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EXTRAPYRAMIDAL SYMPTOM AND AKATHISIA PROFILE OF ILOPERIDONE IN SCHIZOPHRENIA CLINICAL TRIALS

John Lauriello, MD[1]; Rosarelis Torres, PhD[2]; Curt D. Wolfgang, PhD[2]; John Feeney, MD[2]

[1]University of New Mexico, Albuquerque, NM; [2]Vanda Pharmaceuticals Inc., Rockville, MD

Abstract

Introduction: Antipsychotic-induced akathisia and extrapyramidal symptoms (EPS) is physically uncomfortable and can influence functioning, quality of life, and treatment adherence. Iloperidone, a mixed D_2/5-HT_2 antagonist being developed for the treatment of schizophrenia, has been shown to have a low incidence of these effects. Akathisia and EPS were assessed in a pooled analysis of iloperidone clinical data.

Methods: Nine phase II and III double-blind or open-label clinical trials of adults with schizophrenia were included in the analysis. Mean duration of iloperidone treatment was 230±300.5 days; maximum treatment duration was 2 years. Reports of EPS and akathisia as adverse events and changes from baseline in Extrapyramidal Symptoms Rating Scale (ESRS) and Barnes Akathisia Scale (BAS) scores were evaluated.

Results: The pooled safety analysis comprised 4838 patients: 1225 iloperidone 4–8 mg/d; 1533 iloperidone 10–16 mg/d; 452 iloperidone 20–24 mg/d; 546 haloperidol 5–20 mg/d; 311 risperidone 4–8 mg/d; 184 ziprasidone 160 mg/d; and 587 placebo. Treatment-emergent EPS were reported in 18.0% (iloperidone 4–8 mg/d), 20.0% (iloperidone 10–16 mg/d), 15.9% (iloperidone 20–24 mg/d), 59.7% (haloperidol), 29.9% (risperidone), 24.5% (ziprasidone) and 11.6% (placebo) of patients. Mean changes in overall ESRS from baseline to endpoint were –0.7 (iloperidone 4–8 mg/d), –0.8 (iloperidone 10–16 mg/d), –0.1 (iloperidone 20–24 mg/d), 1.3 (haloperidol), –0.4 (risperidone), 0.2 (ziprasidone) and –0.3 (placebo). Treatment-emergent akathisia was reported in 4.2% (iloperidone 4–8 mg/d), 5.2% (iloperidone 10–16 mg/d), 3.3% (iloperidone 20–24 mg/d), 21.2% (haloperidol), 7.1% (risperidone), 8.2% (ziprasidone) and 2.7% (placebo) of patients. Worsening in BAS scores at endpoint were reported in 10.1% (iloperidone 4–8 mg/d), 8.8% (iloperidone 10–16 mg/d), 3.7% (iloperidone 20–24 mg/d), 18.5% (haloperidol), 13.9% (risperidone), 15.6% (ziprasidone) and 11.4% (placebo) of patients.

Conclusions: These results indicate that iloperidone may have a lower propensity to cause EPS or akathisia than haloperidol, risperidone, or ziprasidone, thereby offering a favorable treatment option for schizophrenia. Vanda Pharmaceuticals sponsored this study.

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Introduction

- Antipsychotic-induced akathisia and extrapyramidal symptoms (EPS) are common causes of morbidity, treatment nonadherence, and inadequate response in patients with schizophrenia[1]
- EPS and akathisia increase the risk for suicide among these patients[2-4]
  - Akathisia can be missed clinically without a focused, active inquiry for subjective restlessness and/or behavioral agitation[5]
  - In a study of 58 inpatients with acute psychosis, 74% of patients given the diagnosis of akathisia in accordance with research criteria failed to receive a clinical diagnosis[5]
- Currently available atypical antipsychotics continue to be implicated in the development of EPS and akathisia[1]
- In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), rates of discontinuation due to EPS were modest with the drugs studied (2%–8%)[6] but may have been underestimated owing to methodologic issues[1]
- Iloperidone is a mixed D_2/5-HT_2 antagonist antipsychotic with a high affinity for 5-HT_{2A}, α_1-adrenergic, α_{2C}-adrenergic, D_2, and D_3 receptors[7-9]
  - The D_2/5-HT_2 ratio of K_i values for iloperidone predicts a low EPS liability[6]
  - Iloperidone is under review by the FDA for treatment of schizophrenia
- This safety data set includes information from 9 controlled studies (2 Phase II, 7 Phase III)
- Seven of the 9 studies examined here (1 Phase II and 6 Phase III) include long-term open-label extensions
- The objective of this analysis of pooled data from schizophrenia trials was to assess the effect of treatment with iloperidone on the development of EPS and akathisia

Methods

Study Population

- This analysis examined data pooled from 4838 adult patients with schizophrenia enrolled in 9 phase 2 and 3 double-blind or open-label clinical trials (Table 1)

Outcomes Analyzed

- Rates of EPS and akathisia reported as treatment-emergent adverse events (TEAEs)
- Change from baseline to endpoint in scores on the Extrapyramidal Symptoms Rating Scale (ESRS)
- Change from baseline to endpoint in scores on each of the subscales of the Barnes Akathisia Scale (BAS)

Statistical Analysis

- TEAEs, specifically reports of EPS and akathisia, were summarized by treatment group
- Mean change in EPS from baseline to end of treatment as measured by ESRS and in akathisia using BAS subscale scores were calculated for each treatment group and summarized descriptively
- Study designs did not allow for statistical comparisons between active treatment groups; these investigations were not initiated in light of a prespecified meta-analytic or statistical analysis plan

Results

Demographic and Baseline Characteristics of Study Population

- 3210 patients were treated with iloperidone in 9 clinical trials: 1225 received a modal dose of 4–8 mg/d, 1533 received 10–16 mg/d, and 452 received 20–24 mg/d
- In the acute phase of schizophrenia, the recommended target dose range of iloperidone is 12–24 mg/d administered bid
- In the maintenance phase, iloperidone was administered once daily in the 4–16 mg/d range
- Approximately 90% of patients were previously hospitalized for psychosis

Table 1. Demographic Characteristics of Study Population by Treatment

	iloperidone						
	4–8 mg/d (n=1225)	10–16 mg/d (n=1533)	20–24 mg/d (n=452)	haloperidol 5–20 mg/d (n=546)	risperidone 4–8 mg/d (n=311)	ziprasidone 160 mg/d (n=184)	placebo (n=587)
Age, y							
Mean±SD	37.6±11.0	37.3±10.5	39.6±10.1	36.5±10.7	38.8±11.2	40.1±9.6	39.5±10.3
Median	37.0	37.0	40.0	36.0	39.0	41.0	40.0
Gender, n (%)							
Men	784 (64.0)	993 (64.8)	347 (76.8)	347 (63.6)	214 (68.8)	138 (75.0)	399 (68.0)
Women	441 (36.0)	540 (35.2)	105 (23.2)	199 (36.4)	97 (31.2)	46 (25.0)	188 (32.0)
Race, n (%)							
White	706 (57.6)	876 (57.1)	215 (47.6)	287 (52.6)	210 (67.5)	67 (36.4)	306 (52.1)
Black	248 (20.2)	200 (13.0)	187 (41.4)	71 (13.0)	80 (25.7)	93 (50.5)	222 (37.8)
Asian	172 (14.0)	259 (16.9)	29 (6.4)	119 (21.8)	3 (1.0)	13 (7.1)	19 (3.2)
Other	99 (8.1)	198 (12.9)	21 (4.6)	69 (12.6)	18 (5.8)	11 (6.0)	40 (6.8)

Table 2. Extent of Cumulative Exposure

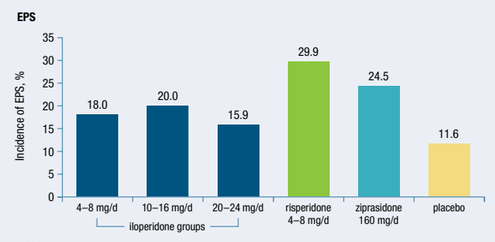
	iloperidone						
	4–8 mg/d (n=1225)	10–16 mg/d (n=1533)	20–24 mg/d (n=452)	haloperidol 5–20 mg/d (n=546)	risperidone 4–8 mg/d (n=311)	ziprasidone 160 mg/d (n=184)	placebo (n=587)
Mean duration of treatment (±SD), d	209.8 (294.9)	296.7 (319.1)	58.6 (122.9)	175 (155.9)	66.1 (87.8)	20 (9.2)	26 (13.7)

- Dosing groups for iloperidone are a function of modal dose and were based on the daily dose that occurred most frequently during the relevant phase of study
- Mean duration of treatment with iloperidone was 230±300.5 days

Treatment-Emergent Adverse Events

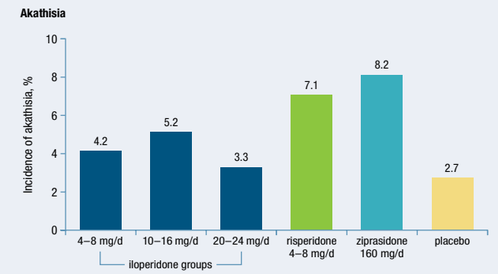
- Rates of both treatment-emergent EPS and akathisia with iloperidone were lower than rates with risperidone and ziprasidone (Figures 1 and 2)
- Treatment-emergent EPS and akathisia were reported in 59.7% and 21.2% of patients treated with haloperidol, respectively (data not shown)

Figure 1. Rates of Extrapyramidal Symptoms* Reported as Treatment-Emergent Adverse Events



*EPS includes: tremor, akathisia, extrapyramidal disorder, muscle rigidity, dyskinesia, postural dizziness, musculoskeletal stiffness, bradykinesia, dystonia, restlessness, abnormal posture, parkinsonism, drooling, balance disorder, movement disorder, cogwheel rigidity, abnormal coordination, gait disturbance, muscle tightness, tongue paralysis, restless legs syndrome, grimacing, involuntary muscle contractions, parkinsonian gait, parkinsonian resting tremor, and feeling jittery.

Figure 2. Rates of Akathisia Reported as Treatment-Emergent Adverse Events



Change in Extrapyramidal Symptom Rating Scale (ESRS)

- At endpoint, improvement in the overall EPS rating in the iloperidone groups, as demonstrated by ESRS scores, was similar to that seen in the placebo group (Table 3)

Table 3. Mean Change in Overall Rating of EPS From Baseline to Endpoint*†

	iloperidone						
	4–8 mg/d (n=1225)	10–16 mg/d (n=1533)	20–24 mg/d (n=452)	haloperidol 5–20 mg/d (n=546)	risperidone 4–8 mg/d (n=311)	ziprasidone 160 mg/d (n=184)	placebo (n=587)
Mean score at baseline	2.40	2.55	1.27	2.59	2.52	1.29	2.23
Mean change in overall EPS score	–0.7	–0.8	–0.1	1.3	–0.4	0.2	–0.3

*Negative values indicate improvement; †Derived from the ESRS

Changes in Barnes Akathisia Scale (BAS)

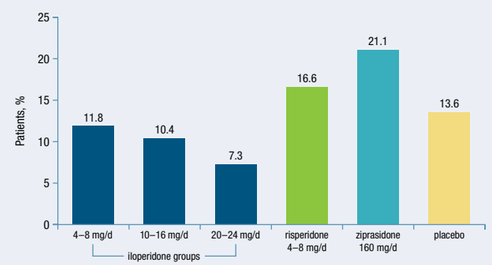
- Fewer patients treated with iloperidone (in any dose group) experienced a worsening of akathisia (increase in BAS score on each respective subscale) compared with patients who received placebo, haloperidol, risperidone, or ziprasidone (Table 4)

Table 4. Proportion of Patients With Worsening of Akathisia From Baseline to Endpoint

	iloperidone						
	4–8 mg/d (n=960)	10–16 mg/d (n=1402)	20–24 mg/d (n=452)	haloperidol 5–20 mg/d (n=428)	risperidone 4–8 mg/d (n=311)	ziprasidone 160 mg/d (n=184)	placebo (n=460)
Objective assessment	10.1%	8.8%	3.7%	18.5%	13.9%	15.6%	11.4%
Subject awareness of restlessness	10.9%	10.3%	7.3%	25.5%	14.9%	19.0%	11.4%
Subjective distress related to restlessness	9.8%	9.2%	5.5%	22.4%	12.5%	19.0%	10.7%

- Patients in the highest iloperidone dosing group (20–24 mg/d) had the lowest rate of worsening of akathisia across all BAS assessments

Figure 3. BAS Global Clinical Assessment of Akathisia: Proportion of Patients With Worsening From Baseline to Endpoint



- 25.0% of patients treated with haloperidol worsened on the BAS Global Clinical Assessment of Akathisia

Conclusions

- The propensity of antipsychotic agents to cause EPS and akathisia remains an important consideration when choosing a treatment for schizophrenia, even with current second-generation medications
  - Treatment-emergent EPS and akathisia may necessitate medication switching, further delaying the treatment goal of acute symptom relief
  - EPS and akathisia can adversely affect treatment adherence and increase the risk for suicide, emphasizing the clinical relevance of these adverse effects
- This pooled analysis of 9 phase II and III clinical trials indicates that iloperidone may be associated with lower rates of EPS and akathisia, similar to those seen with placebo

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The following information concerns a use that has not been approved by U.S. Food and Drug Administration.