 12th day. They could not be asked to come for the assessment on the 14th day, as they are from distant places. The second assessment was done on the 12th day itself. In the haloperidol group, 77.7% and, in risperidone group, 85.2% completed the stipulated 14 days. However, the difference was not statistically significant [Table 1].

Whenever patients developed extrapyramidal side effects, of which dystonia was more frequent, patients were started on the anticholinergic drug. The number of patients in haloperidol group 40.7% had to receive anticholinergic when compared to 3.7% in risperidone group. The difference was statistically significant when Chi-square test was applied ($P < 0.01$).

PANSS, UKU, and DAI difference was found out for each (before Rx minus 14 days of Rx). Mean was calculated for these differences for 2 drugs separately. The *t*-test was used to find the difference between these mean.

For all measures, i.e., DAI, PANSS from 1 to 9, ITAQ, and UKU, the difference between the 1st-day observation and last observation was calculated separately for each patient. The difference was added up, and the mean was calculated. The haloperidol group and the risperidone group were compared using the *t*-test for equality of means.

Results were that there was no statistically significant difference in two groups regarding changes after pharmacotherapy in subjective response, psychopathology, and insight scores. Hence, the effect of two drugs was comparable in 2 weeks' period. Regarding side effects, haloperidol group had significant change, i.e., increase in side effects which were statistically significant when compared to risperidone group.

All the variables DAI, PANSS 1-9, ITAQ, and UKU for the first assessment were compared between the two groups, i.e., haloperidol- and risperidone-receiving groups.

There was statistically significant difference in the subjective response (DAI) score, i.e. haloperidol group ($P = 0.00$) (mean - 2.89) significantly dysphoric when compared to risperidone group (mean + 0.7).

In the PANSS score - negative syndrome and anergia scores, there was a statistically significant difference, i.e. scores are significantly more in risperidone group. Other measure in PANSS, there was no significant difference. Hence, the patients were distributed in both the groups in a comparable way.

In the insight (ITAQ) and side effects (UKU scores), there was no statistically significant difference in both haloperidol and risperidone groups for the day-1 assessment.

All the variables DAI, PANSS 1-9, ITAQ, and UKU for the second assessment were compared between haloperidol and risperidone group.

In the second assessment also, the subjective response (DAI) was dysphoric in the haloperidol group when compared to risperidone group, and the difference was statistically significant.

In the UKU scale, scores (side effects) were statistically significant in the haloperidol group when compared to risperidone group. The difference was more significant in psychic and neurologic side effects [Table 2].

To find whether anticholinergic drugs used had produced the significant change in subjective response, the Chi-square test was applied. There was no statistically significant difference between the groups (i.e., received and not received).

The subjective response was negatively correlated with psychopathology (PAN2-124 positive, negative, and general psychopathology added together), i.e., when psychopathology was high, the subjective response was negative (dysphoric), and when psychopathology was low, the subjective response was positive (non-dysphoric).

The subjective response was inversely correlated with side effects, paranoid score, i.e., when the subjective response was dysphoric (low score) side effects and the paranoid score was high. When the subjective response was non-dysphoric (high score) the, side effects and paranoid scores were low.

This shows that haloperidol group had the number of dysphoric patients (dysphoric-21, non-dysphoric-6) and risperidone group had the lower number of dysphoric patients (dysphoric-8. non-dysphoric 19).

When Chi-square test was applied, there was a significant difference ($P < 0.01$) indicating haloperidol produced significant dysphoric responses.

Table 1: Comparison between the haloperidol group and resperidone group on the scores of first assessment

Scales	*t*-test for equality of means			
	t	df	Significant (two-tailed)	Mean difference
DAI1	−3.46	52	0.00**	−3.63
UKU1P	−0.14	52	0.89	−0.07
UKU1N	0.45	52	0.66	0.04
UKU1A	−1.95	52	0.06	−0.37
UKU1O	−1.44	52	0.16	−0.07

**P<0.01, *P<0.05

Table 2: Comparison of dysphoric and non-dysphoric group

Characteristics	Independent samples *t*-test for the equality of means			
	t	df	Significant (two-tailed)	Mean difference
Age	2.99	52	0.00	5.00
Mean duration of illness	2.18	52	0.03	2.91
Mean psychopathology on the first assessment	−0.27	52	0.79	−0.88
Side effects - final assessment	2.80	52	0.01	2.29
Mean insight - first assessment	−3.05	52	0.00	−4.36
Mean difference in psychopathology	1.54	52	0.13	4.63

In the sex distribution, there was no significant difference between male and female patients. (Chi-square test - $P = 0.777$).

The subjective response rating was on the first assessment. The mean age in the dysphoric group was 33, and the non-dysphoric group was 28 which had the significant difference ($P < 0.00$).

Mean duration of illness in the dysphoric group was 7.43 years and the non-dysphoric group was 4.52 years which had less significance.

The initial mean psychopathology scores were not significantly different in both the groups. The mean difference in psychopathology scores also did not significantly differ in both the groups [Table 3].

The initial dysphoric subjective response was significantly ($P = 0.01$) associated with the increase in side effects. There was a significant difference in mean insight between the dysphoric and non-dysphoric groups. The dysphoric group had lower mean insight (4.48) than the non-dysphoric group (8.84).

The subjective response was dysphoric (negative) when haloperidol was given. The findings of Van Putten and May 1978 and Awad and Hogan 1985 were replicated. Risperidone had the positive subjective response.[3,4] The findings of Voruganti *et al.* 2002 and Hellewell *et al.* 1999 were replicated.[8,9] The haloperidol and risperidone group was comparable in age, sex, literacy, duration of illness, and previous treatment. Haloperidol-receiving patients were more often receiving anticholinergics than risperidone-receiving patients. The side effects at the end of 2 weeks observation were also high in the haloperidol group than risperidone group. This shows that risperidone has advantages over haloperidol in subjective response, side effects, and the need for anticholinergics [Table 4].

Dysphoric respondents had significantly low insight at the onset of treatment. They had more side effects on follow-up [Table 5]. The findings of Rossi *et al.* 2000 are replicated.[10] The findings of Gervin *et al.* 1999 have been replicated as subjective response inversely correlated with side effects. The non-dysphoric group had significantly better insight and less.[11]

The psychopathology did not significantly vary between the two groups. 2 weeks' observation was brief. To establish a difference, a longer duration of observation is needed. Hence, the findings of Van Putten and May 1978 and Hogan and Awad 1980 could not be replicated.[3,12] Other aspects of psychopathology were related to subjective response in that higher the psychopathology more the dysphoric response. If paranoid ideation was high, the subjective response becomes more dysphoric. The subjective response correlated with the total psychopathology paranoid score. The findings of Cabeza *et al.* 2000 were replicated. The subjective response was not altered by the addition of anticholinergic.[13] The findings of Rossi *et al.* 2000 is replicated.[10]

CONCLUSION

The subjective response is correlated with treatment variable. Haloperidol has more dysphoric response, and risperidone has the non-dysphoric response. This confirms the advantage of risperidone over haloperidol. The subjective response is negatively correlated with psychopathology, side effects. As the psychopathology increases, the dysphoria increases. The subjective response is correlated with insight. Dysphoric responders have more side effects at the end of observation. Hence, if there is any dysphoric response to a particular antipsychotic soon after starting the drug it indicates that he may become a poor

Table 3: Comparison between the haloperidol group and risperidone group for the score on the second assessment

Scales	*t*-test for equality of means			
	t	df	Significant two-tailed)	Mean difference
DAI2	−2.54	52	0.01**	−2.59
UKU2P	2.77	52	0.01**	1.19
UKU2N	4.19	52	0.00**	1.15
UKU2A	0.65	52	0.52	0.22
UKU2O	1.21	52	0.23	0.11

**P<0.01, *P<0.05

Table 4: Correlation between subjective response and other variables at the final observation

Subjective response	Psychopathology	Insight	Negative syndrome	Depression	Side effect	Paranoid
Pearson correlation	−0.407	0.153	0.034	−0.011	−0.413	−0.43
Significant (two-tailed)	0.002	0.270	0.807	0.935	0.002	0.00

Table 5: Frequency distribution of antipsychotics in dysphoric and non-dysphoric group

Drug	Count (%)		
	Dysphoric	Non-dysphoric	Total
Haloperidol	21 (71.41)	6 (24)	27 (50)
Risperidone	8 (27.59)	19 (76)	27 (50)
Total	29 (100.00)	25 (100)	54 (100.00)

P<0.01

responder to that drug with more side effects. Hence, the clinician can consider another drug which will improve the subjective response and thereby compliance. In addition to all other factors influencing compliance in patients with schizophrenia, the role of subjective response also should be given importance by the clinician.

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How to cite this article: Geethaanjali V, Jayakrishnaveni C. Evaluation of Subject Response to Antipsychotics - Subjective Aspect and Related Clinical Correlates. Int J Sci Stud 2018;6(3):48-52.

Source of Support: Nil, **Conflict of Interest:** None declared.