

A randomized prospective comparative study of efficacy of asenapine, iloperidone and zotepine in patients with psychosis

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ABSTRACT

Background: Antipsychotic drugs constitute the mainstay in the treatment of schizophrenia and other psychotic disorders. For these medications to be maximally beneficial, they must be efficacious, with an acceptable side effect profile and be taken as prescribed. The objective of the study was to compare the efficacy of iloperidone, asenapine and zotepine in subjects with psychotic disorders.

Methods: Randomized prospective study was conducted in the Department of Psychiatry of a tertiary care hospital, at Mysore, India. Sixty Patients who met the criteria for acute psychosis and schizophrenia according to ICD 10 were recruited. Atypical antipsychotics-asenapine, iloperidone and zotepine were administered and their efficacy was monitored by brief psychiatric rating scale (BPRS), which was administered on day one, week 1, week 3 and week 6.

Results: Out of 60 recruited subjects 31 (51.7%) completed all four visits of the study. Iloperidone and asenapine showed significant improvement in efficacy than zotepine at week 6. Among the total dropouts 55.2% subjects didn't come for follow-up and 44.8% were dropped due to development of side effects.

Conclusions: In patients with acute psychosis and schizophrenia, iloperidone appears more effective and tolerated than the other two. Asenapine was effective but less tolerated and zotepine was less efficacious and produced poor response. Asenapine and zotepine have more dropouts and showed few uncommon extrapyramidal side effects.

Keywords: Atypical antipsychotics, Efficacy, Brief psychiatric rating scale, Psychosis, Schizophrenia

INTRODUCTION

Antipsychotic drugs constitute the mainstay in the treatment of schizophrenia and other psychotic disorders. For these medications to be maximally beneficial, they must have good efficacy with an acceptable side effect profile and be taken as prescribed. Their efficacy is well established in several randomized clinical trials. However, it is not known that how effective they are across the wide range of baseline symptom severity.

Iloperidone, asenapine and zotepine are the newer second generation antipsychotics which are being used to treat psychosis. 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 extrapyramidal symptoms (EPS).¹ Its mechanism of action is mediated by 5-HT_{2A} and D₂ receptor antagonism. In addition, it has a potent antagonistic effect on other serotonergic receptor subtypes such as 5-HT_{2B}, 5-HT_{2C}, 5-HT₆ and 5-HT₇, adrenergic receptor subtypes α _{1A}, α _{2A}, α _{2B}, α _{2C}, 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 α _{2A} receptor subtype.²

Iloperidone is a second-generation antipsychotic drug which was approved by the US Food and Drug Administration (FDA) for the acute treatment of schizophrenia in adults in May 2009.³ It is a pure antagonist and has the most affinity for dopamine D₃ receptors, followed by norepinephrine α -_{2c}, serotonin 5-

hydroxytryptamine (5-HT) 1A, 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.⁴

Zotepine has been in use in Japan since 1982, in Germany since 1990 and in the UK since 1998, but has not yet been approved by Food and Drug Administration (FDA) for use in the USA.⁵ Zotepine is a second generation newly reintroduced antipsychotic drug with a high affinity for human D1-like (D1, D5) and D2-like (D2, D3, D4) dopamine receptors and serotonin subtypes (5HT2a, 5HT2c, 5HT6, 5HT7). It also inhibits norepinephrine re-uptake and it is claimed to be particularly effective for negative symptoms.⁶ Zotepine is at least as effective against all psychopathological symptoms of schizophrenia as conventional antipsychotics.⁷

Recently, with the development of these newer antipsychotics, it is necessary to understand their advantages over the older ones. Few studies have shown that the efficacy of asenapine, iloperidone and zotepine to be superior to other atypical antipsychotics like risperidone, olanzapine.^{2,4,6} However there were no head to head comparative studies between these drugs. Therefore, this study was done to observe and compare the effectiveness of iloperidone, asenapine and zotepine in psychotic patients.

METHODS

Randomized prospective study was conducted in the department of psychiatry of a tertiary care hospital at Mysore, India. Ethical approval was taken from Institutional Ethics Committee of a Tertiary care hospital, Mysore, India. Confidentiality of study subjects was maintained. The patient enrolment was done for 9 months, from December 2014 to August 2015. Conjugative sampling technique was adopted.

The patients those who volunteered to give informed consent, male and female patients in the age range of 18-60 years and newly diagnosed cases as well as those with episodic psychosis those met the criteria for acute psychosis and schizophrenic disorder according to ICD 10 were included. The patients with a known history of poor compliance to treatment (in episodic psychosis), those with severe medical or psychiatric co-morbid disorders and pregnant women were excluded.

The informed consent process was done by authors. The subjects were explained in the language best understood by them about the purpose of study and its benefits to them as well as possible adverse effects. Then, written consent was taken.

Among 96 subjects who were screened and interviewed, a total of 60 were enrolled into the study. The drugs were allotted as per the computerized randomization schedule.

In the study the following dosage was administered- asenapine 10-20 mg, iloperidone 8-16 mg and zotepine 100-400 mg. Iloperidone was started at lowest dose and increased upto 12-16 mg/day in divided doses. Asenapine was started as 5 mg twice a day from day one. Zotepine was started as 50 mg for three days and then increased to 200 mg/day. Any further dosage adjustments were done in subsequent visits. No concomitant medication like benzodiazepines and trihexiphenidyl were allowed. However those who were already taking medication for comorbid stable medical disorders were asked to continue same treatment. Patients were asked to come for follow up on week 1, week 3 and week 6.

The efficacy was monitored by brief psychiatric rating scale (BPRS) which was administered on day one, week 1, week 3 and week 6.⁸ The psychopathology of acutely psychotic and schizophrenia patients were rated on BPRS by the study psychiatrist. Those who had a score of 4 or more on at least one item of psychosis in BPRS were recruited. The primary efficacy measure was the reduction in score of items measuring psychosis. Dose was hiked in those who showed poor efficacy as rated on BPRS till visit three.

Descriptive statistics was applied for socio-demographic data. The distribution of clinical data did not follow normal distribution. Hence non-parametric tests were administered. Analysis was done by using one way ANOVA and repeated measures 2-way ANOVA.

RESULTS

Table 1: Sociodemographic characteristics.

	Characteristics	Frequency (%)
Age group	18-30 years	30 (50)
	>30 years	30 (50)
Sex	Female	33 (55)
	Male	27 (45)
Education	Illiterate	17 (28.3)
	Primary school	15 (25)
	Secondary and more	28 (46.7)
Occupation	Employed	52 (96.8)
	Unemployed	8 (3.2)
Income	<3000	00
	3001-5000	14 (23.3)
	5001-7000	30 (50)
	7001-9000	7 (11.7)
	9001-1200	7 (11.7)
	>12000	2 (3.3)
Domicile	Rural	43 (70.7)
	Sub urban	9 (15)

Marital status	Urban	8 (13.3)
	Divorced	3 (5)
	Married	36 (60)
	Single	20 (33.3)
	Widowed	1 (1.7)
Family type	Alone	4 (6.7)
	Extended	11 (18.3)
	Hostel	1 (1.7)
	Nuclear	44 (73.3)
Diagnosis	Acute psychosis	38 (63.3)
	Schizophrenia	22 (36.7)

Out of 60 recruited subjects 31 (51.7%) completed all four visits of the study. Among these 40% subjects from asenapine group, 65% from iloperidone and 50% from zotepine group completed the study. The rate of drop outs was found to be 48.3%, out of which 55.2% did not come for follow up and 44.8% were dropped due to development of adverse effects. Majority of adverse effects were seen in zotepine group (20.7%), followed by asenapine group (17.2%).

Table 2: Comparison of BPRS score of asenapine, iloperidone and zotepine in different visits.

Drug	BPRS score					F-statistic	P-value
		Baseline	Week 1	Week 3	Week 6		
Asenapine	Number	20	20	10	8	34.312	<0.001
	Mean±SD	26.95±7.28	14.10±5.88	9.50±7.68	3.38±5.98		
Iloperidone	Number	20	20	14	13	59.34	<0.001
	Mean±SD	28.85±8.70	16.95± 8.17	7.43±4.29	1.92±2.60		
Zotepine	Number	20	18	12	10	6.104	0.010
	Mean±SD	27.30±7.27	13.39± 5.40	9.33±8.79	12.60±10.89		
P-value		0.71	0.21	0.71	0.003		

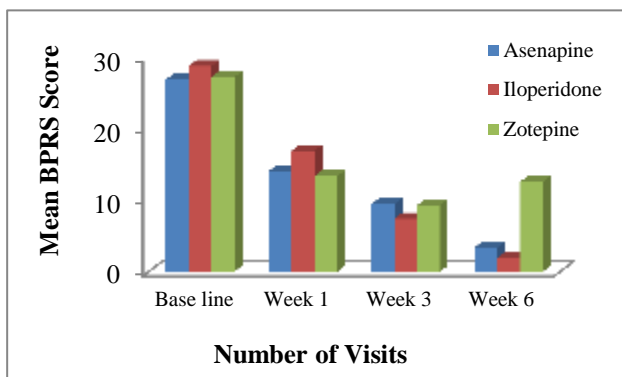


Figure 1: Graph showing mean BPRS score of subjects with psychosis on asenapine, iloperidone and zotepine in different visits.

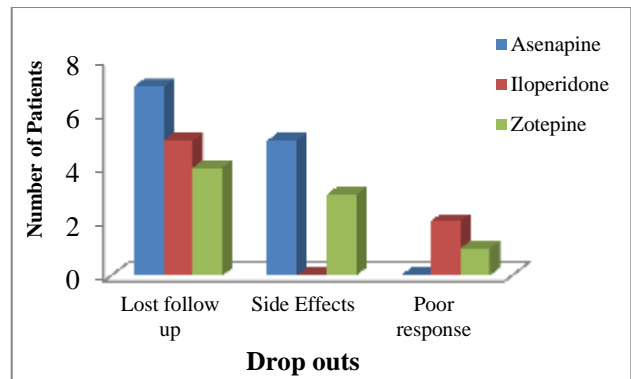


Figure 3: Reasons for the dropouts during the study.

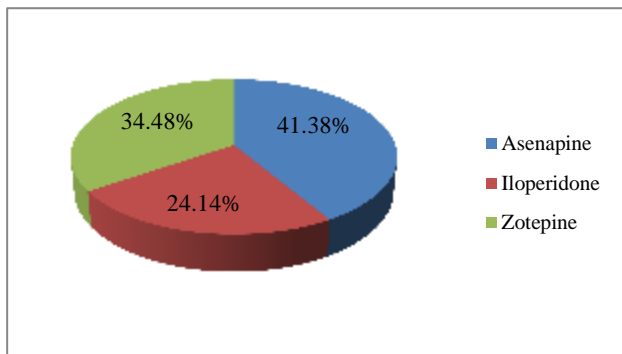


Figure 2: Total dropouts in the study drugs- asenapine, iloperidone and zotepine.

Table 3: Drug induced side effects which made the subjects to dropped from the study.

Side effects	Asenapine (N=5)	Zotepine (N=5)
EPS (dystonia)	2	3
Fatigue / giddiness	1	2
Hypoesthesia of oral cavity	2	-

DISCUSSION

Drug efficacy is one of the important factors in the management of psychotic disorder. The initial experience with an antipsychotic matters a lot for long term compliance. The study was done to evaluate and compare the effectiveness and acceptance of the newer second

generation atypical antipsychotic drugs such as asenapine, iloperidone and zotepine in the short term. Subjects with acute schizophrenia and acute and transient psychotic disorders were recruited as it is convenient to test in short duration.

Out of the recruited 60 subjects, 63.3% of acute psychosis and 36.7% of schizophrenic were recruited. 51.7% successfully completed all 4 visits which included 65% subjects from iloperidone, 50% from zotepine and 40% from asenapine group. Dropout rate was more with asenapine (41.4%) and zotepine (34.5%) than iloperidone (24.1%). Overall dropouts were due to loss of follow up (55.2%), adverse effects (34.5%) and poor response (10.3%).

Literature search revealed that no head to head comparison of these three newer antipsychotic drugs has been done. But these drugs are extensively studied in RCTs with other active comparators and placebo. Asenapine has proven efficacy in acute phases of schizophrenia and mania. In a three week, randomized, double-blind, placebo-controlled trial of asenapine versus olanzapine for treating acute bipolar mania, it was found to be rapidly acting, efficacious, and well tolerated.⁹ In another short term, double blind, double dummy, 3-arm fixed dose controlled trial of six week duration in acute exacerbation of schizophrenia, asenapine achieved a greater change in efficacy (measured using PANSS and BPRS) than placebo.¹⁰

In our study efficacy of asenapine as rated on BPRS was significantly reduced which was comparable to iloperidone and better than zotepine. Asenapine showed more dropouts (12) than other drugs. Of these, maximum dropouts were due to loss in follow-up (7) and rest were due to development of adverse effects. Among adverse effect profile, 2 subjects developed Extrapyramidal symptoms like akathisia and dystonia, which is uncommon in atypical antipsychotics and few were showed hypoesthesia of oral cavity as a result of sublingual route of administration.

In a study, dose range of 4-8 mg and 10-16 mg of Iloperidone was compared with 4-8 mg of risperidone and placebo. Even here iloperidone versus placebo comparisons were insignificant while risperidone fared better than placebo.¹¹ Another comparative study showed iloperidone with ziprasidone in acute exacerbation of schizophrenia using PANSS and inferred that both drugs are superior to placebo.¹² Additional analysis in patients who received active treatment for at least 2 weeks indicated comparable efficacy score reductions at 6 weeks for patients receiving iloperidone 20 to 24 mg/d versus those receiving haloperidol or risperidone. These trials indicate that iloperidone is effective for the treatment of schizophrenia.¹³

Our study showed significant reduction of BPRS score at 6th week in iloperidone as compared to asenapine and

zotepine. Fewer rates of dropouts were observed in subjects on iloperidone. Five subjects were lost in follow up and two subjects were dropped from the study due to poor response at adequate dose.

A study by Petit M et al demonstrated relatively better efficacy of zotepine compared to haloperidol at 8 weeks by BPRS among patients with acute exacerbation of schizophrenia.¹⁴ Another study revealed that zotepine was superior to risperidone in reducing hostility and comparable to olanzapine.¹⁵

In our study zotepine showed significant reduction in BPRS but this was less compared with other two drugs. At 6th week it showed slight increase in BPRS score compared to 3rd week which could be attributed to drug tolerance or therapeutic failure. The rate of dropouts on zotepine was around 34.5%, of which 20.7% were dropped due to development of drug induced side effects such as EPS (3 subjects), fatigue (1 subject) and 2 subjects showed poor response to drug.

The study showed efficacy of asenapine as rated on BPRS was comparable to iloperidone and significantly better than zotepine.

In the first three visits, there was no significant difference in improvement of BPRS scores between three drugs. But in fourth visit (6th week) iloperidone and asenapine showed significant reduction in BPRS score than zotepine thus indicating that acute psychosis and schizophrenia were better controlled with the former two drugs.

CONCLUSION

Out of the three atypical antipsychotics compared here, iloperidone appears most effective and tolerated than asenapine and zotepine in patients with acute psychosis and schizophrenia. Zotepine was less efficacious and produced poor response. Asenapine and zotepine have more dropouts and few subjects developed extrapyramidal side effects.

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