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Comparative Evaluation of Cost – Effectiveness and Medication Adherence Between Olanzapine and Iloperidone in Patients of Psychosis

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ABSTRACT

Background: *To assess the cost – effectiveness between Iloperidone and Olanzapine in relation to different measures of effectiveness and to evaluate significance of medication adherence and costs and outcomes.*
Methods: *A prospective, randomized, comparative, flexible dose clinical study of 1 year duration was conducted in 100 first episode (drug naïve) cases of psychosis attending to psychiatric outdoor patient department of Rohilkhand Medical College and Hospital, Bareilly. 50 patients each in olanzapine (OLZ) and Iloperidone (ILO) group comprised the sample size. Patients were regularly evaluated by senior psychiatrist for dose titration. OLZ 10-20mg/day and ILO 6-12mg/day were used. Least expensive brands available in our hospital pharmacy were used. Cost – effectiveness and medication adherence were measured as per the formula.* ***Results:*** *It was observed that ILO (8mg/day) controlled 65-75% cases and 12mg/day dose controlled ≥ 90% cases of psychosis. Whereas OLZ showed this level of control respectively with 10 – 15mg/day (average 12.5mg/day) and 15-20mg/day (average 17.5mg/d). Since olanzapine in 15-20mg/day dose cause more metabolic adverse events particularly obesity, hyperglycemia and dyslipidemia which need further management hence overall olanzapine is not cost-effective. 42(87.5%) cases had medication possession ratio (MPR) >90% in ILO group compared to 18 (37.5%) cases in OLZ group. Increased medication adherence led to better control and outcomes. Patients with <90% MPR had developed more adverse events and were mostly living in rural areas.* ***Conclusions:*** *Iloperidone is comparatively more cost-effective than olanzapine to control ≥ 90% of patients on long term use.*

Key words: *Cost-effectiveness, Medication possession ratio, Atypical antipsychotics*

INTRODUCTION

Psychosis is a chronic mental disorder requiring prolonged treatment and is categorized under ICD-10, F-20-F-29 group of psychiatric disorders which include schizophrenia, schizotypal disorder, persistent delusion disorder, acute and transient psychotic disorders, induced delusion disorders and schizo-affective disorders. They are characterized by prominent disturbances of thought, perception, affect and behavior.[1]

Atypical antipsychotics such as olanzapine (OLZ) and iloperidone (ILO) are being used as first line antipsychotic agents and are the pharmacological agents of choice because of their effectiveness and safety but there are still many unanswered questions such as which antipsychotic should be used, how efficacious and safe is this therapy and are there any guidelines regarding which antipsychotic to select while initiating treatment with antipsychotic agents. Moreover, data pertaining to comparative evaluation between olanzapine and iloperidone in respect to efficacy, cost-effectiveness, compliance and safety particularly in

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Indian populace are very scarce since iloperidone is a new drug molecule and is a bit costlier agent.[2]

For evaluating incremental cost-effectiveness ratio, the efficacy of the agent is a prime factor, where efficacy is defined as the magnitude of the effect or effectiveness produced by given amount or drug.[3] Drug compliance or drug adherence is also fairly important as most chronic diseases including psychosis need prolonged drug therapy. Good medication adherence may reduce unnecessary medical care costs and decreases the probability of bad outcomes.[4-6] Moreover; it has been observed that the therapeutic effect of a drug depends not only on a patient having treatment prescribed but also on their adherence to or compliance with treatment. Equally important is, does drug treatment reduce overall health cost by reducing patient's need for expensive medical services such as hospitalization and emergency room treatment.[3] The aim of the present study is to assess the cost-effectiveness ratio between olanzapine and iloperidone, in relation to different measures of effectiveness on long-term basis and to evaluate medication adherence significance, costs and outcomes.

METHODS

A prospective, randomized, interventional, open label, flexible dose, comparative clinical study of 1 year duration (May 2016 to April 2017) was undertaken amongst patients attending to psychiatric outdoor patient department of Rohilkhand Medical College and Hospital, Bareilly, diagnosed as cases of psychosis. Approval of study protocol was obtained from Institutional Ethical Committee. Informed consent was taken from each patient or their legal care-takers before enrollment for study purposes and one could withdraw without prejudice at any time. A total of 100 patients (OLZ=50 & ILO=50) comprised of the sample size. Simple randomization was done and the odd numbers were assigned to olanzapine (OLZ) and even numbers to iloperidone (ILO) group, of these two patients dropped out of olanzapine (n=48) during the study period due to extrapyramidal side effects and two patients dropped out of iloperidone group (n=48) due to non-compliance.

Flexible dose schedule of both drugs were used, olanzapine 10-20mg/day and iloperidone 6-12mg/day depending upon assessment of clinical response by consultant psychiatrist, though initially lower doses were initiated. No other antipsychotic drug therapy was administered during the study period though rescue medications like tablets/injections of lorazepam, tab trihexyphenidyl, tab. clonazepam were administered for managing emergency and adverse events, if any. All patients who were enrolled and participated in this clinical study were emphatically told that they have to take the prescribed medicines for at least one year despite adequate control to prevent recurrences of psychosis.

The inclusion criteria comprised of all newly diagnosed, first episode cases of psychosis (ICD-10, F20-F29, drug naïve patients), of age group 18-65 years, of either sex. The exclusion criteria included patients with history of taking antipsychotics before study, pregnant and lactating females, patients with history of significant and untreated medical illnesses including severe cardiovascular, hepatic, renal or untreated thyroid disease, and HIV. Patients currently taking antiepileptic, antidepressants, antiparkinsonian drugs, steroids, contraceptives, propranolol, thiazides diuretics and agents that induce weight loss were also excluded.

A complete preliminary clinical examination was conducted on all study subjects. Socio-demographic data were recorded. Patients were then evaluated by senior consultant psychiatrist. Psychiatric evaluation was done regularly by consultant psychiatrist for titration of dose of the drug, if needed; besides all adverse effects during treatment were recorded in case report form. The efficacy of drug regimen was evaluated clinically by psychiatrist as per response and standard criteria. Body mass index (BMI), blood pressure (BP) and other relevant investigations including fasting blood sugar (FBS) and lipid profile were estimated at baseline and reassessed at 1,3,6,9 and 12 months.

Measuring Cost-effectiveness:

Since psychosis is an important mental disorder requiring more aggressive therapeutic approach hence efficacy of the agent is an important determinant of cost effectiveness. The cost effectiveness ratio usually referred to in pharmacoeconomics is the incremental cost-effectiveness ratio, which compares the costs and effects of one treatment (here, ILO) with those of another (OLZ).[3,7] The incremental cost-effectiveness ratio is defined as the difference in cost of two treatments (ILO vs. OLZ) divided by the difference in their effectiveness:

$$\text{Cost/Effectiveness} = \frac{\text{Cost of Iloperidone} - \text{Cost of Olanzapine}}{\text{Effectiveness of Iloperidone-Effectiveness of Olanzapine}}$$

The incremental cost effectiveness ratio can be minimized either by decreasing the cost or by increasing the effectiveness of drug therapy.[3,7,8] The goal is to achieve smallest cost-effectiveness ratio. Efficacy is defined here as the magnitude of effect or effectiveness produced by a given amount (mg) of drug i.e. effectiveness per unit dose. It is inverse of potency, which is the amount of drug required to produce a given effect.[3] In the present study, cost effectiveness of atypical antipsychotics has been expressed in relation to the proportion of patients showing $\geq$ 90% controlled cases of psychosis although different measures of effectiveness exists.

Measuring Medication Adherence:

The treatment compliance/medication adherence was evaluated at each monthly visit using tablet counts and questioning the patient's relatives. Medication possession ratio (MPR) has also been used to calculate medication adherence measurement.[9] The prescription date of atypical antipsychotic agent for the patient was treated as index-date. All enrolled patients of psychosis were followed for 1 year and were in constant communication. These days were

referred to as tracking days. MPR was calculated as follows:

$$\text{Medication possession ratio} = \frac{\text{(Total days of atypical Antipsychotic prescription) x 100}}{\text{Total tracking days}}$$

Good medication adherence group had MPR more than 90% and poor medication adherence group had MPR <90%.[9] Of the different brands of olanzapine and Iloperidone which were available in our hospital pharmacy, the brands which were least expensive on yearly basis namely Torrent Pharma (2.5, 5 & 10mg) for olanzapine, and Sun Pharma (2, 4 & 6mg) for Iloperidone were used in the present study.

RESULTS

Table-1 & 2 show comparative monthly, three monthly, six monthly and yearly costs of acquisition and cost difference between the two agents in respect to effectiveness as procured from our hospital pharmacy. It can be well visualized that comparative cost of acquisition of olanzapine is fairly low as compared to iloperidone in all dose ranges. It has been observed that Iloperidone in lower doses (8mg/day) controlled between 65-75% of patients of psychosis whereas olanzapine showed this level of control with 10 – 15mg/day (average 12.5mg/day) dose. Further, Iloperidone with 12mg/day dose controlled 90% or more percentage of patients 'goal relief' and that olanzapine required 15 - 20mg/day (average 17.5mg/day) for such a level of control. Moreover, olanzapine at these doses leads to more incidence of metabolic adverse effect which require treatment along with repeated titration of dose thus escalating the cost of treatment. Indeed, Iloperidone (12mg/day) despite higher cost was found to be more efficacious with minimal adverse events compared to olanzapine (17.5mg/day). In the present study, the effectiveness is expressed as adequate control in 90% or more percentage of patients the 'goal relief' and costs are expressed as annual drug costs based on supply from our hospital pharmacy, then iloperidone 12mg/day had lowest cost-effectiveness ratio compared to olanzapine average 17.5mg/day since olanzapine evokes more adverse effects at these doses. However, if adequate control is required between 65-75% of patients, then olanzapine, which had the lowest price, has the lowest – cost effectiveness ratio i.e. most cost effective based on the assumption that once drug titration has been completed, the cost of long-term maintenance therapy is principally the direct drug-procurement costs.[3,7] Moreover, at these doses olanzapine elicited lesser incidence of metabolic or extrapyramidal adverse effects. Table 3 shows comparative medical possession ratio (MPR) between ILO and OLZ groups. Of 48 patients of ILO group who completed the study 42(87.5%) cases had MPR >90% and 12.5% had MPR <90%. Respective comparative values in OLZ group were 18 (37.5%) cases showed MPR more than 90% and 30 (62.5%) cases showed MPR <90%. It has been observed that increased medication adherence as noted with tablet counts and based on interrogations of the patients or their relatives as also with MPR >90% led to better control and outcomes. Further, patients with <90% MPR had developed more adverse events owing to poor compliance and paid more emergency visits to hospital and these patients were mostly living in rural areas.

DISCUSSION

Schizophrenia is one of the most debilitating disorders with devastating effects on victims and their families and it extracts enormous economic cost from the society[10]. Atypical antipsychotics are the sheet anchors for the therapy of psychosis owing to improvement in negative symptoms and lack of extrapyramidal symptoms.[11,12] Despite a large number of atypical antipsychotics belonging to different pharmacological classes being currently available yet the choice is based not only on superior clinical efficacy and outcomes, but also on cost-effectiveness, compliance, tolerability and safety profile as well as quality of life considerations. Olanzapine and iloperidone are being considered for long term comparative evaluation in respect to cost-effectiveness and medication adherence in view of their proven efficacy, better compliance, minimal adverse effect profile and tolerability. However, detail comparative data for iloperidone and olanzapine are quite scarce and probably this is the first Indian study in respect to efficacy, cost-effectiveness, and medication adherence although comparative data on above aspects on prolonged therapeutic use of statins and antihypertensive agents are available in literature.[13-16] For severe cases of psychosis that were more aggressive, high efficacy atypical antipsychotics were preferred and in these cases efficacy is the important determinant of cost effectiveness. The goal is to find the treatment with least cost with maximum effectiveness and choosing the treatment with the smallest (most favourable) cost–effectiveness ratio. It can be judged that cost-effectiveness ratio can be minimized by decreasing cost or increasing effectiveness.[3] The equation does not, moreover specify how costs and effectiveness be defined. The cost is expressed in currency and it may be noted that compared to our hospital pharmacy, if the bulk purchases had been made directly from stockiest/distributor then the costs of drug might be further decreased. The effectiveness can be expressed in number of ways.[3] The measures of effectiveness that we had considered in present study is first the dose (costs) which adequately controlled 90% or more patients (goal relief), with minimal co-morbidity conditions such as hyperglycemia or dyslipidemia and/or obesity requiring additional treatment. On these parameters, iloperidone despite being costly compared to olanzapine is more cost effective. Since, the cost that must be considered includes visits to medical college, laboratory tests and procurement of drugs. Moreover, cost will not only include the costs of atypical antipsychotic therapy and dose titration but also include cost pertaining to medical treatments for dyslipidemia, hyperglycemia, obesity and other relevant adverse effects which definitely escalates the cost of therapy.

Table1. Comparative Acquisition Costs Monthly, Three Monthly, Six Monthly and Yearly Between Olanzapine and Iloperidone In Different Dose Ranges.

COSTS	OLANZAPINE					ILOPERIDONE
	2.5mg @ Rs. 12/10tab.	5 mg@Rs. 20/10tab.	10mg@Rs. 28/10tab.	2mg @ Rs. 46/10tab.	4mg @ Rs. 70/10tab.	6mg @ Rs. 78/10tab.
Monthly	Rs. 36/-	Rs. 60/-	Rs. 84/-	Rs. 138/-	Rs. 210/-	Rs. 234/-
Three Monthly	Rs. 108/-	Rs. 180/-	Rs. 252/-	Rs. 414/-	Rs. 630/-	Rs. 702/-
Six Monthly	Rs. 216/-	Rs. 360/-	Rs. 504/-	Rs. 828/-	Rs. 1260/-	Rs. 1404/-
Yearly	Rs. 432/-	Rs. 720/-	Rs. 1008/-	Rs. 1656/-	Rs. 2520/-	Rs. 2808/-

Table 2. Shows Cost Differences Between Iloperidone And Olanzapine.

VARIABLES	OLZ	ILO	COST DIFFERENCE ILO-OLZ			
			1 Month	3 Months	6 Months	12 Months
65-75% Patients adequately controlled costs	Average dose 12.5mg/day (10mg+2.5mg) Rs. 40/10tab.	Average dose 8mg/day (tab. 6mg+2mg) Rs. 124/10tab.	372-120 = Rs. 252	1116-360 = Rs. 756	2250-720= Rs. 1530	4464-1440= Rs. 3024
≥ 90% patients adequately controlled Costs	Average dose 17.5mg/day (10+5+2.5mg) Rs. 60/ 10tab.	Average dose 12mg/day (6+6mg) Rs. 156/10 tab.	Rs. 468-180 = Rs. 288	1404-540 = Rs. 864	2808-1080= Rs. 1728	5616-2160= Rs. 3456

Though olanzapine and iloperidone with comparative equal effectiveness, provide adequate control at lower doses in 65-75% of patients here only drug price is the determing factor for cost-effectiveness. Note, that once drug titration has been done and patient adequately controlled, the costs of long-term maintenance therapy are basically the direct drug acquisition costs from hospital pharmacy. The effectiveness of atypical antipsychotics increases with doses but efficacy is a fixed property of each atypical antipsychotics agent. In order to optimize cost-effectiveness, the level of effectiveness required to treat the specific patient or patient groups must be considered.[7] Investigators have reported that both olanzapine and iloperidone are equally effective. They cause fewer relapses with reduced hospital stay, number of physician's visit and overall care cost. Interestingly, atypical antipsychotics (especially olanzapine) lead to obesity, hyperglycemia and dyslipidemia, all important risk factors for CHD, hence survival of patients is the ultimate measure of atypical antipsychotics effectiveness, not even the 'goal relief' target. Thus, the actual cost will also include not just therapy with atypical antipsychotics and its titration but also medical treatments for risk factors for CHD. We have not measured the effectiveness in terms of survival as the number of life years saved since the study was only for 1 year and the sample size is small.

We have already reported comparative incidence of adverse events with olanzapine and iloperidone.[17]. Though there was a possibility of coronary artery disease because of presence of obesity, dyslipidemia and hyperglycemia but in the present study none of the patients was admitted for this purpose or as a matter of fact for any other mental related conditions.

Table3: - Shows comparative medication possession ratio (MPR) between olanzapine and Iloperidone cases

Variables	OLZ No. (%)	ILO No. (%)
MPR > 90%	18 (37.5%)	42 (87.5%)
MPR <90%	30 (62.5%)	6 (12.5%)
Total Cases	48 (100%)	48 (100%)

Medication compliance/adherence is a multidimensional phenomenon based on five sets of interrelated factors namely social and economic factors, concerning physician and his team and system related factors, condition related factors, therapy related factors and finally patients–related factors.[18]. Social and economic factors cast immense influence as not only a large majority of Indians are poor but they also lack insurance coverage. Second, for health care team and system related factors, presently we do not have adequate health care resources to take care of patients having chronic diseases especially chronic mental disease. Though physicians are concerned with challenges of patient's non-adherence to anti-psychotic therapy. Third, for condition–related factors, the health status of patients affects illness related demands. Fourth, therapy–related factors, atypical antipsychotics are prime effective agents popularly used worldwide and these have become first choice agents. Fifth, patients-related factors, since perceptions, beliefs and attitude of patients will affect their

medication adherence behaviour. Indeed, patient's personal reasons and beliefs may also play a role for being non-adherent.[19] Besides, physician's encouraging suggestions usually positively affect the patient's behaviour.[9]

In the present study, drug adherence was measured through self/relatives, friends report and pharmacy refill data as well as medication possession ratio. Medication possession ratio (MPR) was also used as one of the marker of medication adherence in our study. This is based on the recommendations of the International Society for Pharmacoeconomics and Outcomes Research.[20] Medication adherence measurement was based on literature review.[21,22] Further, a systematic review of the methods currently being used to assess adherence and persistence in pharmacoepidemiological and pharmacoeconomics studies indicated that MPR is a popular measure.[23] Advantages of using MPR measure include the ease of calculation and interpretability.[23]

We have observed that higher medication adherence (>90%) will lead to better control of psychosis patients and health related outcomes. These findings are consistent with previous studies.[6,9] Moreover, patients having 90% to 100% medication adherence were significantly less likely to be hospitalized and that patients with < 90% MPR developed more adverse events and had more emergency visits to hospital and these patients were mostly living in rural area. Li et al[9] in their study also noted that for people with MPR≥ 80% the probability of all – cause hospitalization was significantly lower than patients of the MPR < 80% group thus supporting our observations. In support of our observations they also observed that people living in suburban or rural areas had higher probability of hospitalization compared to people living in urban areas. Further, these authors also observed that men and elderly had higher probability of having good statin adherence.[9] We have not observed such a correlation in our study. Though lower medication adherence have also been reported in older age group.[24] Since our study included only newly diagnosed cases and these were less complicated cases hence neither hospitalization of patients nor any worse outcomes during the treatment process was noted. Yet, it may be emphasized that problem of medication non-adherence remains a significant barrier to successful treatment though not easily assessed.

The failure to reach 'goal relief' is partly due to low medication adherence, inadequate treatment, failure to properly titrate dose and low efficacy therapy. It may be emphasized that drug titration should be recommended until patients reach 'goal relief' ie. adequate control in 90% or greater percentage of patients or the maximum dose has been administered, if the initial dose is inadequate. In this situation, effectiveness is appropriately measured as the percentage of patients attaining 'goal relief'. The cost includes all related costs (drugs, visit to medical college, physicians, consultation, laboratory investigations etc).

Interestingly, 34-52% of patients doubted the necessity of prolonged drug treatment despite being adequately controlled or lacked knowledge about the efficacy of these drugs on prolonged administration, 15-30% of patients were worried about adverse events in particular about obesity, hyperglycemia, dyslipidemia, behavioral alterations and other co morbidities, and 10-15% had encountered practical problems regarding information about the anti-psychotic agents and prolonged intake of drugs and these were associated with increased unintentional non-adherence. A positive association was observed between worry about side effects and intentional non-adherence. Besides, patient's practical problems also deserve attention since these were associated with unintentional non – adherence. Wouters et al[25] suggested that the 'tailored medicine inventory' can aid clinicians in formulating adherence improving interventions to the needs of individual patients. These authors opined that in future, such individually tailored interventions might reduce the substantial non–adherence problems.

CONCLUSION

The incremental cost-effectiveness can be minimized either by decreasing the cost or by increasing the effectiveness of therapy. The actual cost will include not only the cost of medicine and its titration but also laboratory investigations and treatments for the adverse events. An increased medication adherence leads to better outcomes and reduces costs. Effective interventions may be applied to the poor medication adherence group to improve their health care outcomes. Physician's suggestions positively affect the patient's behaviour and encourages good medication adherence.

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