Switching to Iloperidone: An Omnibus of Clinically Relevant Observations from a 12-Week, Open-Label, Randomized Clinical Trial in 500 Persons with Schizophrenia

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Abstract

Objective: To describe secondary analyses from a 12-week, randomized, open-label trial where adult schizophrenia outpatients receiving risperidone, olanzapine, or aripiprazole were switched to iloperidone. **Methods:** Patients were randomized into two groups: one where the antecedent antipsychotic dose was titrated downwards to zero over 2 weeks (n=240), and the other group where the antecedent antipsychotic was abruptly stopped (n=260). Adaptations of the Clinical Global Impression scale were used to evaluate clinical changes. Other assessments included the reporting of adverse events (AEs), study discontinuation, body weight, and metabolic variables. **Results:** Improvement was steady throughout the study for both gradual- and immediate-switch groups starting at Week 1 and continuing through Week 12. Discontinuations due to AEs in the first 2 weeks of treatment were higher for the immediate-switch group compared with the gradual-switch group (10.8% vs. 5.4%, NNT 19, 95% CI 10–151). Fewer patients in the gradual-switch group experienced dizziness as an AE, whereas a higher percentage of patients in the immediate-switch group exhibited earlier onset of a therapeutic response within the first 2 weeks; both groups were comparable thereafter with low rates of dizziness and similar efficacy outcomes. **Conclusions:** Switching to iloperidone can be accomplished either with a gradual crossover or immediate discontinuation of the prior antipsychotic; however, the immediate-switch method is associated with greater proportion of initial dizziness. The observed outcomes are consistent with what has been previously reported regarding iloperidone's favorable akathisia/EPS profile and modest impact on somnolence/sedation, body weight, and metabolic variables.

Key Words: Efficacy, Iloperidone, Safety, Schizophrenia, Switching, Tolerability

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Submitted: June 24, 2014; Revised: July 20, 2014; Accepted: August 25, 2014

Introduction

Switching antipsychotic medications in persons with schizophrenia is common. Clinicians and their patients spend a considerable amount of time and effort to find which medication "works well enough," is "tolerated well enough," and to which the patient is willing to adhere (1, 2).

Iloperidone is an atypical antipsychotic approved for the treatment of schizophrenia (3). It is not a metabolite or derivative of any other available antipsychotic, and has a well-defined efficacy and tolerability profile in patients with schizophrenia (2). Iloperidone has a relatively high affinity

Clinical Implications

The overall pattern of results regarding ratings of efficacy and safety/tolerability outcomes after switching to iloperidone from risperidone, olanzapine, or aripiprazole, as observed in this study, suggests that iloperidone is an appropriate antipsychotic choice for adherent, nontreatment-resistant patients who are experiencing inadequate efficacy and/or poor tolerability with their current therapy. Clinicians should remain mindful of any withdrawal effects that can be encountered when abruptly switching from other antipsychotics.

Other than a few subtle clinical considerations, such as the incidence of noradrenergic alpha 1 receptor antagonism related dizziness, switching to iloperidone by either a gradual or immediate method did not generally reveal any relevant differences in ratings of overall efficacy and safety/tolerability outcomes. The observed outcomes are consistent with what has been previously reported regarding iloperidone's favorable EPS profile and modest impact on somnolence/sedation, body weight, and metabolic variables.

for noradrenergic alpha-1 receptors (Ki 0.36 nM), compared with the affinity for serotonin 5-HT2A and dopamine D2 receptors (Ki 5.6 and 6.3 nM, respectively). Thus, in order to minimize the potential for postural hypotension attributable to noradrenergic alpha-1 receptor antagonism, iloperidone requires a four-to-seven day titration to its therapeutic target dose range of 6–12 mg twice daily. Iloperidone also exhibits an average increase of the ECG QTc interval by 9 msec when dosed at 12 mg twice daily. The tolerability profile of iloperidone is also noteworthy in terms of modest weight gain and glucose elevation, generally minor changes in lipids, minimal prolactin elevation, and rates of extrapyramidal adverse effects (EPS), including akathisia, similar to that observed in placebo-treated patients (3, 4).This is a report of additional analyses from a 12-week, randomized, open-label trial where 500 adults diagnosed with schizophrenia experiencing inadequate efficacy and/or poor tolerability on risperidone, olanzapine, or aripiprazole were switched to iloperidone (5).

Methods

The objective of this multi-center, U.S.-based, open-label, 12-week study (clinicaltrials.gov registry: NCT01207414) was to evaluate the impact on clinical outcomes of two switching strategies (gradual vs. immediate) to iloperidone, titrated to 6–12 mg twice daily, among adult outpatients with *DSM-IV-TR* schizophrenia experiencing persistent symptoms and/or undesired side effects on their current therapy of risperidone, olanzapine, or aripiprazole, at daily doses that were below or at the maximum approved by the U.S. Food and Drug Administration (risperidone 16 mg/day, olanzapine 20 mg/day, or aripiprazole 30 mg/day) (5). All subjects, therefore, had a clinical reason to change therapies and clinicians considered iloperidone to be a reasonable next therapeutic option. The study was reviewed and approved by an Institutional Review Board at each study center and all subjects provided written informed consent before study participation. Please refer to the primary publication for additional information regarding inclusion/exclusion criteria (5).

A total of 500 patients were randomized 1:1 to either gradually taper the dose of their prior antipsychotic (risperidone, n=175; olanzapine, n=155; aripiprazole, n=170) over the first 2 weeks of iloperidone use (decrease to 50% on Day 1, 25% at Week 1, 0% at Week 2) or switch immediately to iloperidone (see Figure 1). All patients initiated iloperidone on Day 1 and received a titration pack to start at 1 mg twice daily and reach 6 mg twice daily (12 mg total daily dose) on Day 4. After reaching the 12-mg total daily dose, at any time during the remainder of the study, investigators were allowed to make necessary dose increases or decreases, within the 12–24 mg daily range, with dose increments not to exceed 2 mg twice daily (5).

The Clinical Global Impression (CGI) scale formed the basis of the outcomes used in this study. The CGI-Severity subscale (CGI-S) covers a 7-point range from 1 (not at all ill) to 7 (extremely ill) (6) and correlates with both the Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale (7, 8). However, because the global CGI-S may be less sensitive to different aspects of pharmacologic response in clinical trials (9), it was adapted for this study by separating out the efficacy (E-CGI-S) and safety (ST-CGI-S) domains (10). The integrated CGI-S (I-CGI-S) combines the individual E-CGI-S and ST-CGI-S scores into a single, unified measure of severity. The I-CGI measure of clinical change (I-CGI-C) was used to evaluate clinical changes.

This secondary report focuses on several clinically relevant questions not specifically addressed in the primary publication (5), namely:

1. initial 2-week outcomes, rates of response, and overall trajectory of response;
2. potential influencers of efficacy and tolerability, such as pre-switch medication (i.e., cohort), reason for switch, and ethnicity; and,
3. shifts in body weight and metabolic variables.

No hypothesis testing was done. For binary variables, number needed to treat (NNT) was calculated when contrasting groups at the same time point and are provided in the report whenever the 95% CI for the NNT did not include infinity (11); absolute whole values of NNT are given (i.e., rounded up and unsigned). For the non-binary variables, analysis of (co)variance (AN[C]OVA) was used to analyze the I-CGI-C and changes from baseline in the E-CGI-S, ST-CGI-S, and I-CGI-S with baseline (if applicable), treatment, cohort, and treatment-by-cohort interaction as explanatory variables for the three cohorts combined, and with baseline (if applicable) and treatment as the explanatory variables for each cohort, at each time point (week). Least-squares mean (LSM), LSM difference of the treatment groups, and 95% CIs for the difference based on the fitted linear model are reported. Missing data were imputed using the last-observation-carried-forward (LOCF) method. All statistical analyses for continuous variables were performed using SAS® Version 9.2 (SAS Institute Inc., Cary, NC, USA). These data, with the exception of the NNT analyses, have been previously presented as posters at national conferences (12-23).

Results

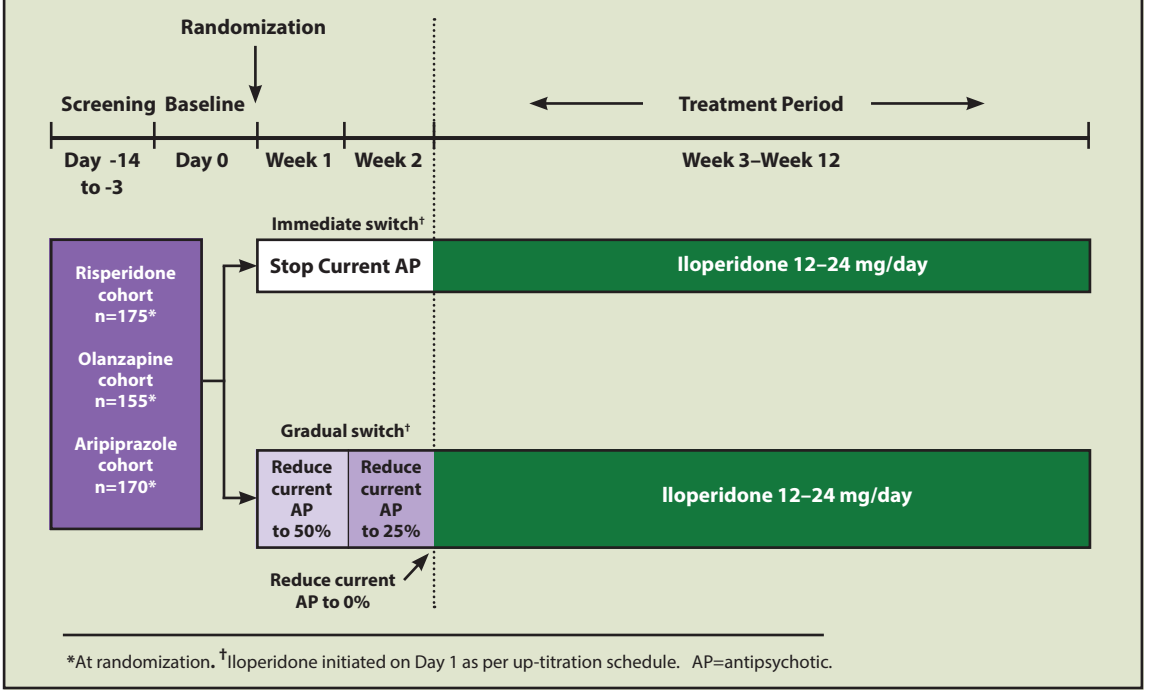
A total of 500 patients were randomized, with 240 to the gradual-switch group and 260 to the immediate-switch group (5). A total of 175, 155, and 170 patients were switched from risperidone, olanzapine, and aripiprazole, respectively, and thus represent three separate cohorts. A total of 346 completed the study (168 in the gradual- and 178 in the immediate-switch groups).

Iloperidone 6 mg twice daily (i.e., 12 mg/day total daily dose) was the most common of the prescribed iloperidone doses administered at the end of the study (46.6% of patients) and mean (standard deviation [SD]) and median dose of iloperidone at study end was 16.7 (4.5) mg/day and 16.0 mg/day, respectively. Mean (±SD) age of participants was 43.3±11.0 years, and 56.6% were Black/African American, and 67.0% were male. Please refer to the primary publication for additional information regarding baseline demographic and clinical characteristics (5). In the total sample, I-CGI-C LSM scores at Week 12 (primary outcome variable) were 2.83 for the gradual- and 2.84 for the immediate-switch groups (LSM difference -0.012, CI -0.232, 0.208), indicating clinical improvement for both groups but no difference between groups. Incidence of adverse events (AEs) was similar in both switch groups.

Initial 2-Week Outcomes

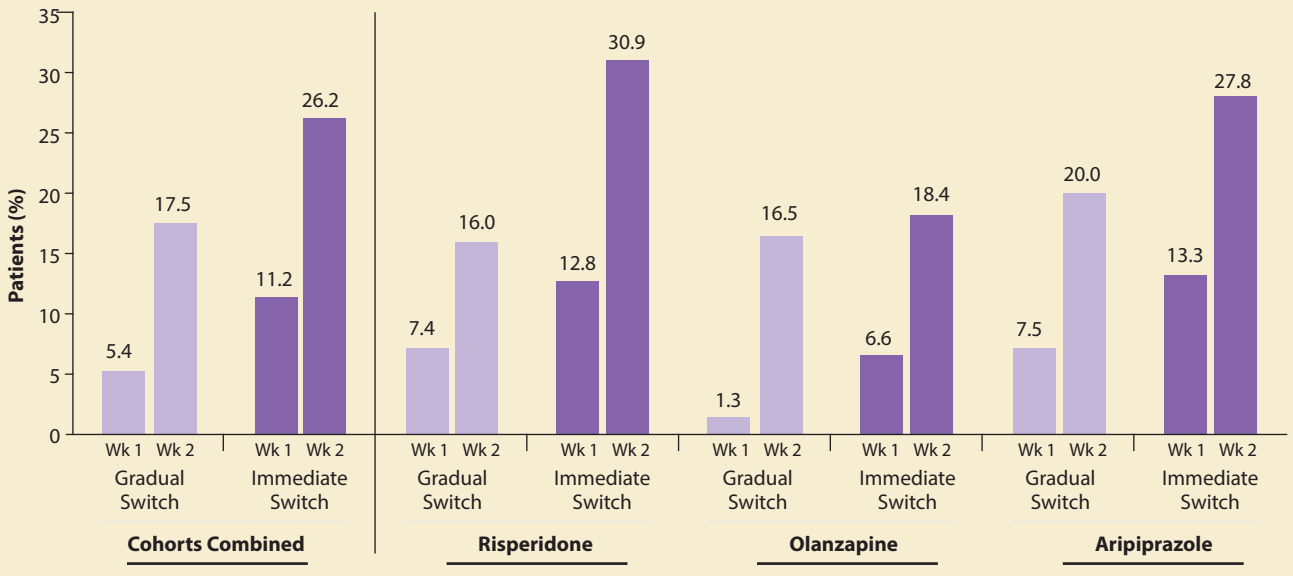
Global improvements were observed in the first two weeks (see Figure 2), as noted by categorical changes in I-CGI-C scores: percentages of patients with a rating of much or very much improved (i.e., the top two improvement categories) were 5.4% (Week 1) and 17.5% (Week 2) in the gradual-switch group and 11.1% (Week 1) and 26.1% (Week

Figure 1 Study Design



*At randomization. †Iloperidone initiated on Day 1 as per up-titration schedule. AP=antipsychotic.

Figure 2 Initial 2-Week Outcomes: I-CGI-C Responders*



*Defined as a rating of much or very much improved. I-CGI-C=Integrated Clinical Global Impression of Change.

2) in the immediate-switch group (12). Advantage for immediate vs. gradual switching evidenced an effect size of a NNT of 18 (CI 10–108) at Week 1 and a NNT of 12 (CI 7–71) at Week 2. Outcomes for the different cohorts (i.e., switched from risperidone, olanzapine, or aripiprazole) were numerically similar. Conversely, the percentage of patients with a rating of much or very much worse were 0.8% (Week 1) and 0.8% (Week 2) in the gradual-switch group and 3.1% (Week 1) and 4.2% (Week 2) in the immediate-switch group (NNT for avoiding worsening was 30 [CI 17–141] at Week 2, demonstrating an advantage for the gradual-switch group).

Over the first two weeks of iloperidone treatment, discontinuations for any reason occurred in 8.7% of patients in the gradual-switch group vs. 10.0% in the immediate-switch group (12, 13). Discontinuations due to AEs were higher for the immediate-switch group compared with the gradual-switch group (10.8% vs. 5.4%, respectively, NNT 19, CI 10–151). Discontinuations due to AEs were higher in Week 1 vs. Week 2 in both switch groups (gradual switch, 4.6% vs. 0.9%; immediate switch, 6.9% vs. 4.0%), as well as for each cohort (risperidone, 4.0% vs. 3.0%; olanzapine, 5.8% vs. 2.0%; aripiprazole, 7.6% vs. 2.5%). Discontinuation due to AEs remained at low rates beyond Week 2 as well (14); over the course of the entire 12-week study, AEs led to study discontinuation in 10.4% of patients in the gradual-switch group and 15.0% in the immediate-switch group (5).

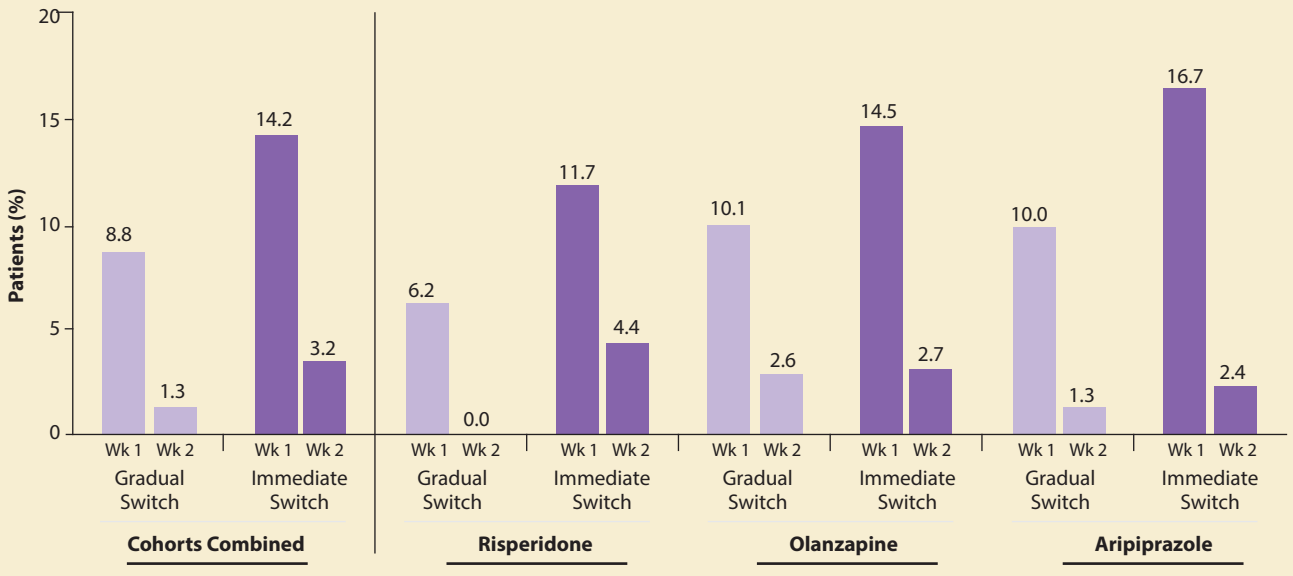
Incidence of AEs in general was higher during Week 1 vs. Week 2 for both groups (gradual switch, 46.7% vs. 26.4%; immediate switch, 52.3% vs. 29.7%). Overall, during the first week of iloperidone treatment, patients who switched from risperidone had the lowest incidence of AEs (40.6% of patients) compared with those who switched from olanzapine (52.3%) or aripiprazole (56.5%), yielding NNT advantages for where the pre-switch medication was risperidone vs. olanzapine (NNT 9, CI 5–102), and vs. aripiprazole (NNT 7, CI 4–19). Table 1 lists the most common AEs for Weeks 1 and 2.

Dizziness (see Figure 3) was the most common AE associated with iloperidone switch and incidence of dizziness was lower in the gradual-switch group (8.8%) vs. the immediate-switch group (14.2%) group during Week 1. In Week 2, both switch groups demonstrated a decline from Week 1 rates (gradual switch, 1.3%; immediate switch, 3.2%). During Week 1, discontinuations due to dizziness occurred most frequently in patients who immediately (vs. gradually) switched from aripiprazole (5.6% vs. 0%) or risperidone (1.1% vs. 0%) compared with olanzapine (1.3% for both switch methods). Overall, numerically fewer discontinuations due to dizziness occurred during Week 2.

In general, rates of orthostatic hypotension were low. Across the entire 12-week study period, there were 2.6% patients with orthostatic hypotension, including 1.7% from the gradual-switch group and 3.5% in the immediate-switch group.

Thus, switching from risperidone, olanzapine, or aripiprazole to iloperidone either gradually or immediately demonstrated subtle clinical differences regarding clinical response within the first 2 weeks of therapy. Whereas a gradual switch (i.e., cross-titration) revealed lower initial rates of dizziness, an immediate switch appeared to yield a higher

Figure 3 Initial 2-Week Outcomes: Dizziness as a TEAE*



*Includes postural dizziness. TEAE=treatment-emergent adverse event.

percentage of responders within the first 2 weeks. Incidence of overall AEs and discontinuations due to AEs decreased over the first 2 weeks of iloperidone treatment, regardless of prior antipsychotic.

Rates of Response over 12 Weeks

In this analysis, percentage of responders (I-CGI-C score <4) was summarized by visit and dosage range (12–16 mg/day and 20–24 mg/day, based on the most frequent dose taken during the treatment period) for the three cohorts (risperidone, olanzapine, and aripiprazole) combined and separately (15). For the three cohorts (risperidone, olanzapine, aripiprazole) combined at Week 12, in the gradual-switch group, 76.2% (96/126) of patients in the iloperidone 12–16 mg dose group and 86.2% (75/87) in the iloperidone 20–24 mg dose group were responders; in the immediate-switch group, 85.0% (125/147) and 83.8% (62/74), respectively, were responders.

Patterns of change in percent responders over the 12-week period differed between switch groups and iloperidone dose range (see Figure 4). For the individual cohorts, changes in response to iloperidone between switch groups within each dose group were similar to that of the 3 cohorts combined, with some noteworthy variation. For the individual cohorts, responder rates at Week 12 ranged between 73.7% (for olanzapine to iloperidone 12–16 mg/day, gradual switch) and 95.7% (for aripiprazole to iloperidone 20–24 mg/day, immediate switch); comparing these two extremes yields a NNT of 5 (CI 3–18).

Overall, at Week 12, iloperidone response rates were similar regardless of switch approach or iloperidone dose. Because of the flexible-dose design of the study, persons with an increase in dose may represent those with symptoms that are more difficult to treat and, hence, less likely to be classified as a responder, particularly in the first 4 weeks of the study. For the combined cohorts, between 76% and 86% of the patients responded over the 12 weeks of the study.

Shifts in Metabolic Variables

The tolerability profile of iloperidone is noteworthy in terms of modest weight gain and glucose elevation, and minor changes in lipids (3, 4). Measures of body weight, and fasting lipids and glucose, were obtained in this study (5, 16) and are summarized in Table 2. Findings for the gradual- and immediate-switch groups were generally similar, with the exception of the proportion with shifts from baseline to Week 12 in high-density lipoprotein (16.9% and 7.4% for the gradual- and immediate-switch groups, respectively, NNT 11, CI 6–50).

In summary, the proportions of patients who experienced metabolic shifts following a switch to iloperidone from risperidone, olanzapine, or aripiprazole were between 0% and 16.9%, depending on the metabolic variable and switch strategy, and were consistent with data in the product label, with weight gain being somewhat less than previously reported (3).

Ethnicity

Clinical outcomes and tolerability of iloperidone treatment in Caucasian and African-American patients were examined (17). Of the 500 randomized subjects, 190 (38.0%)

Table 1 Most Common TEAEs within the First Two Weeks*

TEAE, % (n)	Cohorts Combined				Risperidone			
	Gradual		Immediate		Gradual		Immediate	
	Wk 1 (n=240)	Wk 2 (n=231)	Wk 1 (n=260)	Wk 2 (n=249)	Wk 1 (n=81)	Wk 2 (n=78)	Wk 1 (n=94)	Wk 2 (n=91)
Total TEAEs	**46.7 (112)**	**26.4 (61)**	**52.3 (136)**	**29.7 (74)**	**39.5 (32)**	**15.4 (12)**	**41.5 (39)**	**35.2 (32)**
Dizziness†	8.8 (21)	1.3 (3)	14.2 (37)	3.2 (8)	6.2 (5)	0	11.7 (11)	4.4 (4)
Dry mouth	9.2 (22)	2.2 (5)	13.1 (34)	4.0 (10)	3.7 (3)	1.3 (1)	8.5 (8)	4.4 (4)
Fatigue	4.2 (10)	0.4 (1)	2.7 (7)	1.6 (4)	3.7 (3)	0	2.1 (2)	1.1 (1)
Insomnia‡	3.3 (8)	2.2 (5)	6.5 (17)	0.4 (1)	2.5 (2)	0	6.4 (6)	1.1 (1)
Nasal congestion	4.2 (10)	0.9 (2)	1.9 (5)	0.4 (1)	2.5 (2)	0	0	1.1 (1)
Nausea	4.2 (10)	0.4 (1)	4.2 (11)	0.8 (2)	1.2 (1)	0	1.1 (1)	2.2 (2)
Palpitations	1.3 (3)	0.4 (1)	3.8 (10)	0.4 (1)	1.2 (1)	0	2.1 (2)	1.1 (1)
Sedation	3.8 (9)	1.7 (4)	3.8 (10)	2.8 (7)	3.7 (3)	0	3.2 (3)	2.2 (2)
Somnolence	5.8 (14)	0.9 (2)	4.6 (12)	2.0 (5)	6.2 (5)	1.3 (1)	5.3 (5)	2.2 (2)
Weight increased	2.9 (7)	0.9 (2)	1.9 (5)	0.4 (1)	2.5 (2)	0	0	0

TEAE, % (n)	Olanzapine				Aripiprazole			
	Gradual		Immediate		Gradual		Immediate	
	Wk 1 (n=79)	Wk 2 (n=77)	Wk 1 (n=76)	Wk 2 (n=73)	Wk 1 (n=80)	Wk 2 (n=76)	Wk 1 (n=90)	Wk 2 (n=85)
Total TEAEs	**41.8 (33)**	**39.0 (30)**	**63.2 (48)**	**20.5 (15)**	**58.8 (47)**	**25.0 (19)**	**54.4 (49)**	**31.8 (27)**
Dizziness†	10.1 (8)	2.6 (2)	14.5 (11)	2.7 (2)	10.0 (8)	1.3 (1)	16.7 (15)	2.4 (2)
Dry mouth	11.4 (9)	3.9 (3)	11.8 (9)	4.1 (3)	12.5 (10)	1.3 (1)	18.9 (17)	3.5 (3)
Fatigue	1.3 (1)	1.3 (1)	3.9 (3)	0	7.5 (6)	0	2.2 (2)	3.5 (3)
Insomnia‡	3.8 (3)	5.2 (4)	11.8 (9)	0	3.8 (3)	1.3 (1)	2.2 (2)	0
Nasal congestion	1.3 (1)	0	0	0	8.8 (7)	2.6 (2)	5.6 (5)	0
Nausea	6.3 (5)	1.3 (1)	6.6 (5)	0	5.0 (4)	0	5.6 (5)	0
Palpitations	2.5 (2)	0	5.3 (4)	0	0	1.3 (1)	4.4 (4)	0
Sedation	1.3 (1)	3.9 (3)	2.6 (2)	2.7 (2)	6.3 (5)	1.3 (1)	5.6 (5)	3.5 (3)
Somnolence	5.1 (4)	1.3 (1)	3.9 (3)	0	6.3 (5)	0	4.4 (4)	3.5 (3)
Weight increased	1.3 (1)	1.3 (1)	0	0	5.0 (4)	1.3 (1)	5.6 (5)	1.2 (1)

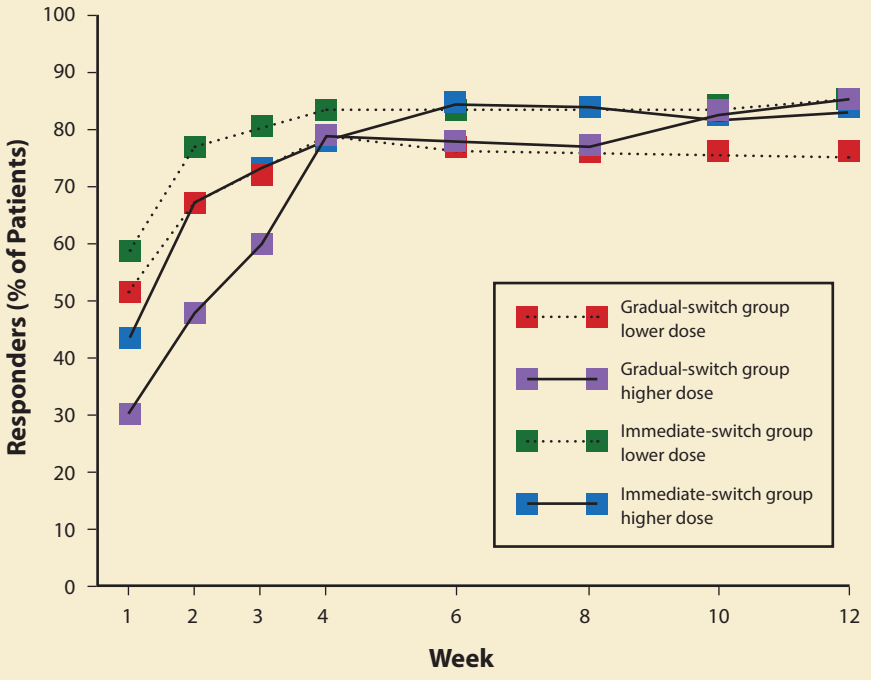
*≥5% for Week 1 or Week 2 in either switch group in the risperidone, olanzapine, or aripiprazole cohorts.
†Includes postural dizziness. ‡Includes initial insomnia. TEAE=treatment-emergent adverse event.

were Caucasian (gradual switch, n=84; immediate switch, n=106) and 283 (56.6%) were African American (gradual switch, n=139; immediate switch, n=144). Baseline characteristics were similar for Caucasian and African-American patients with the exception of fasting triglyceride levels, which were higher in the former group (mean 152.6 mg/dL [Caucasian] and 113.1 mg/dL [African American]).

I-CGI-C scores at Week 12 were similar in Caucasian and African-American patients, regardless of switch approach. In the Caucasian subgroup, LSM scores at Week 12 were 2.98 for the gradual- and 2.91 for the immediate-switch groups (LSM difference 0.071, CI -0.32, 0.47); in the African-American subgroup, scores were 2.73 and 2.85, respectively (LSM difference -0.114, CI -0.40, 0.17).

The most common AEs were dizziness and dry mouth for the Caucasian subgroup (14.3% and 17.9%, respectively [gradual switch] and 27.4% and 24.5%, respectively [immediate switch]) and for the African-American subgroup (18.7% and 18.1% [gradual switch] and 20.8% and 18.1% [immediate switch]). A greater proportion of patients in the Caucasian subgroup discontinued due to AEs than in the African-American subgroup (21.1% [40/190] vs. 7.8% [22/283]), producing a NNT of 8 (CI 5–15). In the Caucasian subgroup the most common AEs leading to discontinuation were dizziness and insomnia (each n=2) in the gradual-switch group and dizziness (n=7) in the immediate-switch group. In the African-American subgroup, in the gradual-switch group, no AE leading to discontinuation occurred in

Figure 4 Response Rates by Switch Group and Dose Group from Week 1 to Week 12 for All Cohorts Combined



Number of Responders

	Gradual-switch group		Immediate-switch group	
	Lower dose	Higher dose	Lower dose	Higher dose
Wk 1	66	26	86	32
Wk 2	85	42	113	50
Wk 3	91	52	118	54
Wk 4	100	69	123	58
Wk 6	97	68	124	63
Wk 8	96	67	123	62
Wk 10	96	72	124	61
Wk 12	96	75	125	62

Note: A responder was defined as having an I-CGI-C score <4. Lower dose and higher dose were defined as iloperidone 12–16 mg/day and 20–24 mg/day, respectively. I-CGI-C=Integrated Clinical Global Impression of Change.

>1 patient; in the immediate-switch group, dizziness (n=3) was the most common AE leading to discontinuation.

Mean (standard deviation) weight gain from baseline to Week 12 was 0.9 (3.6) kg and 0.8 (4.0) kg, for Caucasian and African-American patients, respectively. For Caucasian and African-American patients, there were no clinically relevant changes from baseline to Week 12 in fasting metabolic measures. Despite differences between the ethnic subgroups in baseline triglyceride levels, iloperidone did not meaningfully alter these values (Caucasian, mean 152.6 mg/dL [baseline] and 151.3 mg/dL [Week 12]; African American, mean 113.1 mg/dL [baseline] and 124.6 mg/dL [Week 12]).

In summary, other than a greater proportion of patients in the Caucasian subgroup discontinuing due to AEs than in the African-American subgroup, there were no substantive differences in clinical outcomes or tolerability (including metabolic variables) between the Caucasian and African-American subgroups in this study.

Trajectory of Improvement

Improvement was relatively steady throughout the study for both gradual- and immediate-switch groups for the I-CGI-C, starting at Week 1 and continuing weekly through Week 12 (see Figure 5) (18). Trajectories for the E-CGI-S, ST-CGI-S, and I-CGI-S were similar. For the three cohorts combined, differences in scores between treatment groups were not clinically meaningful at any time point for any of these variables. Similarly, for the individual cohorts, improvements were similar and differences in scores between treatment groups were generally not clinically meaningful.

Switching because of Efficacy

We examined the clinical outcomes for those patients whose reason for switch was inadequate efficacy (19-21).

Of the randomized subjects, 170 were switched from aripiprazole. Among the 123 patients who switched due to efficacy, LSM change from baseline to Week 12 scores on the E-CGI-S improved by -0.84 for the gradual- and -0.99 for the immediate-switch group (mean baseline score: 4.3 for each group). Switching immediately from aripiprazole to iloperidone conferred higher percentages of patients exhibiting much or very much improved scores on the I-CGI-C assessing clinical outcomes over the first 4 weeks (10.6%, 25.8%, 33.3%, and 45.5%, at Weeks 1, 2, 3, and 4, respectively) compared with the gradual-switch group (5.3%, 10.5%, 19.3%, and 31.6%, at Weeks 1, 2, 3, and 4, respectively), yielding

Table 2 Metabolic Variables

Outcome	Gradual-Switch Group	Immediate-Switch Group
Mean (standard deviation) changes from baseline to Week 12		
Body weight (kg)	+0.9 (3.94)	+0.8 (3.59)
Glucose (mg/dL)	+7.7 (26.69)	+7.5 (32.79)
Total cholesterol (mg/dL)	−0.4 (29.58)	−4.3 (33.67)
Low-density lipoprotein (mg/dL)	−3.2 (25.37)	−1.0 (24.47)
High-density lipoprotein (mg/dL)	−0.8 (9.73)	−0.6 (8.79)
Triglycerides (mg/dL)	+14.8 (70.32)	−6.3 (97.49)
Proportion with shifts from baseline to Week 12		
Body weight ≥7% increase	9.6%	7.7%
Glucose <100 mg/dL to ≥126 mg/dL	11.1%	7.5%
Total cholesterol <200 mg/dL to ≥240 mg/dL	1.6%	2.9%
Low-density lipoprotein <100 mg/dL to ≥160 mg/dL	0	1.4%
High-density lipoprotein ≥40 mg/dL to <40 mg/dL	16.9%	7.4%
Triglycerides <150 mg/dL to ≥200 mg/dL	8.8%	8.8%

a NNT value at Week 2 of 7, CI 4–49. Conversely, patients exhibiting much or very much worsening on the I-CGI-C over the first 4 weeks were 1.5% for each week for the immediate-switch group, and 1.8%, 0%, 1.8%, 3.5% per respective week in the gradual-switch group.

Of the randomized subjects, 175 were switched from risperidone. Among the 98 patients who switched due to efficacy issues, LSM change from baseline to Week 12 scores on the E-CGI-S improved by -0.95 for the gradual- and -1.14 for the immediate-switch group (mean baseline scores: 4.2 and 4.4, respectively). Switching immediately from risperidone to iloperidone conferred higher percentages of patients exhibiting much or very much improved scores on the I-CGI-C assessing clinical outcomes compared to a gradual switch, with the largest percentage difference observed at Week 4, 52.8% vs. 24.4%, yielding a NNT of 4 (CI 3–10). Conversely, patients exhibiting much or very much worsening on the I-CGI-C over the first 4 weeks were not reported in the gradual-switch group, and were reported in 3.8% to 7.5% of patients in the immediate-switch group.

Of the randomized subjects, 155 were switched from olanzapine. Among the 76 patients who switched due to efficacy, LSM change from baseline to Week 12 scores on the E-CGI-S improved by -0.85 for the gradual- and -0.73 for the immediate-switch group (mean baseline scores: 4.4 and 4.3, respectively). In contrast to what was observed with switching from aripiprazole or risperidone, switching either gradually or immediately from olanzapine to iloperidone resulted in a similar percentage of patients much or very much improved at each week of iloperidone treatment (Week 1: 0% and 6.3%, Week 2: 18.2% and 18.8%; Week 3: 27.3% and 21.9%; Week 4: 27.3% and 25%, respectively). Conversely, patients exhibiting much or very much worsening on the I-CGI-C over the first 4 weeks were reported in the gradual-switch group for up to 2.3% of patients, and were reported in 3.1% of patients at each week in the immediate-switch group.

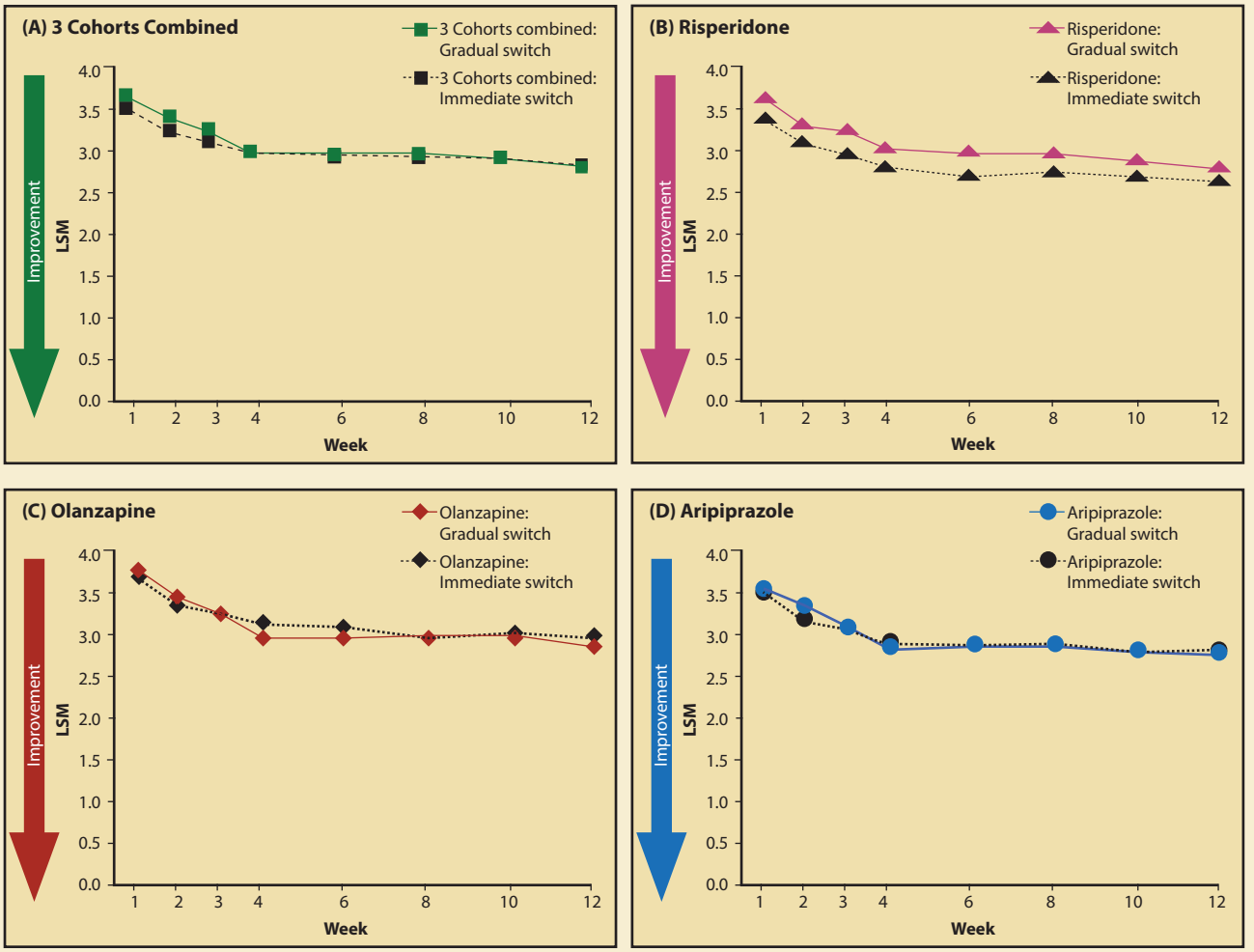
Thus, in general, when reason for switch was efficacy, efficacy rating improvements occurred. This was observed when switching to iloperidone either immediately or gradually, from aripiprazole, risperidone, or olanzapine.

Switching because of EPS

From the available data, iloperidone is indistinguishable from placebo in terms of EPS and akathisia (3, 4). Given this, a relevant clinical question is whether or not an EPS reason for switch from current therapy affects tolerability (19-21). In general, switching to iloperidone from aripiprazole, risperidone, or olanzapine, either immediately or gradually, revealed improvements in the previous EPS issues, based on ST-CGI-S scores and few AE reports.

Of the 25 randomized subjects switched from aripiprazole because of EPS-related issues, the only reported EPS-related adverse events over 12 weeks were anxiety (potentially confused for akathisia) (n=3) in the gradual-switch group and dyskinesia (n=1) in the immediate-switch group. Of the 29 subjects switched from risperidone because of EPS-related issues, the only reported EPS-related adverse events

Figure 5 Change (LSM) in I-CGI-C Scores by Switching Approach over Time for (A) Cohorts Combined, (B) Risperidone, (C) Olanzapine, and (D) Aripiprazole



I-CGI-C=Integrated Clinical Global Impression of Change, LSM=least-squares mean.

over 12 weeks were dyskinesia (n=1) and anxiety (n=2) in the immediate-switch group, with none in the gradual-switch group. Of the 17 subjects switched from olanzapine because of EPS-related issues, the only reported EPS-related adverse events over 12 weeks were restlessness (n=1) in the gradual-switch group and extrapyramidal disorder, agitation, and anxiety (each n=1) in the immediate-switch group.

In summary, switching to iloperidone from aripiprazole, risperidone, or olanzapine, either immediately or gradually, because of EPS, revealed overall improvements in the previous EPS issues.

Switching because of Somnolence/Sedation

Rates of somnolence/sedation with iloperidone are modest (3, 4). Clinically relevant somnolence/sedation is a commonly encountered side effect of many antipsychotic medications, and may trigger a switch in treatment, such as to iloperidone (22).

Of the 500 randomized subjects, 53 (10.6%) switched primarily due to somnolence/sedation (gradual switch, n=26; immediate switch, n=27) from risperidone (n=24), olanzapine (n=23), and aripiprazole (n=6). Among these patients, LSM I-CGI-C score at Week 12 was 2.88 for the gradual-switch and 2.41 for the immediate-switch group.

The most commonly reported AEs over 12 weeks were dizziness (30.8%) and dry mouth and headache (both 19.2%) in the gradual-switch group and dizziness (25.9%) and dry mouth and somnolence (both 18.5%) in the immediate-switch group. Somnolence was reported as an AE by a total of 8/53 (15.1%) patients (gradual switch, n=3; immediate switch, n=5) and 1 patient (immediate-switch group,

risperidone cohort) discontinued due to somnolence in this subgroup. LSM change scores for the ST-CGI-S were -1.42 and -1.72, demonstrating an improvement from baseline (mean baseline score: 3.7 and 3.9).

Thus, in patients who switched from their prior treatment due to somnolence/sedation, efficacy rating improvements and a positive safety/tolerability profile were observed upon switching either gradually or immediately to iloperidone. Somnolence was reported by 15% of patients within this subgroup over the 12 weeks of iloperidone treatment.

Switching because of Weight Gain

Patients with schizophrenia often change antipsychotics due to tolerability issues, with weight gain a common reason for switching (23).

Of the 500 randomized subjects, 77 (15.4%) switched due to weight gain (gradual switch, n=35; immediate switch, n=42) from risperidone (n=22), olanzapine (n=39), and aripiprazole (n=16). Mean (SD) weight and body mass index (BMI) at baseline were 101.3 (27.9) kg and 34.3 (7.7) kg/m^2 for the gradual-switch and 101.8 (25.3) kg and 35.1 (10.8) kg/m^2 for the immediate-switch groups. Baseline mean weights for patients in the olanzapine cohort (95.0 kg for the gradual-switch group and 94.2 kg for the immediate-switch group) were lower than for those switched from risperidone or aripiprazole, where mean weights ranged from 102.5 kg to 114.8 kg, depending on the switch group. Similarly, baseline BMIs in the olanzapine cohort (32.6 kg/m^2 for the gradual-switch group and 31.2 kg/m^2 for the immediate-switch group) were lower than for those switched from risperidone or aripiprazole, where mean BMIs ranged from 35.5 kg/m^2 to 40.3 kg/m^2, depending on the switch group.

Weight gain was reported as an AE by 2/77 (2.6%) patients (gradual switch, n=1; immediate switch, n=1; both in the olanzapine cohort) and no patients discontinued due to weight gain in this subgroup. Mean (SD) weight gain from baseline to Week 12 was 0.7 (2.9) kg and 0.4 (3.7) kg, respectively, and 1/35 (2.9%) and 2/41 (4.9%) patients experienced weight gain ≥7% (ns when comparing switch groups). Additional categorical changes in weight are listed in Table 3, including weight loss.

Thus, in patients switching to iloperidone from prior treatment due to weight gain, patients' weight exhibited negligible change from baseline, with no discontinuations because of weight gain, and 3/76 (3.9%) experiencing weight gain ≥7% from baseline.

Discussion

As concluded in the primary study report (5), switching to iloperidone from risperidone, olanzapine or aripiprazole, either immediately or gradually, appears safe and well tolerated.

AEs leading to discontinuation of iloperidone ranged from 7% to 18% of patients depending on the switch strategy and cohort. In general, discontinuations due to AEs were somewhat higher for the immediate-switch group compared with the gradual-switch group (NNT 19). This is partly driven by the AE of dizziness. The incidence of dizziness and resultant discontinuations in the gradual-switch group may have been lower than in the immediate-switch group due to alpha-1 receptor habituation from the pre-switch agent (24). Thus, although both switch approaches are appropriate when switching to iloperidone from risperidone, olanzapine, or aripiprazole, a gradual-switch approach may confer a slight advantage related to tolerability and adherence by minimizing the potential for exposure-related transient dizziness. This needs to be placed into context with additional data noting that there was a small advantage for a rating of much or very much improved on the I-CGI-C score for immediate vs. gradual switching, with a NNT of 18 at Week 1 and a NNT of 12 at Week 2.

No differences at Week 12 were observed when examining responder rates (I-CGI-C score <4) for the different switch strategies and cohorts for patients whose most common dose was 12–16 mg/day vs. 20–24 mg/day. However, the trajectory of achieving response did demonstrate some differences: patients whose most common dose was 20–24 mg/day had lower rates of response earlier in the study, presumably when they were receiving lower doses. Because iloperidone was flexibly dosed and patients receiving higher doses may actually be more symptomatic and more difficult to treat, dose response could not be assessed as would be possible using a fixed-dose trial design (25).

Changes in metabolic variables were similar to that described in product labeling (3). Although iloperidone's impact on metabolic variables is modest, and although iloperidone has advantages over some other agents such as olanzapine (26), routine monitoring of metabolic variables is recommended (3).

Ethnicity does not appear to impact on overall response or tolerability of iloperidone when patients are switched from risperidone, olanzapine, or aripiprazole. There were no clinically relevant differences in changes in metabolic variables. However, a greater proportion of patients in the Caucasian subgroup discontinued due to AEs than in the African-American subgroup (NNT 8). This may be a chance finding, and further studies examining tolerability differences with iloperidone among different ethnic groups may be helpful.

Switching to iloperidone because of efficacy reasons resulted in clinical improvement over time, with little in the way of differences between switch strategies under most sce-

narios. This finding is not unusual for open-label switch studies where there is an inherent expectation bias for improvement based on dissatisfaction with the prior treatment. The lack of a comparative control further limits interpretability.

Table 3 Weight Change in Patients Switched to Iloperidone because of Weight Gain* in Patients with a Post-Baseline Weight Measurement

Patients, n (%)	Gradual Switch	Immediate Switch
Cohorts Combined	**n=32 (%)**	**n=40 (%)**
Weight gain		
0 to ≤2 kg	8 (25.0)	9 (22.5)
>2 to ≤5 kg	6 (18.8)	6 (15.0)
>5 to ≤10 kg	3 (9.4)	4 (10.0)
Weight loss		
0 to <5 kg	14 (43.8)	18 (45.0)
≥5 to <10 kg	1 (3.1)	3 (7.5)
Risperidone	**n=10 (%)**	**n=11 (%)**
Weight gain		
0 to ≤2 kg	1 (10.0)	5 (45.5)
>2 to ≤5 kg	5 (50.0)	1 (9.1)
>5 to ≤10 kg	1 (10.0)	2 (18.2)
Weight loss		
0 to <5 kg	2 (20.0)	3 (27.3)
≥5 to <10 kg	1 (10.0)	0
Olanzapine	**n=15 (%)**	**n=20 (%)**
Weight gain		
0 to ≤2 kg	4 (26.7)	3 (15.0)
>2 to ≤5 kg	1 (6.7)	2 (10.0)
>5 to ≤10 kg	1 (6.7)	2 (10.0)
Weight loss		
0 to <5 kg	9 (60.0)	10 (50.0)
≥5 to <10 kg	0	3 (15.0)
Aripiprazole	**n=7 (%)**	**n=9 (%)**
Weight gain		
0 to ≤2 kg	3 (42.9)	1 (11.1)
>2 to ≤5 kg	0	3 (33.3)
>5 to ≤10 kg	1 (14.3)	0
Weight loss		
0 to <5 kg	3 (42.9)	5 (55.6)
≥5 to <10 kg	0	0

*In patients with a post-baseline weight measurement.

Switching to iloperidone because of EPS-related issues resulted in overall improvement in tolerability regarding EPS, as evidenced by very low AE rates related to EPS during the study, consistent with iloperidone's low propensity to cause EPS (3, 4). Switching to iloperidone because of somnolence/sedation resulted in efficacy rating improvements and a positive safety/tolerability profile upon switching either gradually or immediately. Somnolence was reported by 15% of patients within this subgroup over the 12 weeks of iloperidone treatment, consistent with product labeling which describes rates of somnolence with iloperidone 20–24 mg/day, iloperidone 10–16 mg/day, and placebo, to be 15%, 9%, and 5%, respectively.

Switching to iloperidone because of weight gain resulted in the observation of negligible change in weight from baseline, with a mean weight gain from baseline to Week 12 of 0.7 kg and 0.4 kg in the gradual- and immediate-switch groups, respectively. There were no discontinuations because of weight gain in this subgroup, and 3/76 (3.9%) experienced weight gain ≥7% from baseline. This subgroup of patients switching to iloperidone because of weight gain differed in terms of weight changes exhibited by the entire study population where, during the 12-week treatment period, there was a mean change in weight of approximately 0.8 kg and an increase in weight ≥7% occurred in 8.7% (43/492) of patients (5). The latter remains lower than the values reported in product labeling, where in four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in adult subjects, the proportion of subjects with ≥7% gain in body weight was 18%, 12%, and 4%, for iloperidone 20–24 mg/day, iloperidone 10–16 mg/day, and placebo, respectively (3).

As noted in the original report (5), the observed efficacy changes are reassuring in that if iloperidone is selected as a switch agent primarily for tolerability, it is likely that relative efficacy will be sustained, including switches from risperidone or olanzapine, which have ranked high in terms of relative efficacy when comparing antipsychotics (27).

Limitations include that patients in this study were considered to be reasonably adherent and were not treatment resistant, thus the results observed may not apply to patients who may be candidates for clozapine or who require treatment with a long-acting injectable antipsychotic. Although our sample size is relatively large, 500 subjects vs. the 240 to 311 subjects enrolled in similarly designed 6- to 8-week switch studies of lurasidone (28), aripiprazole (29), and ziprasidone (30), no extension beyond the 12 weeks was planned. When examining the different cohorts in our study, the numbers of subjects available for analysis get substantially smaller when reasons for switch are explored. Further evaluation of events of clinically meaningful prolonged ECG QTcF intervals were not performed beyond what is contained in the primary report (5) since events of QTcF >450 ms for men or >470 ms for women were infrequent, occurring in 8 (1.7%) patients, with no intervals >500 ms.

As already noted, dose response cannot be adequately ascertained using a flexible-dose design, and the open-label design and absence of a placebo control does not allow for an adequate assessment of treatment effect; improvement may be a function of time and/or the result of receiving care within the context of a structured clinical trial.

Conclusions

The overall pattern of results regarding ratings of efficacy and safety/tolerability outcomes after switching to iloperidone from risperidone, olanzapine, or aripiprazole, as observed in this study, suggests that iloperidone is an appropriate antipsychotic choice for adherent, nontreatment-resistant patients who are experiencing inadequate efficacy and/or poor tolerability with their current therapy. Clinicians should remain mindful of any withdrawal effects that can be encountered when abruptly switching from other antipsychotics.

Other than a few subtle clinical considerations, such as the incidence of noradrenergic alpha 1 receptor antagonism related dizziness, switching to iloperidone by either a gradual or immediate method did not generally reveal any relevant differences in ratings of overall efficacy and safety/tolerability outcomes. The observed outcomes are consistent with what has been previously reported regarding iloperidone's favorable EPS profile and modest impact on somnolence/sedation, body weight, and metabolic variables.

Acknowledgments

Funding for this study was provided by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, which contributed to the design of the study, collection and analysis of the data, and authorship of the manuscript. All authors contributed to and approved the final manuscript.

Author Disclosures

In the past 36 months Leslie Citrome has engaged in collaborative research with, or received consulting or speaking fees from Alexza, Alkermes, AstraZeneca, Avanir, Bristol-Myers Squibb, Eli Lilly, FORUM, Forest, Genentech, Janssen, Jazz, Lundbeck, Medivation, Merck, Mylan, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, Takeda, Teva, and Valeant. In the past 36 months Peter Weiden has engaged in collaborative research with, or received consulting or speaking fees from Alkermes, Delpor, FORUM, Forest, Genentech, Janssen, Lundbeck, Neurocrine, Otsuka, Reckitt Benckiser, Sunovion, and Vanda. In the past 36 months Gus Alva has engaged in collaborative research with, or received consulting or speaking fees from Accera, Forest, Otsuka, Pfizer, Novartis, Sunovion, Genentech, Tau Rx, FORUM, AstraZeneca, Takeda, Lundbeck, Janssen, Roche, Merck, and Neuroptix. In the past 36 months Ira Glick has engaged in collaborative research with, or received consulting or speaking fees from Otsuka, Pfizer, Novartis, Vanda, Takeda, Sunovion, Shire, Janssen, Alkermes, Lilly, Merck, and FORUM. In the past 36 months Richard Jackson has engaged in collaborative research with, or received consulting or speaking fees from Bristol-Myers Squibb, Eli Lilly, Forest, Otsuka, Novartis, Shire, Sunovion, Takeda, AstraZeneca, Lundbeck, Noven, Otsuka, and Pfizer. In the past 36 months Greg Mattingly has engaged in collaborative research with, or received consulting or speaking fees from Arbor, AstraZeneca, Corcept, Eli Lilly, FORUM, Forest, Glaxo Smith Kline, Janssen, Lundbeck, Merck, Novartis, Noven, Organon, Otsuka, Pfizer, Shire, Solvay, Sunovion, Takeda, Vanda, and Wyeth. Farid Kianifard, Xiangyi Meng, and Adam Winseck are full-time employees of Novartis Pharmaceuticals Corporation.

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