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Cost – Effectiveness of Antipsychotic Medications: Comparative evaluation of conventional versus newer agents in treatment of stable schizophrenic patients

KEYWORDS: Schizophrenia, antipsychotics, costs, effectiveness.

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ABSTRACT *The aim of the study was to compare the cost effectiveness among conventional antipsychotics, haloperidol and thioridazine with newer agents, olanzapine and risperidone in the treatment of stable schizophrenic patients. The results of this analysis showed that direct medication cost of conventional antipsychotics was much higher as compared to newer ones. Newer antipsychotics were found to be more cost effective in the treatment of schizophrenia.*

INTRODUCTION

Schizophrenia is a chronic, debilitating major psychiatric disorder requiring life long treatment. The financial costs of treating schizophrenia are enormously high. This is due to the early onset of the disease, need for hospital care, ongoing clinical care, rehabilitation and support services. So, the socio-economic status of the society in terms of loss of productivity and mortality impacts a significant problem in the course of the disease[1]. Evaluation of cost-effectiveness among various antipsychotic agents in an important issue while treating such a condition.

Preliminary data suggests that the newer antipsychotic agents are real alternatives to traditional ones in first-episode patients and in those who have responded poorly to the conventional agents[2] or cannot tolerate the side effects.

Therefore, the present study was conducted to evaluate the cost-effectiveness of newer versus conventional agents in treatment of schizophrenic patients.

MATERIAL AND METHODS

Study Design

An open label randomized prospective study was conducted in stable schizophrenic patients for a 12 week period. A total of 40 patients diagnosed according to DSM IV criteria were divided into four groups. Group I (n=10) received haloperidol (5-20 mg/day), Group II (n=10) received thioridazine (50-800 mg/day), Group III(n=10) received olanzapine (5-20 mg/day) and Group IV (n=10) received risperidone (1-12 mg/day).

Prior to the initiation of the study, an informed written consent from the legal guardian of the patient was obtained after full explanation of the elements contained in the research protocol.

The inclusion criteria for this study were as follows:

- Patients of both sexes with age above 15 years
- Stabilized schizophrenia patients on conventional antipsychotic, haloperidol
- Brief psychiatric Rating Scale (BPRS) scores more than or equal to 24.

The exclusion criteria included:

- Women of reproductive age group without adequate contraception.
- Pregnant or lactating mothers.
- Serious medical illnesses.
- History of leukopenia without a clear etiology.
- History of severe allergies or multiple adverse drug reaction.
- Epileptic patient.
- Neurological or organic syndrome.
- Abnormal ECG.
- History of drug abuse including alcohol.
- Liver and kidney diseases.

Efficacy Variable:

The primary evaluation of efficacy for symptom control to endpoint improvement on the psychometric scales, that is PANSS[3] (Positive and negative symptoms scale). Assessments were completed at each scheduled visit during the total duration of 12 weeks study trial period.

The PANSS includes 3 scales and 30 items : 7 items make up the positive scale, next 7 items make up the negative scale and 16 items make up the general psychopathology scale. Individual items are scored with values range from 1 to 7. Scores above 1 indicate that a clinical symptom is present and ratings of 2-7 indicate increasing severity. The potential range for the positive and negative scales is 7-49, and the range for the general psychopathology scale is 16-112.

Evaluation of Cost of treatment:

Cost of prescriptions were calculated based on IDR[4] for each patient in each group. Further, the direct medication cost (in rupees) which included cost of antipsychotic drugs and concomitant medications were analyzed and compared between each treatment group.

Evaluation of Cost Effectiveness:

The Clinical Global Impressions (CGI) scale[5] consists of three global subscales, that is Severity of Illness(SI), Global Improvement (GI) and Efficacy Index (EI) were used for assessment of effectiveness. SI and GI scores range from 1 = not ill at all to 7 = among the most extremely ill.

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Efficacy Index (EI) is actually a ratio of benefit to risk, that attempts to assess the overall efficacy of treatment in relation to its adverse reactions. Scores range from 0 = marked improvement and no side effects to 4 = unchanged or worse and side effects outweigh therapeutic effects.

Statistical Analysis
For intragroup comparison at o week versus 12 weeks. Intergroup comparison between the four treatment groups was done using unpaired 't' test. The value of $p<0.05$, $p<0.001$ was considered statistically significant.

RESULTS
Patient Disposition and Baseline Demographics:
The sociodemographic characteristics of the patients are summarized in Table 1.

Total number of forty patients of stable schizophrenia with duration of illness ranging from 1 to 20 years, were included in the study. Out of these, 26 patients were in the age group of 17 to 30 years whereas 14 were in the range of 31 to 62 years. Subcategories of schizophrenia, as diagnosed by DSM-IV criteria revealed 26 patients were paranoid, 08 disorganised, 4 undifferentiated type and 2 of residual type.

Drug Dosages:
Table 2 shows that the antipsychotic drugs were administered in different dosage range. After 2 weeks of titration phase, mean daily doses were 17 mg of haloperidol , 350 mg of thioridazine and 11.5 mg of olanzapine, 4.85 mg of risperidone with dosage adjustments permissible in between also. At 12th week, daily maintenance doses were 18.5 mg of haloperidol, 560 mg of thioridazine and 13 mg of olanzapine, 5.6 mg of risperidone. All doses of antipsychotic medications were well within the therapeutic range.

Efficacy Analysis
All the four groups were effective significantly ($p<0.001$) in reducing symptoms at the end of 12 weeks (Table 3). More pronounced and early effects were seen with olanzapine and risperidone from 6 weeks ($p<0.001$) onwards.

Direct Medication Cost of Antipsychotic Treatment
Table 4 shows the direct medication cost per day of treatment in the different groups at baseline (first week) and at end of study at 12 weeks. The average direct medication cost per day of haloperidol and thioridazine group increased from approximately Rs. 4.50 to Rs. 11.50 and Rs. 11.00 to Rs. 35.50 at Ist and 12 weeks respectively. In olanzapine and risperidone group, the increase was meagre from Rs. 3.50 to Rs. 6.50 and Rs. 2.00 to Rs. 4.50 at Ist and 12 weeks respectively.

Cost-effective Analysis
As shown in figure 1, all the 4 drugs showed improvement on CGI (SI) and CGI (GI) scales whereas with olanzapine greater changes at 3,6 and 12 weeks were observed in comparison to thioridazine, but risperidone and haloperidol exhibited significant change only at 12 weeks.

Figure 2 shows that in CGI (EI) efficacy index, all four drugs showed similar improvement, however olanzapine was found to exceed the efficacy of thioridazine at the end of 12 weeks.

Concomitant Medications
Concomitant medications like anticholinergics, antidepressants and anxiolytics (as shown in Table 5) were used during the study trial, being maximum number in the haloperidol and thioridazine group.

DISCUSSION
In the treatment of psychosis, there is no evidence that any of the dopamine receptor antagonists(DRAs) is more effective than any other. Because thioridazine and mesoridazine have been associated with prolongation of the QT interval of the ECG, these agents should be reserved for patients who do not respond to other antipsychotics. The choice among the other dopamine receptor antagonists is based on prior responses – both objective improvement and the patient's subjective response to the drug – available routes of administration and dosage forms, side effect profiles and cost.

The introduction of the serotonin - dopamine antagonists(SDAs) like clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole at this time – has complicated the decision making process, as these agents have certain advantages when compared with conventional agents. The most important advantage is that SDAs cause substantially less extrapyramidal side effects than do dopamine receptor antagonists. Clozapine has been demonstrated to be effective for patients who remain symptomatic on a dopamine receptor antagonists. There is some evidence indicating that SDAs are more effective than DRAs for treatment of negative symptoms. An additional advantage of SDA other than risperidone is that they are less likely to elevate prolactin. As a result, these agents may be helpful for women who experience galactorrhoea and irregular menses with dopamine receptor antagonists. All of these advantages of SDAs indicate that the DRAs are likely to play a declining role in the treatment of psychosis.

How much these drugs differ in their clinical profile is unknown. The low side effect profile of the new SDAs make them attractive first line agents in first - break patients. Preliminary data suggest that these drugs, example olanzapine have additional antidepressant effects in schizophrenic patients. However, anecdotal evidence suggests that an unsatisfactory response to one SDA may not preclude a positive response to any other and that addition of a traditional agent may increase effectiveness as well. Although some of the newer atypical antipsychotics have been shown to be effective in treatment - resistant schizophrenic patients, example risperidone, olanzapine, but until more studies are published, clozapine will still remain the drug of choice in these patients. However, clinicians should try the newer agents first in chronic patients with serious residual symptoms, as they may be more effective than the traditional agents are with fewer side effects. These atypical antipsychotics can be differentiated on the basis of their tolerability profiles, such as weight gain, hyperlipidemia, diabetes risk, QTc effects, sexual side effects, orthostatic hypotension and sedation.

Populations that may continue to receive dopamine receptor antagonists include patients who require treatment with a long - acting depot drug and those who experience minimal side effects on DRAs. Further, cost of therapy among the newer and conventional agent may be another determinant for their use in treatment of schizophrenia.

The evaluation of cost effectiveness of antipsychotic drugs is an important issue while treating a chronic and lifelong disorder like schizophrenia. Final costs of haloperidol and thioridazine treatment were comparatively higher than the cost of olanzapine and risperidone treatment in the present study, in part due to use of concomitant medications

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like anticholinergics etc.

Present study does indicate that newer antipsychotic agents, that is olanzapine and risperidone are more cost-effective as compared to the conventional antipsychotics.

One study[6] observed that olanzapine treated patients experienced clinical improvement that translated into savings in cost of care. Another study[7] have shown, olanzapine to be a cost-effective alternative to conventional agent for the treatment of moderate to severely ill patients with long standing schizophrenia.

Newer antipsychotics, such as risperidone produce better cognitive function in patients with schizophrenia than do conventional neuroleptics, which implies that the indirect costs of the illness will be less in patients treated with risperidone[8].

These patients in addition may also be having depression, excitement, agitation and anxiety with sleep disturbances, for which antidepressants, mood stabilizers and anxiolytics respectively are coadministered[9,10,11]. In present study it was seen that proportion of patients treated with newer antipsychotics, olanzapine and risperidone taking other concomitant medications were comparatively smaller than the proportion of patients treated with conventional ones. These findings are in consonance with previous reports[12] of the increased use of other medications as adjuncts with conventional antipsychotics in the therapy of schizophrenia.

In the present study the direct medication cost of conventional antipsychotics was much higher as compared to newer ones. Newer antipsychotics were found to be more cost effective in the treatment of schizophrenia.

Preliminary pharmacoeconomic studies suggest that the cost of treatment are sometimes offset by the greater efficacy. With the newer agents, the decreased hospitalizations, the better quality of life, the fewer side effects and the great improvements in some schizophrenic patients will make treatment with these agents worthwhile.

Pharmaceutical companies will continue to search for better antipsychotic compounds, which may not affect dopamine or serotonin activity. At this time, though the available new drugs are real alternatives to traditional agents in first - episode patients and in those that have responded poorly to traditional agents or cannot tolerate the side effects. The new agents have raised hope for patients and their families.

CONCLUSION

In conclusion, from the results of the present comparative clinical study of conventional and newer antipsychotics, it was found that overall, the use of the more effective, better tolerated newer antipsychotics should reduce the cost of schizophrenia and improve patient's quality of life.

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Sociodemographic profile of Schizophrenic patients (n=40)

Variable	Variants	Group I n=10 n(%)	Group II n=10 n(%)	Group III n =10 n(%)	Group IV n = 10 n(%)
Age (in years)	mean ± SE	35.5 ± 4.47	28.7 ± 2.78	26.7 ± 1.54	29.9 ± 4.17
	Range	21 - 60	16 - 40	20 - 35	17- 62
Sex	Male	10	6	6	6
	Female	0	4	4	4
Marital Status	Single	6 (60.0)	4 (40.0)	4 (40.0)	2 (20.0)
	Married	4 (40.0)	6 (60.0)	4 (40.0)	6 (60.0)
	Others[1]	0	0	2 (20.0)	2 (20.0)
Occupation	Professional	4 (40.0)	2 (20.0)	3 (30.0)	1 (10.0)
	Non-Professional	5 (50.0)	7 (70.0)	7 (70.0)	5 (50.0)
	Others[2]	1(10.0)	1(10.0)	0	4 (40.0)
Education	Literate	10 (100.00)	8 (80.0)	10 (100.0)	8 (80.0)
	Illiterate[3]	0	2 (20.0)	0	2 (20.0)
Income	High	7 (70.0)	7 (70.0)	8 (80.0)	7 (70.0)
	Middle	3 (30.0)	3 (30.0)	2 (20.0)	2 (20.0)
	Low[4]	0	0	0	1 (10.0)
Religion	Hindu	8 (80.0)	8 (80.0)	9 (90.0)	8 (80.0)
	Muslim	1 (10.0)	2 (20.0)	0	1 (10.0)
	Others[5]	1(10.0)	0	1 (10.0)	1 (10.0)
Type of Schizophrenia	Paranoid	5 (50.0)	6 (60.0)	8 (80.0)	7 (70.0)
	Disorganized	3 (30.0)	2 (20.0)	1 (10.0)	2 (20.0)
	Undifferentiated	1 (10.0)	2 (20.0)	0	1 (10.0)
	Residual	1(10.0)	0	1 (10.0)	0
Duration of Illness (in years)	mean ± SE	10.9 ± 1.78	3.8 ± 1.07	4.1 ± 0.70	6.6 ± 1.57
	Range	2 - 20	1 - 12	1 - 7	1 - 18

Note: Group I patients received haloperidol treatment. Group II patients received thioridazine treatment. Group III patients received olanzapine and Group IV patients received risperidone treatment.

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Included divorced, remarried, separated.

Professional included engineer, teacher, computer professional. Non-professional included student, halwai, contractor, shop-keeper, others included housewife, unemployed.

Literate included one who could speak and write one language. Illiterate included one who could speak but not able to write.

High-income group included those who earn > Rs 5000per month, middle group in between Rs 2000 – Rs 5000 per month and low income was < Rs 2000per month.

Other religions included Christians, Sikhs.

Table 2
Dosing Schedule of antipsychotic drugs per day at different time intervals

Time Intervals	0 Weeks				3 Weeks				6 Weeks				12 Weeks			
	H	T	O	R	H	T	O	R	H	T	O	R	H	T	O	R
mean daily dose ± S.E.	8.5 ± 0.76	175 ± 8.33	6 ± 0.40	2.5 ± 0.16	17 ± 1.10	350 ± 14.91	11.5 ± 0.76	4.85 ± 0.18	18.5 ± 0.76	475 ± 15.38	13 ± 1.10	5.85 ± 0.14	18.5 ± 0.76	560 ± 14.54	13 ± 1.10	5.6 ± 0.27
Dosage range	5 - 10	150 - 200	5 - 7.5	2 - 3	10 - 20	300 - 400	10 - 15	4 - 6	15 - 20	400 - 550	10 - 20	5 - 6.5	15 - 20	500 - 600	10 - 20	5 - 7.5

H – Haloperidol T – Thioridazine O – Olanzapine R - Risperidone

Table 3
Evaluation of antipsychotic drugs on changes in PANSS scores(mean ± SE) in schizophrenic patients at different time intervals.

Time Intervals in weeks	PANSS			
	Haloperidol n=10	Thioridazine n=10	Olanzapine n=10	Risperidone n=10
0	75.1 ± 0.74	75.1 ± 0.91	77.1 ± 0.69	75.4 ± 1.25
3	66 ± 0.45**	66.8 ± 0.88**	65.7 ± 0.72**	64.5 ± 1.06**
6	62.1 ± 0.53 **	63.2 ± 0.85**	58.1 ± 0.4** $	58.8 ± 0.95**¦
12	60.1 ± 0.57 **	60.5 ± 0.69**	51.6 ± 0.3**$£	55.4 ± 0.89**¦

* p value < 0.05, ** p value < 0.001 versus o week values *
$; p < 0.001 versus corresponding haloperidol and thioridazine group values at 6 and 12 weeks.
£ ; p < 0.001 versus risperidone group values at 12 weeks
¦; p < 0.001 versus corresponding haloperidol and thioridazine group values at 6 and 12 weeks.

Table 4
Direct Medication Cost per day of treatment in the different groups at Ist week (baseline) and at 12 weeks (endpoint)

Time Intervals in weeks	DIRECT MEDICATION COST (Rs per day)			
	HALOPERIDOL	THIORIDAZINE	OLANZAPINE	RISPERIDONE
Ist	4.27 ± 0.40	10.92 ± 0.42	3.08 ± 0.28	1.98 ± 0.14
12th	11.22 ± 0.99	35.35 ± 0.93	6.56 ± 0.55	4.32 ± 0.38

Table 5
Concomitant Medications Used In Different Treatment Groups at Various Time Intervals

Time Intervals in weeks	CONCOMITANT DRUGS	HALOPERIDOL n = 10	THIORIDAZINE n = 10	OLANZAPINE n = 10	RISPERIDONE n = 10
		(n)	(n)	(n)	(n)
0	Anticholinergics Antidepressants Anxiolytics	- - -	- - -	- - -	- - -
3	Anticholinergics Antidepressants Anxiolytics	9 4 1	- 5 1	- - -	- -
6	Anticholinergics Antidepressants Anxiolytics	3 5 2	- 5 3	- - 1	2 2 -
12	Anticholinergics Antidepressants Anxiolytics	3 6 2	- 6 3	- 1 -	2 - 1

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Figure - 1: Effect of haloperidol (H), thioridazine (T),olanzapine (O) and risperidone (R) on mean changes in CGI Severity of Illness (SI) and Global Improvement (GI) at 0 week (baseline) and at end of 12 weeks (endpoint)

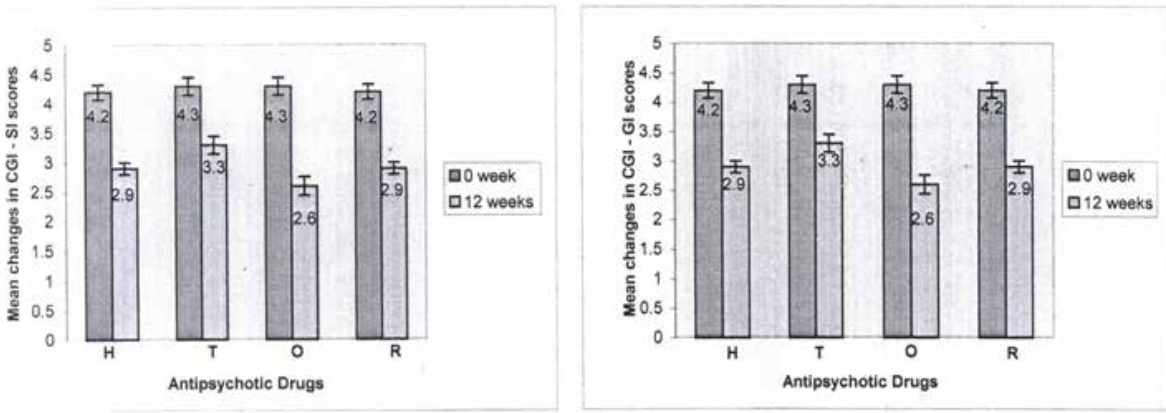
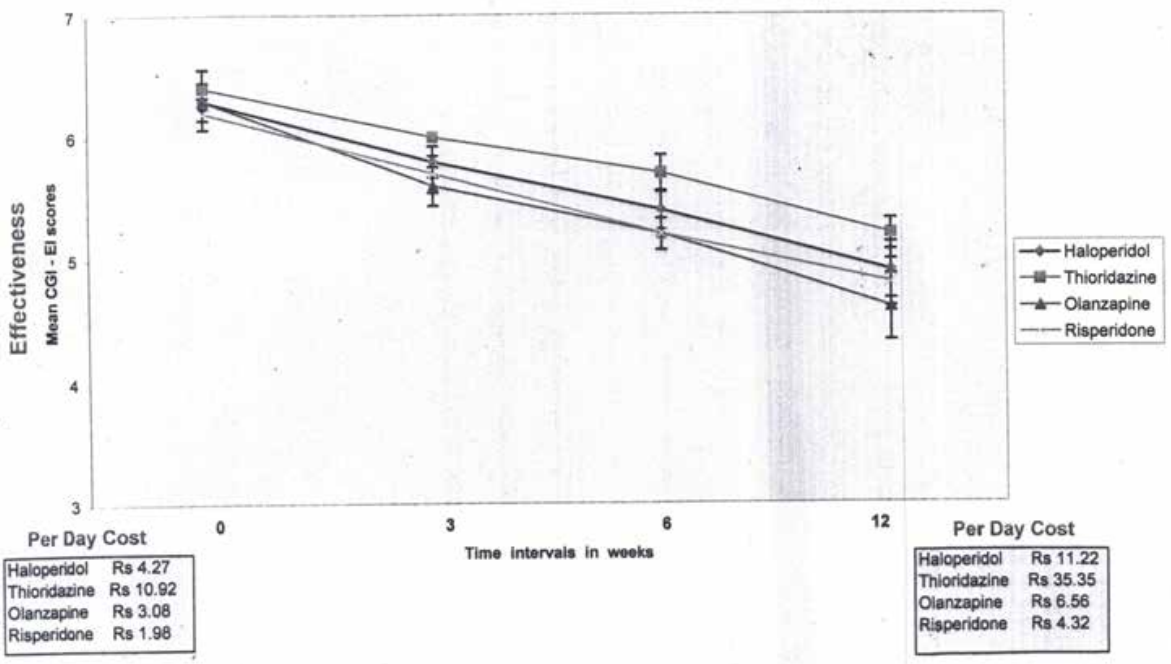


Figure - 2: Average treatment cost per day for haloperidol, thioridazine, olanzapine and risperidone treatment with their effectiveness as evaluated on CGI Efficacy Index (EI) at o week and 12 weeks



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