

Comparison of Adverse Effects of Newer Atypical Antipsychotics: An Evidence Based Review

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ABSTRACT

Aim: To Compare the safety of asenapine and iloperidone as per information available in public domain. **Method:** In addition to their USFDA approved prescribing information, literature on these two drugs from Pubmed indexed journals in English language were searched for appropriate information. We found 8 relevant articles on asenapine and iloperidone, results of which are discussed in this review. Data on the adverse effects commonly reported for atypical antipsychotics were collected from these articles and compared. Descriptive statistics was used to present the results. **Results:** Iloperidone is more frequently found to be associated with QTc prolongation (dose dependent), orthostatic hypotension & related dizziness (despite slow up-titration), weight gain and antimuscarinic side effects. On other side, asenapine is more frequently associated with extrapyramidal side effects and akathisia as well as the only one associated with headache, oral hypoesthesia and adverse event related discontinuations. **Conclusion:** Although, asenapine appears to be less frequently associated with adverse events commonly associated with atypical antipsychotics,

complex sublingual dosing and higher discontinuation related to adverse events offsets this safety advantage. More importantly, both these agents require close counselling of patients for adequate compliance and/or combination with other antipsychotic to achieve optimum antipsychotic efficacy in Indian context.

Key words: Adverse events, Antipsychotics, Asenapine, Iloperidone, Extrapyramidal side-effects, Indian context.

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INTRODUCTION

The “older” atypical antipsychotic drugs such as clozapine, olanzapine, quetiapine, risperidone, ziprasidone and aripiprazole were systematically reviewed for their safety profile in number of meta-analysis^{1,2} and research studies like CUTLASS³ & CATIE.⁴ The commonly reported adverse effects of these drugs include weight gain, extra pyramidal symptoms including tardive dyskinesia, antimuscarinic side effects, dyslipidemia, diabetes mellitus, prolactin elevation, QTc prolongation and sedation.⁵

Two atypical antipsychotics iloperidone and asenapine have been recently approved for acute treatment of schizophrenia by Drug Controller General (India) in February and April month of 2011, respectively.⁶ Both of them were claimed to be safer than older agents. However, there is no publication comparing two of them with each other in terms of their safety in Indian context. Therefore we conducted this study on safety comparison of these newer agents as per information freely available in public domain.

MATERIALS AND METHODS

This was an evidence based study on adverse effects of asenapine and iloperidone. Our interest in this subject started with an “Atypical Antipsychotic Drug Class Review Summary of Findings” published in The Oregon State Drug Review Newsletter of November 2011,⁷ which briefly reviewed the ‘newest’ atypical antipsychotics. The literature search strategy was to identify English language medical literature with appropriate information available as freely available full text journal articles indexed in PUBMED database. We found 8 relevant articles on asenapine⁸⁻¹⁰ and iloperidone,¹¹⁻¹⁵ results of which are discussed in this review. Prescribing

information of asenapine¹⁶ (“SAPHRIS”) and iloperidone¹⁷ (“FANAPT”) were obtained from DailyMed website.

Data on the adverse effects commonly reported for atypical antipsychotics⁵ were collected from these articles and compared between the two drugs to identify their benefits and disadvantages over each other. It is pertinent to note here that we included safety data of only schizophrenia trials in this review as both products are approved only for that indication in India.⁶

Descriptive statistics was used to present the results.

RESULTS

Weight gain

Asenapine was associated with slightly higher weight gain than placebo with incidence of approximately 4.9% for gain of $\geq 7\%$ weight from baseline with mean weight gain of around 1.1 kg over treatment periods up to 6 weeks.¹⁶ In long-term Clinical Trials, asenapine was associated with cumulatively higher incidence 14.7% for gain of $\geq 7\%$ weight from baseline with mean weight gain of around 0.9 kg over treatment periods up to 52 weeks.¹⁶ In short term Clinical Trials, iloperidone was found to be associated with apparently higher weight gain than placebo with incidence of approximately 13% for gain of $\geq 7\%$ weight from baseline with mean weight gain of around 2 kg over treatment periods up to 6 weeks,¹⁷ which appeared to be dose dependent. Long-term Clinical Trials demonstrated that most (2/3) of weight gain with iloperidone appeared to happen during first 6 weeks indicating plateau effect in this effect with only small (1/3) amount of weight gain during rest of the 46 weeks of the 52 weeks

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of treatment period leading to mean weight gain of 3.8 kg.¹³ Results of weight gain obtained in short-term trials are shown in Table 1 and results obtained in long-term trials are shown in Table 3.

Extra-pyramidal Symptoms

In short term Clinical Trials up to 6 weeks, asenapine was found to be associated with approximately 6% incidence of akathisia and approximately 10% incidence of other EPS, both of which were apparently higher than that with placebo as well as appeared dose dependent.¹⁶ In long-term Clinical Trials of 30 weeks, asenapine was associated with apparently continuous reports of akathisia during both early (3.6% in first 4 weeks) and late phase (6.2% in last 26 weeks).⁹ In short term Clinical Trials up to 6 weeks, Iloperidone was associated with similar incidence of EPS as well as akathisia than placebo with incidence of approximately 3% & 1%, respectively.¹⁷ Long-term Clinical Trials of 52 weeks demonstrated that iloperidone was associated with small incidence (3.8%) of akathisia and very small incidence (<1%) of other EPS, showing apparent plateau of EPS after early phase of 6 weeks.¹⁴ Results of extra-pyramidal symptoms obtained in short term trials are described in Table 1 and results obtained in long-term trials are described in Table 3.

Metabolic Side Effects

In short term Clinical Trials up to 6 weeks, both asenapine as well as iloperidone were associated with small but apparently high increase in mean blood glucose levels (3.2 mg/dL¹⁶ as well as ≈7 mg/dL,¹⁷ respectively) compared to placebo. In long-term Clinical Trials up to 52 weeks, asenapine was once again associated with small increase in mean blood glucose levels (2.4 mg/dL),¹⁶ whereas iloperidone was associated with reduction in blood glucose levels possibly due to reversal of levels increased with pre-trial antipsychotics.¹⁷ Results of blood glucose level changes were obtained in short term trials have been described in Table 2 and results obtained in long-term trials were described in Table 4.

In short term Clinical Trials up to 6 weeks, both asenapine as well as iloperidone were associated with small but apparently high increase in mean fasting serum levels of cholesterol (0.4 mg/dL¹⁶ as well as ≈8.1 mg/dL,¹⁴ respectively) and low density lipoproteins – LDL (1.3 mg/dL¹⁶ as well as 9.03 mg/dL,¹⁷ respectively) compared to placebo. However, the changes in high density lipoproteins (HDL) and triglycerides (TG) were comparable to placebo.^{16,17} In long-term Clinical Trials up to 52 weeks, asenapine was associated with mild increase in mean fasting serum levels of cholesterol (6 mg/dL)¹⁶ and LDL (9.8 mg/dL),¹⁶ whereas, iloperidone was associated with reduction in mean fasting serum levels of cholest-

Table 1: Symptomatic Adverse events commonly associated with atypical antipsychotics in short term clinical trials of asenapine and iloperidone

Drugs	Asenapine				Iloperidone			
	Placebo	5 mg BID	10 mg BID	Overall	Placebo	10-16 mg/day	20-24 mg/day	Overall
<i>Weight Gain</i>								
≥7% gain (%)	1.6	4.4	4.8	4.9	4	12.8	18.2	13
Mean gain (kg)	0.1	1	0.9	1.1	-0.1	2	2.7	2
Incidence (%) of AE	< 1	2	2	3	1	1	9	-
<i>Extra-pyramidal Symptoms (EPS)</i>								
EPS (%)	7	9	12	10	4 & 2*	5	4	3*
Akathisia (%)	3	4	11	6	2.7 & 0*	1.7	2.3	1*
Tremor (%)	-	-	-	-	1.9	2.5	3.1	-
Additional Comments	Change in 3 EPS scales equivalent to placebo				Anticholinergic use 9% equivalent to placebo 7.3%			
<i>Antimuscarinic Side Effects</i>								
Dry mouth (%)	1	3	1	2	1	8	10	-
Constipation (%)	6	7	4	5	-	-	-	-
Tachycardia (%)	-	-	-	-	1	3	12	-
Blurred vision (%)	-	-	-	-	2	3	1	-
Dry mouth (%)	1	3	1	2	1	8	10	-
<i>Orthostatic hypotension & related side effects</i>								
Orthostatic hypotension (%)	-	-	-	<2	1 & 8.3 [@]	3 & 21.2 [@]	5 & 13.6 [@]	-
Syncope (%)	-	-	-	-	0.2	-	0.4	-
Hypotension (%)	-	-	-	-	<1	<1 & 3.8 [@]	3 & 4.8 [@]	-
Dizziness (%)	4	7	3	5	7 [@] & 2*	10 [@]	20 [@] & 7*	-
<i>Sleep related side effects</i>								
Somnolence (%)	7	15	13	13	5 & 2.7 [@]	9 & 5.7 [@]	15 & 8 [@]	11.9
Insomnia (%)	13	16	15	15	-	-	-	-
Prolactin elevation related events (%)	0	-	-	0.4	<1	2	2	-

4-week fixed dose study; * Short term trial compared to ziprasidone; & @ haloperidol & risperidone comparative study

Table 2: Investigations related adverse events commonly associated with atypical antipsychotics in short term clinical trials of asenapine and iloperidone

Drugs	Asenapine				Iloperidone			
	Placebo	5 mg BID	10 mg BID	Overall	Placebo	10-16 mg/day	20-24 mg/day	Overall
<i>Blood level changes</i>								
Glucose (mg/ dL)	-0.2	3.8	1.1	3.2	-0.5 [‡] , -3.6 & 3.2 [*]	9	6.6 [‡] , 16.2 & 7.9 [*]	-
Cholesterol (mg/ dL)	-2.2	-2.4	3.3	0.4	-2.17 [‡] , -7.7 & -0.5 [*]	-	8.18 [‡] , 0.0 & 8.1 [*]	-
LDL (mg/ dL)	0.1	-0.2	2.6	1.3	-1.41 [‡]	-	9.03 [‡]	-
HDL (mg/ dL)	0.5	0.4	1	0.5	-3.35 [‡]	-	0.55 [‡]	-
Triglycerides (mg/ dL)	-7.6	-1.9	0.1	3.8	16.47 [‡] , -35.4 & 19.5 [*]	-	-0.83 [‡] , -26.5 & 0.8 [*]	-
Prolactin (ng/mL)	-10.7	-	-	-6.5	-6.3 [‡] & -57.4	-23.1	2.6 [‡]	-
Prolactin 4xULN (%)	0.6	-	-	2.6	-	-	-	-
<i>Change in QTc Interval</i>								
QTc Change (msec)	0	-	-	2-5	0	3.9	9.1, 11.4 [*] & 19 [§]	-

4-week fixed dose study; * Short term trial compared to ziprasidone; & \$ along with metabolic inhibitors.

Table 3: Symptomatic adverse events commonly associated with atypical antipsychotics in long term clinical trials of asenapine and iloperidone

Drugs	Asenapine			Iloperidone		
	Early	Late	Overall	Early	Late	Overall
<i>Weight Gain</i>						
≥7% gain (%)	- (6 wk) & 1.8 (4 wk)*	3.7 (46 wk) & 7.3 (26 wk)*	14.7 (52 wk)	-	-	-
Mean gain (kg)	-	-	0.9 (52 wk)	2.6 (6 wk)	1.2 (46 wk)	3.8 (52 wk)
Other comments	Higher incidence with body mass index < 23 (22%) vs. > 27 (9%)			More than 2/3 of gain in first 6 weeks		
<i>Extra-pyramidal Symptoms (EPS)</i>						
EPS	-	-	-	0.6 (6 wk)	-	0.8 (52 wk)
Akathisia	3.6 (4 wk)*	6.2 (26 wk)*	-	3.5 (6 wk)	-	3.8 (52 wk)
<i>Antimuscarinic side effects</i>						
Dry mouth (%)	0.8* (4 wk)	2.3* (26 wk)	-	-	-	-
<i>Orthostatic hypotension related side effects</i>						
Dizziness (%)	4.4* (4 wk)	5.4* (26 wk)	-	-	-	-
Syncope (%)	-	-	0.6* (30 wk)	-	-	-
<i>Sleep related side effects</i>						
Somnolence	9.8* (4 wk)	13.7* (26 wk)	-	-	-	2 (52 wk)
Insomnia	11.1* (4 wk)	18.9* (26 wk)	-	-	-	18.1 (52 wk)
Sedation	3.6* (4 wk)	5.2* (26 wk)	-	-	-	-
Prolactin elevation related events	-	-	-	-	-	0.3 (52 wk)

* Data from switchover trial versus olanzapine.

terol and LDL possibly due to reversal of levels increased with pre-trial antipsychotics.¹⁷ Results of lipid level changes obtained in short term trials are described in Table 2 and results obtained in long-term trials are described in Table 4.

Prolactin Elevation

In short term Clinical Trials up to 6 weeks, although asenapine was associated with reduction in mean prolactin levels (6.5 ng/mL) similar to placebo¹⁶ possibly due to reversal of levels increased with pre-trial antipsychotics, increase to level ≥ 4 times upper limit of normal range in prolactin (2.6%) as well as prolactin elevation related side effects (0.4%) was

seen in apparently higher proportion of subjects than placebo.¹⁶ On other hand, in short-term Clinical Trials, iloperidone was associated with decrease in prolactin levels, which was reduced with increase in dose of iloperidone compared to placebo suggesting possibly a dose dependent potential to elevate prolactin levels^{14,17} with slightly high incidence (2%) of prolactin elevation related side effects in high dose groups.¹⁷ In long-term Clinical Trials of 52 weeks, asenapine was again associated with reduction in prolactin levels,¹⁶ whereas, for iloperidone data on prolactin levels was not available, but prolactin elevation related side effects were reported in small proportion (0.2 to 0.3%) of patients.¹⁷ Results of prolactin level changes obtained in short term trials are described in Table 2

Table 4: Investigation related adverse events commonly associated with atypical antipsychotics in long term clinical trials of asenapine and iloperidone

Drugs	Asenapine			Iloperidone		
	Early	Late	Overall	Early	Late	Overall
<i>Blood level changes</i>						
Glucose (mg/ dL)	-	-	2.4 (52 wk)	-3.6 (3-6 mnth)	-9 (6-12 mnth)	-18 (>12 mnth)
Cholesterol (mg/ dL)	-	-	6 (52 wk)	-19.4 (3-6 mnth)	-23.2 (6-12 mnth)	-19.4 (>12 mnth)
TG (mg/ dL)	-	-	9.8 (52 wk)	-26.6 (3-6 mnth)	-35.4 (6-12 mnth)	-17.7 (>12 mnth)
Prolactin (ng/mL)			-26.9 (52 wk)	-	-	-
<i>Change in QTc Interval</i>						
QTc change (msec)	-	-	-	3.2 (6 wk)	-	10.3 (52 wk)

and results obtained in long-term trials are described in Table 4. Results of prolactin elevation related adverse events obtained in short term trials are described in Table 1 and results obtained in long-term trials are described in Table 3.

QTc Prolongation

In short term Clinical Trials, asenapine was associated with small (2 to 5 msec) increase in mean QTc interval,¹⁶ whereas iloperidone was associated with significant increase in mean QTc interval (up to 11.4 msec),¹⁴ which appeared to be dose dependent as well as it was further increased by combining with metabolic inhibitors (19 msec).¹⁷ In long-term Clinical Trials of 52 weeks, iloperidone was again associated with increase in mean QTc interval, which was continuous during early (3.2 msec in first 6 weeks) and late phase (10.3 msec at the end of 52 weeks).¹⁴ Results of QTc interval changes obtained in short term trials are described in Table 2 and results obtained in long-term trials are described in Table 4.

Antimuscarinic Side Effects

In short term Clinical Trials up to 6 weeks, asenapine was associated with antimuscarinic events of dry mouth (2%) and constipation (5%) at comparable level to placebo,¹⁶ whereas, iloperidone was associated with higher incidence of dry mouth (\approx 9%) as well as tachycardia (\approx 7.5%) compared to placebo that increased with dose, but the rate for blurring of vision (1%) was comparable to placebo.¹⁷ On the contrary, in long-term Clinical Trials of 30 weeks, asenapine was associated with small proportion of patients reporting dry mouth (up to 2.3%) which was continuously reported in both early (0.8% in first 4 weeks) and late (2.3% in last 26 weeks) phase, possibly related to sublingual dosing rather than antimuscarinic side effects.⁹ Results of antimuscarinic side effects obtained in short term trials are described in Table 1 and results obtained in long-term trials are described in Table 3.

Orthostatic Hypotension

In short-term Clinical Trials up to 6 weeks, asenapine was associated slightly higher incidence of dizziness (5%) than placebo, however the incidence of orthostatic hypotension was reported at low rate (<2%) than placebo.¹⁶ In long-term Clinical Trials up to 30 weeks, asenapine was associated with fair incidence of dizziness (5.4%), most of which was reported during first 4 weeks (4.4%).⁹ On the contrary, in short-term Clinical Trials, compared to placebo, iloperidone was associated with higher incidence of orthostatic hypotension (up to 21.2%),¹³ hypotension (up to 4.8%)¹³ and syncope (0.4%),¹⁷ as well as apparent higher incidence of dizziness (up to 20%),¹³ which was dose dependent. Unfortunately data on orthostatic hypotension or related side effects was not available from long-term Clinical Trials of iloperidone.¹⁴ Results of orthostatic hypoten-

sion and related side-effects obtained in short term trials are described in Table 1 and results obtained in long-term trials are described in Table 3.

Sleep Related Side Effects

In short-term Clinical Trials up to 6 weeks, both asenapine (13%)¹⁶ and iloperidone (11.9%)¹⁷ were associated with apparently high incidence of somnolence compared to placebo, which increased with dose for iloperidone, but not for asenapine. In short-term Clinical Trials, asenapine was also associated with high rate of insomnia (15%)¹⁶ that was fairly similar to placebo, which might be related to the schizophrenia itself or other concomitant medications. In long-term Clinical Trials up to 52 weeks, iloperidone was associated with small incidence of somnolence (2%),¹⁴ but asenapine was associated with high incidence (13.7%), most of which was reported in first 4 weeks (9.8%).⁹ Both asenapine (18.9%)⁹ and iloperidone (18.1%)¹⁴ were associated with high incidence of insomnia, which was continuously reported in both early and late phase for asenapine. Results of sleep related side-effects obtained in short term trials are described in Table 1 and results obtained in long-term trials are described in Table 3.

Other side effects

Asenapine is also associated with headache in long term studies at 8.5% in first 4 weeks (early) and 14.5% in next 26 weeks (late).⁹ It is also associated with oral hypoesthesia related to sublingual dosing with placebo at 1%, with 5 mg BID at 6%, with 10 mg BID at 7% (overall 5%).¹⁶ Compared to iloperidone, which reported adverse event related discontinuation at the same rate as placebo,¹⁴ asenapine reported higher rate of adverse event related discontinuation than placebo (mostly related to somnolence, abdominal pain and nausea).⁹ A case series of 57 schizophrenic Indian patients treated with iloperidone¹⁵ reported nasal congestion as most frequent adverse event with incidence as high as 40.35%.

DISCUSSION

Asenapine is only available as a sublingual tablet due to its high first pass metabolism (bioavailability is 35% sublingually & < 2% orally), which makes it difficult to administer drug for patients of schizophrenia and mania.¹⁰ It is recommended as 5 mg twice daily for the treatment of schizophrenia. Escalation to 10 mg twice daily dosing is recommended after 1 week, only when tolerated. To maximise sublingual absorption, patients are recommended to allow asenapine tablet to dissolve in saliva and not to eat or drink for 10 min after its administration.⁷ Compliance to such dosing requirement appears quiet difficult during acute treatment of schizophrenia, unless prescriber appropriately consults the patients. In addition, side effects of oral hypoesthesia and paresthesia further add to the difficulty in achieving compliance. No wonder the product is report-

ed to have numerically higher discontinuation rate than that of olanzapine in comparative switchover trial (36.6% vs. 24.6%) linked to lack of efficacy (3% vs. 2.6%) and adverse events (15.8% vs. 10.6%).⁹

Prescriber should consider the risk of QTc prolongation associated with iloperidone while deciding to prescribe it. It has been recommended to be titrated slowly, starting with 1 mg twice daily with daily dosage adjustment of ≤ 2 mg twice daily to achieve target dose of 6 to 12 mg twice daily, to avoid orthostatic hypotension due to its strong α_1 blocking properties.⁷ It certainly discourages to use it in acute treatment of schizophrenia as single agent due to such slow titration leading to delay of 1 to 2 weeks in controlling symptoms of schizophrenia, especially when published Clinical Trial blames such delay in therapeutic response for higher discontinuation rates in first 2 weeks.¹³ In Indian healthcare field, where delay in controlling symptoms frequently results in change of the treating doctor, it becomes obvious choice that iloperidone is mainly co-prescribed with multiple agents for the acute treatment of schizophrenia that compensates for such a delay.

In the safety comparison between the two, iloperidone was more frequently found to be associated with QTc prolongation (dose dependent), orthostatic hypotension & related dizziness (despite slow up-titration as recommended), weight gain (apparently dose dependent) and antimuscarinic side effects (apparently dose-dependent). On other side, asenapine was more frequently associated with extra-pyramidal side effects and akathisia (apparently dose dependent) as well as the only one associated with headache, oral hypoesthesia (related to sublingual dosing) and adverse event related discontinuations.

Importantly in Indian context, both of these agents have met with higher discontinuation rates in early treatment due to complex dosing (sublingual dosing for asenapine⁹ and slow up-titration for iloperidone¹³) as well as delay in achieving optimum efficacy. Hence, while deciding to use any of these agents, prescriber must closely consult patients and/ or relatives about adequate compliance to achieve optimum efficacy of these products seen in controlled Clinical Trials. Alternately, author feels that these agents may be combined with other atypical antipsychotic or conventional antipsychotic during initial period to quickly achieve the therapeutic efficacy, followed by tapering them off when optimum efficacy for the newer products is achieved.

CONCLUSION

Amongst the two agents, asenapine appeared 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 offsets this safety advantage. Overall both these agents require close counselling of patients for adequate compliance and/ or combination with other antipsychotic to achieve optimum antipsychotic efficacy in Indian context.

LIMITATIONS

As this review is based on published evidence from Global Clinical Trials of asenapine and iloperidone, incidence of the adverse effects may differ in Indian patients from that reported in this article due to differences

of genetic factors and ethnic perceptions. Hence, readers are requested to use this review as indicator of the differences between the two newer drugs.

CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATION USED

USFDA: United States Food & Drug Administration; **CUTLASS:** Cost Utility of The Latest Antipsychotics in Schizophrenia Study; **CATIE:** Clinical Antipsychotics Trial of Intervention Effectiveness; **EPS:** Extra Pyramidal Side-effects; **mg:** Milligram; **dL:** Deciliter; **HDL:** High Density Lipoprotein; **LDL:** Low Density Lipoprotein; **TG:** Triglyceride; **BID:** Twice Daily.

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