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SAFETY COMPARISON OF NEWER ATYPICAL ANTIPSYCHOTICS RECENTLY INTRODUCED IN INDIA: MONITORING IN ACTUAL PRACTICE CONDITIONS

Psychiatry

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ABSTRACT

Aim of the study was to assess the occurrence of adverse events with asenapine and iloperidone under actual practice conditions. Hundred schizophrenics of either sex, age 18 to 55 years, who were prescribed either drug for the treatment were recruited from SEP-13 to JAN-15 after written informed consent, provided patient diary and were followed up over 12 months for detecting adverse events. During personal visit, patients were interviewed by ASEQ to identify adverse events. Adverse events were compared between the two drugs using Chi-square test. Most patients reported at least 1 adverse event. Asenapine group reported more adverse events of moderate intensity (P=0.0047) with no severe event in both groups. Iloperidone group reported weight gain more frequently (P=0.0191), possibly due to concomitant mood stabilizers. Both groups reported equal frequency of rest all adverse events. In conclusion, both drugs report fairly similar frequency of adverse events in actual practice conditions.

KEYWORDS:

Asenapine, Iloperidone, newer atypical antipsychotics, adverse events

INTRODUCTION

Two atypical antipsychotics asenapine and iloperidone have been recently approved for acute treatment of schizophrenia in adults by Drug Controller General (India) in April and February of 2011, respectively[1]. Both of them have been claimed to be safer than their congeners namely olanzapine and risperidone, respectively. We have already compared the published data on these two newer drugs in a review article published separately[2]. Amongst the two agents, asenapine appears to be less frequently associated with adverse events commonly associated with atypical antipsychotics. But complex sublingual dosing and higher discontinuation related to adverse events compared to iloperidone makes up for this safety advantage. Overall both these agents require close counseling of patient for adequate compliance and/ or combination with other antipsychotic to achieve optimum antipsychotic efficacy in Indian context. However, as experienced for atypical antipsychotic government sponsored metanalaysis[3,4], prospective cost-effectiveness analysis namely CATIE[5] & CUtLASS[6], results of Industry sponsored Clinical Trials cannot be extrapolated to the benefits in actual practice conditions.

To cater this unmet need of safety and adverse effect data on these newer atypical antipsychotic drugs in head to head comparison under actual clinical practice conditions, we conducted a prospective monitoring of adverse effects with these newer atypical antipsychotic drugs in patients visiting psychiatric clinics and hospitals based at Ahmedabad under actual practice conditions for a period of 1 year.

MATERIALS AND METHODS:

The study was conducted in psychiatric hospitals and clinic based at Ahmedabad after approval of Human Research Ethics Committee of the institute. A protocol was developed to monitor commonly reported adverse effects of atypical antipsychotics namely extra pyramidal symptoms, antimuscarinic side effects, metabolic side effects including weight gain, side effects related to prolactin elevation and sleep related side effects[7]. The study was retrospectively registered on Clinical Trial Registry of India with registration no. CTRI/ 2016/08/007225.

Study included 100 schizophrenic patients (50 on each study drug) of either sex, age 18 to 55 years, who were prescribed any of the two newer antipsychotic drugs at two Psychiatric Hospitals and a Psychiatric Clinic based at Ahmedabad from September, 2013 to January, 2015 after they provided written informed consent for participating in the study in a patient information sheet and informed consent form translated to their vernacular language. Patients having any sign/ symptom of pregnancy or present history of any of the side effects under study were excluded from the study. Patients were selected based on the judgment of the treating psychiatrist and were prescribed the study drugs by the psychiatrists themselves to represent actual practice conditions. Patients were discontinued from the study if they did not wish to continue, they changed treating psychiatrist, lost to follow-up or study drug was discontinued by treating psychiatrist.

Protocol was designed in a way to only monitor the side effects without interfering with the actual practice conditions of the treating psychiatrists. Protocol included an Antipsychotic Side-effects Evaluation Questionnaire (ASEQ) developed clubbing some of the items from Drug Induced Extra-Pyramidal Symptom (DIEPS)[8] questionnaire and Schizophrenia Quality of Life Scale (SQLS)[9] with its translation to vernacular languages to personally interview patients for detection of adverse events. Patients were followed up at approximately 3 (telephonic), 6 (visit to hospital/ clinic), 9 (telephonic) and 12 (visit to hospital/ clinic) months of treatment. All suspected adverse experiences detected through ASEQ, records of patient diary, telephonic or personal inquiry to the patients were confirmed with treating psychiatrists before documenting them as adverse events. Detected adverse events were analysed by WHO-UMC criteria[10] to determine causality. Chi-square test was performed on frequently reported adverse events between the two groups to analyse statistical significance. P value less than 0.05 was considered significant.

RESULTS

Despite non-randomized allocation to both medications, both groups appear to be similar in demographic characteristics like middle age (Mean±SD, 34.38±9.48 years for asenapine and 38.7±10.15 years for iloperidone), average weighing (Mean±SD, 61.72±14.77 kg for asenapine and 63.04±15.26 kg for iloperidone) Indian males and females in approximately equal proportions (33:17 for asenapine and 25:25 for iloperidone). More than half (64%) of patients in both groups did not complete the 12 months of follow-up.

Iloperidone group reported slightly higher no. of adverse events (107 vs. 94) in slightly higher proportion of patients (74% vs. 66%, P = 0.2801 by Chi-square test) compared to asenapine group. However, the asenapine group had significantly higher proportion of adverse events with moderate intensity (25/94 vs. 11/107, P = 0.0047) compared to iloperidone group. There was no adverse event of severe intensity or serious adverse event in either group. Intensity classification of adverse events observed in our study is displayed in table 1.

TABLE – 1 INTENSITY OF ADVERSE EVENTS IN EACH STUDY GROUP

Intensity	Iloperidone	Asenapine	Total
Mild	96	69	165
Moderate	11	25*	36
Severe	0	0	0

* P = 0.0047 between two groups by Chi-square test

Most of the adverse events did not need change in the study drug (99/107 in iloperidone group; 83/94 in asenapine group) or concomitant medications (100/107 in iloperidone group; 82/94 in asenapine group). Action taken for management of adverse event observed in our study is displayed in table 2.

TABLE – 2 ACTION TAKEN FOR MANAGEMENT OF ADVERSE EVENTS IN EACH STUDY GROUP

Treatment given	Iloperidone	Asenapine	Total
Increased dose	3	5	8
Decreased dose	1	1	2
Discontinued	4	5	9
No change	99	83	182
Total	*107*	*94*	*201*
Added Conc. Medicine	4	8	12
Increased dose of Conc. Medicine	1	2	3
Decreased dose of Conc. Medicine	2	2	4
No change in Conc. Medicine	100	82	182
Total	107	94	201

More than half of the adverse events (60/107 in iloperidone group; 50/94 in asenapine group) could be followed up till their resolution in the study and rest could not be due to study discontinuation. Outcome of the adverse events observed in our study is displayed in table 3.

TABLE – 3 OUTCOME OF ADVERSE EVENTS IN EACH STUDY GROUP

Outcome	Iloperidone	Asenapine	Total
Resolved	60	50	110
Unknown	47	44	91
Total	107	94	201

Both groups reported fairly similar events (P>0.05 by Chi-square test) of extra pyramidal symptoms, antimuscarinic events, Prolactin related events, CNS adverse events, gastrointestinal events, worsening Schizophrenia and other events. However, iloperidone group reported significantly higher no. of weight gain related events (14 vs. 4, P = 0.0191 by Chi-square test), which could be due to concomitantly prescribed lithium and sodium valproate. Incidence of major group of adverse events with both drugs observed in our study is displayed in table 4.

TABLE – 4 MAJOR GROUPS OF ADVERSE EVENTS IN PATIENTS (N) OF EACH STUDY GROUP

Group of Events	Iloperidone	Asenapine	Total
Extra pyramidal symptoms	7	9	16
Antimuscarinic events	17	18	35
Weight gain	14*	4	18
Prolactin related events	1	2	3
CNS adverse events	21	15	36
Gastrointestinal events	12	11	23
Other events	7	7	14

DISCUSSION

The National Institute of Mental Health, USA conducted Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[11] had discontinuation rates ranging from 64% to 82% enlightening the harsh reality of antipsychotic treatment over 18 months. Hence, our study results with 64% discontinuation rate for asenapine as well as iloperidone over 12 months are in line with the CATIE study. Discontinuation rate due to adverse events in Clinical Trials were 9% and 5% with asenapine[12] and iloperidone, respectively, which were 8% and 8% in our study, respectively. Hence, the results are close to the reported discontinuation rates. Overall both these agents require close counselling of patient for adequate compliance and/ or combination with other antipsychotic to achieve optimum antipsychotic efficacy in Indian context.

Percentage of patients reporting at least 1 adverse event with asenpine treatment was 66% in our study, which is little lower than that of 76.9% rate observed in Clinical Trials[13]. Rates of EPS were 18% and 14% with asenapine and iloperidone, respectively, in our study, which were at 13 to 23%[12] and 7 to 8%[14], respectively, in published Clinical Trials. Slightly higher rate of EPS observed with iloperidone in our study might be related to concomitantly prescribed antipsychotic to cover up the slow up-titration period. Rates of antimuscarinic side effects were 36% and 34% with asenapine and iloperidone, respectively, in our study, which were at 5 to 10%[12] and 14 to 23%[14], respectively, in published Clinical Trials. Higher rate of antimuscarinic effects observed in our study appears to be related to concomitantly prescribed anticholinergic as prophylaxis of EPS in all study patients. Rates of substantial weight gain (>7% from baseline) with asenapine[12] & iloperidone[15] have been reported in publisher literature at 14.7% & 12-18%, respectively, which was reported in our study at 8% & 24%, respectively. Possible reasons for high reports of weight gain for iloperidone are concomitant prescription of lithium or valproate, which is indicated to double the incidence in literature[7]. Rates of adverse events possibly related to prolactin elevation with asenapine[12] & iloperidone[15] have been reported in Published literature at 0.4% & 0.03%, respectively, which was reported in our study at 4% & 2%, respectively. Possible reasons for frequent adverse events possibly related to prolactin elevation are concomitant prescription of antidepressants, mood stabilizers and sedatives. Central nervous system events have been reported in published literature at 49.2% and 33% with asenapine[13,16] and iloperidone [14,15], respectively, which was reported at 30% and 42%, respectively, in our study. Possible reasons for the different rates could be due to differences in perceiving dizziness, associated with postural hypotension caused by iloperidone, as headache by Indian patients as well as high rate of CNS events due to concomitant medications. Gastrointestinal adverse effects were reported at rate of 22% and 30% with asenapine[16] and iloperidone[14], respectively, during Clinical Trials, which were in our study at fairly similar rate, 22% and 24%, respectively.

The treating psychiatrists at Ahmedabad do not practice monitoring of metabolic side effects and prolactin related events of antipsychotics through laboratory investigations as well as do not monitor cardiovascular events with monitoring ECG of the patients. Hence, we did not find any report of dysglycemia, dyslipidemia or QTc prolongation in our study.

LIMITATIONS

As the study was non-randomized, uncontrolled use of concomitant medications and lack of systematic follow-up of patients undertaken in Clinical Trials certainly limits the clear extrapolation of these results. However, this study conducted under actual treatment conditions can serve as potential indicator of the different results that can be observed in actual practice conditions compared to the Clinical Trials.

CONCLUSIONS

Both drugs reported fairly similar frequency of adverse events in actual practice conditions. Our study clearly indicates that the adverse event profile of newer antipsychotic observed under actual practice conditions differs somewhat compared to that observed in Clinical Trials due to different combinations of drugs used in practice. In our study iloperidone was slightly more associated with EPS, substantial weight gain and CNS effects compared to the rates observed in published Clinical Trials. Both treatments were more commonly associated with antimuscarinic affects in our study due to regular use of trihexyphenidyl in all study patients to prevent EPS.

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