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RESEARCH ARTICLE

A randomized prospective comparative study of weight gain between asenapine and iloperidone in patients with psychosis

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ABSTRACT

Background: Second-generation antipsychotics (SGAs) are better for psychotic disorders, and they can induce weight gain and other serious metabolic adverse effects which can lead to non-adherence and medical comorbidities. Iloperidone and asenapine, the newer SGAs with favorable short-term side effect profile. **Aims and Objective:** The aim of this study was to compare the weight gain propensity associated with new SGAs drugs-asenapine and iloperidone. **Materials and Methods:** Randomized prospective study was conducted from December 2014 to August 2015 in the Department of Psychiatry, Tertiary Care Hospital, Mysore. 60 patients who met the criteria for acute psychosis and schizophrenia according to ICD 10 were recruited. Atypical antipsychotics, asenapine (5-20 mg), and iloperidone (8-24 mg) were administered, and their weight was measured using the digital weighing scale on day 0 (baseline), week 1, week 3, and week 6. **Results:** Out of 60 recruited subjects, 51 (85%) completed all four visits of the study, 41.67% with asenapine, 43.3% with iloperidone. Mean weight gain was 2.18 ± 1.84 kg with iloperidone and 1.63 ± 1.28 kg with asenapine, but it was not statistically significant between the groups. Weight gain was dose dependent; 3.56 kg mean weight gain with 15-20 mg of asenapine and 3.36 kg with 18-24 mg iloperidone-treated patients which was statistically significant. **Conclusion:** Mild to moderate weight gain was seen in both asenapine and iloperidone and it was dose dependent. Iloperidone showed more weight gain than asenapine.

KEY WORDS: Second-Generation Antipsychotics; Metabolic Adverse Effects; Weight Gain

INTRODUCTION

The introduction of second-generation antipsychotics (SGAs) over the last two decades generated considerable optimism that better antipsychotic treatments for psychotic disorders were possible. SGAs offer several tolerability benefits over the first-generation antipsychotics (FGAs), particularly with respect to extrapyramidal symptoms (EPS). However, SGAs can induce weight gain and other serious metabolic adverse effects which can lead to non-adherence and medical comorbidities.[1]

Many patients suffering from mental disorders, when exposed to psychotropic medications (SGAs) gain significant weight with or without other side effects, which may create added psychological or physiological problems that need to be addressed.[2] SGAs such as olanzapine, risperidone, clozapine, and paliperidone were largely studied for efficacy and adverse effects. Iloperidone and asenapine, the newer SGAs with favorable short-term side effect profile were studied here for weight gain.

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Asenapine is a novel atypical antipsychotic agent approved by the US Food and Drug Administration (FDA) for the treatment of acute manic episodes in adults with bipolar I disorder and acute schizophrenia. It is available in sublingual formulations with therapeutic potential for psychotic illness and a limited propensity to induce EPS.[3] Its mechanism of action is mediated by 5-hydroxytryptamine 2A (5-HT2A) and D2 receptor antagonism. In addition, it has a potent antagonistic effect on serotonergic receptor subtypes 5-HT2B, 5-HT2C, 5-HT6 and 5-HT7, adrenergic receptor subtypes α1A, α2A, α2B, α2C, and dopaminergic receptor subtypes D3 and D4. It has been suggested that it might provide an additional aid for the remission of cognitive and negative symptoms due to its antagonistic effect on α2A receptor subtype.[4]

Iloperidone was the SGA drug which was approved by the US FDA for the acute treatment of schizophrenia in adults in May 2009.[5] It is a pure antagonist and has the most affinity for dopamine D3 receptors, followed by norepinephrine α-2c, serotonin 5-HT1A, dopamine D2A, and 5-HT6 receptors in decreasing affinities. It is the first antipsychotic drug with specific genetic markers to help clinicians determine efficacy. The most common adverse effects were dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight gain.[6]

Several studies comparing safety profile of asenapine and iloperidone with placebo and other arms have reported weight gain as an adverse effect with both. Meta-analysis indicates a significantly higher weight gain with asenapine and iloperidone than placebo. There are not many heads to head comparison studies between asenapine and iloperidone for weight gain.

Hence, this study was done to monitor and to compare weight gain in new SGAs drugs-asenapine and iloperidone.

MATERIALS AND METHODS

The study was conducted in Psychiatry Department of tertiary care hospital at Mysore after obtaining Institutional Ethical Committee clearance.

Study Design

A randomized prospective study.

Patient Selection Criteria

The patients who visited Psychiatry Department of tertiary care hospital at Mysore, India, during the study period and fulfilled the inclusion criteria were recruited.

Inclusion Criteria

- The patients those who volunteered to give informed consent
- Male and female patients in the age range of 18-60 years
- Newly diagnosed cases as well as those with episodic psychosis who met the criteria for acute psychosis and schizophrenic disorder according to ICD 10.

Exclusion Criteria

- The patients with a known history of poor compliance to treatment (in episodic psychosis)
- Those with severe medical or psychiatric comorbid disorders
- Pregnant women.

Sample Size Determination

The patient enrolment was done for 9 months, from December 2014 to August 2015 in Psychiatric Department, K. R. Hospital, Mysore Medical College and Research Institute, Mysore. A total number of 60 patients who fulfilled the inclusion criteria were recruited during the study period.

Data Collection Tool

A total of 60 subjects were enrolled into the study. After the diagnostic interview and written informed consent, the patient was administered Brief Psychiatric Rating Scale[7] and a general physical examination was performed, along with a record of body weight using electronic digital body weight weighing scale. The drugs were allotted as per the computerized randomization schedule. Asenapine was administered at the dose of 10-20 mg, and iloperidone was at the dose of 12-24 mg. Any further dosage adjustments were done in subsequent visits. No concomitant medication like benzodiazepines and trihexyphenidyl were allowed. The patients were asked to come for follow-up on week 1, week 3, and week 6. The weight was measured and noted in each visit.

Data Analysis and Interpretation

Data were entered into Microsoft Excel and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 23.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation for continuous variables and frequency and percentage were calculated for categorical variables. Chi-square test and Fischer's test (when appropriate) were used to find an association between predictor and outcome variables for categorical variables. Unpaired *t*-test and analysis of variance tests were used to find the association between predictor and outcome variables for normally distributed data having 2 and more than 2 categories, respectively. The level of significance will be set at 0.05.

Table 1: Sociodemographic characteristics and its association with weight gain

Demographic profile	Characteristics	Number (%) *N*=60	Weight gain mean±SD *N*=51	*P* value
Age (in years)	18-25	17 (33.3)	1.75±2.09	0.699
	26-40	36 (40)	1.80±1.43	
	>40	7 (10)	2.36±1.62	
Gender	Male	27 (45)	2.40±1.83	0.04
	Female	33 (55)	1.45±1.40	
Education	Illiterate	44 (28.3)	1.95±1.77	0.56
	Literates	16 (23.3)	1.65±1.36	
Occupation	Employed	35 (56.7)	2.10±1.75	0.217
	Unemployed	25 (43.3)	1.52±1.47	
Family income	12,001-15,000	2 (3.3)	4.50±0.71	0.017
	3001-5000	14 (23.3)	1.92±1.54	
	5001-7000	30 (50)	1.30±1.14	
	7001-9000	7 (11.7)	2.38±1.71	
	9001-12000	7 (11.7)	2.89±2.54	
Family type	Alone	5 (6.7)	1.00±0.71	0.5
	Extended	11 (18.3)	2.21±1.74	
	Nuclear	44 (1.7)	1.89±1.70	
Marital status	Married	36 (60)	1.80±1.23	0.87
	Separated	3 (5)	2.40±3.40	
	Single	21 (33.3)	1.91±2.11	
Domicile	Rural	43 (71.7)	1.75±1.56	0.689
	Suburban	9 (15)	2.10±2.62	
	Urban	8 (13.3)	2.29±1.30	
Diagnosis	Acute psychosis	34	1.70±1.32	0.424
	Schizophrenia	26	2.08±2.02	

P<0.05 considered statistically significant. SD: Standard deviation

Table 2: Association of mean weight gain at 6th week between asenapine and iloperidone (N=51)

Drug	Weight gain mean±SD	*P* value
Asenapine	1.63±1.28	0.161
Iloperidone	2.18±1.84	

SD: Standard deviation

Table 3: Association between dose of asenapine and iloperidone to mean weight gain (N=51)

Drug	Dose in mg/day	Mean±SD	*P* value
Asenapine	5-10	1.09±0.9	<0.001
	15-20	3.56±0.9	
Iloperidone	8-12	1.14±0.97	<0.001
	18-24	3.36±1.81	

SD: Standard deviation

Ethical Approval

The study was conducted after obtaining Institutional Ethical Committee clearance. Confidentiality of the study subjects was maintained.

RESULTS

Out of the recruited 60 subjects of acute psychosis and schizophrenia, 85% successfully completed all 4 visits which included 43.3% subjects from iloperidone and 41.67% from asenapine group. The dropout rate was 15%. Overall, dropouts were due to loss of follow-up (5%), poor patient compliance (3.33%), and adverse effects (6.67%).

DISCUSSION

Weight gain in psychiatric populations is a common clinical challenge. Being overweight or obese has been acknowledged as a public health problem due to its correlation with mortality and increased comorbidity of other physical disorders.[2]

Out of the recruited 60 subjects of acute psychosis and schizophrenia, 85% successfully completed all 4 visits which included 41.67% from asenapine and 43.3% subjects from iloperidone. Main reasons for discontinuation were insufficient response (asenapine 1.67%: Iloperidone 3.33%); adverse effects (5%: 1.67%) and loss of follow-up (1.67%: 1.67%).

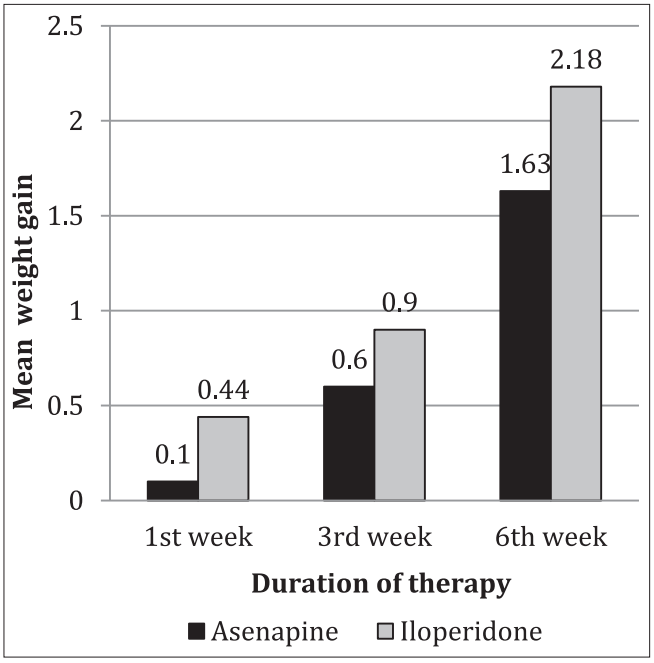

Figure 1: Graph showing mean weight gain of asenapine and iloperidone at 1st, 3rd and 6th week of therapy (N = 51)

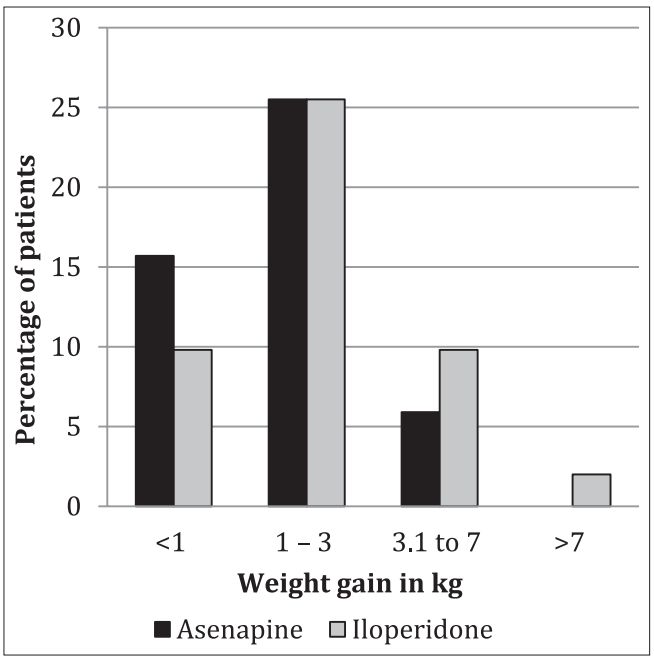

Figure 2: Association of percentage of patients with weight gain (kg) between asenapine and iloperidone

Asenapine and iloperidone were extensively studied in randomized controlled trials with other active comparators and placebo. 52 weeks double-blind study by Schoemaker et al. showed asenapine (12%) caused less weight gain than olanzapine (29%)[8] and another study showed 4.3% of patients in the asenapine group showed a 7% or greater increase in their body weight as compared to 1.9% of patients in the placebo group, while the risperidone-treated group showed 17% incidence of significant weight gain.[9] A study by Kane et al. showed both asenapine and haloperidol resulted in minimal (<6%) weight gain over 6 weeks.[10] This study showed that there was an increase in mean weight of 1.63 kg (<6%) in 6 weeks trial with asenapine and it was dose dependent, which correlates with other studies.

A comparative study between iloperidone and ziprasidone showed iloperidone patients gained 2.8 kg while ziprasidone patients gained 1.1 kg.[11] 6 weeks study by Kane et al. showed that iloperidone was associated with a 2.6 kg weight gain, whereas haloperidol weight gain was 0.6 kg. It also showed that weight gain by iloperidone depends on the target dose, with 18% of patients receiving higher doses (20-24 mg/day) meeting categorical cut-off criteria for >7% gain in body weight compared to only 12% of patients receiving lower doses of iloperidone (10-16 mg/day).[12] In our study, iloperidone showed a mean weight gain of 2.13 kg of 6 weeks treatment trial which was similar to above studies and more weight gain seen in the subjects who received higher doses (18-24 mg) compared to subjects who received lower doses (8-12 mg).

This study showed weight gain with both asenapine and iloperidone and higher doses were associated with increased weight gain. Significant weight gain was seen in male patients as well as in high economic status. The majority of patients in both the groups showed a weight gain of around 1-3 kg. This weight gain could be attributed to antagonism of 5-HT2C/5-HT1A/H1/D2 receptors.[13,14] However, it is difficult to accurately determine whether they gained weight from a medication and/or as a result of other lifestyle changes. Mean weight gain was more with iloperidone in all three visits. Hence, iloperidone has more propensities to produce weight gain when compared with asenapine.

Limitations of the Study

Short-term low sample size study and conducted at a single hospital.

CONCLUSION

Short-term weight gain study showed mild to moderate weight gain in both asenapine and iloperidone and it was dose dependent. Iloperidone showed more weight gain than asenapine. Hence, this side effect should be taken into consideration before prescribing these medications, especially in patients at high risk. long-term large sample size multi-centric studies are needed to confirm the above findings.

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