

Changes in weight and metabolic parameters following long-term iloperidone use: A meta-analysis of data from 9 Phase II and III trials of iloperidone*

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Received 10 September 2012; revised 9 October 2012; accepted 18 October 2012

ABSTRACT

Objective: To determine the impact of iloperidone treatment on metabolic parameters. **Methods:** Data were analyzed from 3210 patients who received iloperidone and 587 patients who received placebo for up to 2 years during 9 Phase II and Phase III studies (integrated safety database). Patients were pooled by most frequent iloperidone dose into 3 groups: 4 - 8 mg/d, 10 - 16 mg/d, and 20 - 24 mg/d. Laboratory data from 8 studies were random (fasting and non-fasting) while patients from 1 study (n = 447) were all sampled at fasting. **Results:** Mean (standard deviation [SD]) weight gain from baseline to endpoint was 2.1 (6.8) kg for all patients on iloperidone. Fasting mean (SD) total cholesterol changes from baseline to end of study were 8.2 (31.6) for iloperidone and -2.2 (35.2) mg/dL for placebo. Fasting mean (SD) triglyceride changes during this period were iloperidone: -0.83 (82.3); placebo: 16.5 (113.1) mg/dL. Fasting mean (SD) glucose changes were iloperidone: 6.6 (24.0); placebo: -0.05 (17.0) mg/dL from baseline to end of study. Glycosylated hemoglobin levels were unchanged following iloperidone treatment. **Conclusion:** These data suggest a metabolic profile for iloperidone of modest weight gain accompanied by small changes in lipids and glucose that are unlikely to be of clinical concern.

Keywords: Dyslipidemia; Glucose; Iloperidone; Long-Term; Metabolic; Weight

1. INTRODUCTION

Patients with schizophrenia have a higher rate of obesity and cardiovascular disease compared with the general population [1,2], and these co-morbidities may contribute to these patients' greater overall risk of sudden death [3,4]. In addition to the genetic and lifestyle factors that

can predispose patients with schizophrenia to disease, some antipsychotic medications are associated with weight gain and changes in glucose and lipids [5-7]. Each antipsychotic drug has a different metabolic profile, in part because of their unique receptor-binding patterns [8]. Monitoring patients' metabolic profile during antipsychotic drug use is therefore an important part of patient risk-management for the clinician, and the weight, glucose, and lipid profiles associated with specific antipsychotic agents should, among other factors, be taken into account when choosing agents [9].

Iloperidone is a mixed D₂/5-HT_{2A} antagonist atypical antipsychotic for the treatment of schizophrenia in adults. In this report, we describe changes in weight and other metabolic parameters associated with iloperidone treatment using data from the integrated safety database of over 3200 patients who received iloperidone.

2. METHODS

The full integrated safety database includes all adult patients enrolled in 9 clinical studies who received at least 1 dose of study drug—3210 patients were exposed to iloperidone during any phase of the studies (Tables 1 and 2) and the detailed methods and enrollment criteria for each study have been previously published in a series of articles [10-13]. A total of 1344 patients were exposed to iloperidone during the double-blind phase of 4 randomized, placebo-controlled studies (Studies 3000, 3004, 3005, and 3101); 281 patients were exposed to iloperidone during a long-term, active-control phase and/or an open-label extension phase of these studies; and 1585 patients were exposed to iloperidone during 5 active-controlled studies (Studies 2001, 2328, 3001, 3002, and 3003). Patients with a Diagnostic and Statistical Manual, 4th Edition (DSM-IV) [14] diagnosis of schizophrenia or schizoaffective disorder were exposed to iloperidone for up to 2 years. Patients were pooled according to their modal (most frequent) dose into 3 groups for analysis: iloperidone 4 - 8 mg/d, 10 - 16 mg/d, and 20 -

*Competing interests: All authors are employees of Novartis Pharmaceuticals Corporation.

Table 1. Clinical studies included in the integrated summary of safety.

Study	Study Design	Treatments	Subjects (N)	Publications
2001	6-Week randomized, DB, parallel-group, placebo- and active-controlled	Iloperidone (8 or 12 mg/d) Haloperidol (10 or 15 mg/d) Placebo	120	None
2328 ^a	Randomized, open-label, QT-interval safety study with up to 3 treatment periods, multicenter	Iloperidone (16 or 24 mg/d) Ziprasidone (160 mg/d) Quetiapine (750 mg/d)	183	None
3000	6-Week randomized, DB, parallel-group, placebo- and active-controlled	Iloperidone (4, 8, or 12 mg/d) Haloperidol (15 mg/d) Placebo	621	Potkin <i>et al.</i> , 2008; Weiden <i>et al.</i> , 2008
3001	6-Week randomized, DB, parallel-group, active-controlled, followed by a 46-week double-blind extension phase	Iloperidone (4 - 16 mg/d) Haloperidol (5 - 20 mg/d)	600	Kane <i>et al.</i> , 2008
3002	6-Week randomized, DB, parallel-group, active-controlled phase, followed by a 46-week double-blind extension phase	Iloperidone (4 - 16 mg/d) Haloperidol (5 - 20 mg/d)	557	Kane <i>et al.</i> , 2008
3003	6-Week randomized, DB, parallel-group, active-controlled phase, followed by a 46-week double-blind extension phase	Iloperidone (4 - 16 mg/d) Haloperidol (5 - 20 mg/d)	487	Kane <i>et al.</i> , 2008
3004	6-Week randomized, DB, parallel-group, placebo- and active-controlled	Iloperidone (4 - 8 mg/d or 10 - 16 mg/d) Risperidone (4 - 8 mg/d) Placebo	616	Potkin <i>et al.</i> , 2008 Weiden <i>et al.</i> , 2008
3005	6-Week randomized, DB, parallel-group, placebo- and active-controlled group	Iloperidone (12 - 16 mg/d or 20 - 24 mg/d) Risperidone m (6 - 8 mg/d) Placebo	706	Potkin <i>et al.</i> , 2008 Weiden <i>et al.</i> , 2008
3101	4-Week randomized, DB, parallel-group, placebo- and active-controlled	Iloperidone (24 mg/d) Ziprasidone (160 mg/d) Placebo	593	Cutler <i>et al.</i> , 2008

^aPatients treated during period 1 only (antipsychotic alone given at target dose for 5 days); DB = double blind.

Table 2. Patients exposed to iloperidone.

Studies	Iloperidone dose groups, patients, n			Placebo
	4 - 8 mg/d	10 - 16 mg/d	20 - 24 mg/d	
Phase 2				
2001	19	76	-	-
2328	6	31	69	-
Phase 3				
3000	265	131	-	127
3001	213	269	-	-
3002	172	304	-	-
3003	132	294	-	-
3004	240	142	-	155
3005	171	259	117	158
3101	7	27	266	147
Total N	1225	1533	452	587
Cumulative exposure, patient years	703.64	1245.39	72.52	41.71

24 mg/d. Patients were weighed and blood samples were obtained at baseline and periodically at study visits; standard laboratory chemistry was performed at pre-specified intervals. In one of the 9 studies (Study 3101),

blood samples were obtained at fasting, whereas other study protocols did not require that blood samples be obtained under fasting conditions. In all studies, changes in weight and laboratory parameters from baseline to various time points were summarized by iloperidone dose. In addition, in Study 3101, the number and percentage of patients transitioning from normal to high or low mean fasting lipid and glucose levels was determined.

3. RESULTS

Baseline characteristics for patients in the 9 studies are shown in **Table 3**.

3.1. Weight Change

Across all studies from baseline to endpoint, the overall mean (standard deviation [SD]) weight change was 2.1 (6.8) kg (n = 3075). In the 4 short-term, placebo-controlled studies, mean (SD) weight changes from baseline were 1.4 (3.8) kg, 2.0 (3.8) kg, and 2.7 (3.6) kg for patients receiving iloperidone 4 - 8 mg/d (n = 455), iloperidone 10 - 16 mg/d (n = 481), and iloperidone 20 - 24 mg/d (n = 391), respectively, and -0.1 (2.9) kg (n = 576) for those receiving placebo. A gain of $\geq 7\%$ of body weight during the placebo-controlled studies was reported in 11% of patients on iloperidone 4 - 8 mg/d, 12%

Table 3. Demographics and baseline characteristics of patients included in the integrated summary of safety.

Characteristic	Iloperidone dose groups, patients, n (%)			Placebo n = 587
	4 - 8 mg/d n = 1225	10 - 16 mg/d n = 1533	20 - 24 mg/d n = 452	
Sex				
Male	784 (64.0)	99 (64.8)	347 (76.8)	399 (68.0)
Female	441 (36.0)	540 (35.2)	105 (23.2)	188 (32.0)
Age, y, median (range)	37.0 (18 - 68)	37.0 (17 - 69)	40.0 (18 - 65)	40.0 (18 - 69)
Race				
Asian	172 (14.0)	259 (16.9)	29 (6.4)	19 (3.2)
Black/African American	248 (20.2)	200 (13.0)	187 (41.4)	222 (37.8)
White	706 (57.6)	876 (57.1)	215 (47.6)	306 (52.1)
Other	99 (8.1)	198 (12.9)	21 (4.6)	40 (6.8)
Age at diagnosis, y				
<18	209 (17.1)	252 (16.4)	67 (14.8)	104 (17.7)
18 - 24	498 (40.7)	680 (44.4)	199 (44.0)	253 (43.1)
25 - 44	471 (38.4)	555 (36.2)	172 (38.1)	201 (34.2)
45 - 65	37 (3.0)	29 (1.9)	9 (2.0)	19 (3.2)
>65	0	0	0	0
Missing	10 (0.8)	17 (1.1)	5 (1.1)	10 (1.7)
Previous hospitalization for psychosis				
Yes	1095 (89.4)	1369 (89.3)	415 (91.8)	564 (96.1)
No	129 (10.5)	162 (10.6)	34 (7.5)	20 (3.4)
Unknown	1 (0.1)	2 (0.1)	3 (0.7)	3 (0.5)

on 10 - 16 mg/d, and 18% on 20 - 24 mg/d (an overall mean of 14% of patients in the combined iloperidone dose groups) versus 4% of patients on placebo.

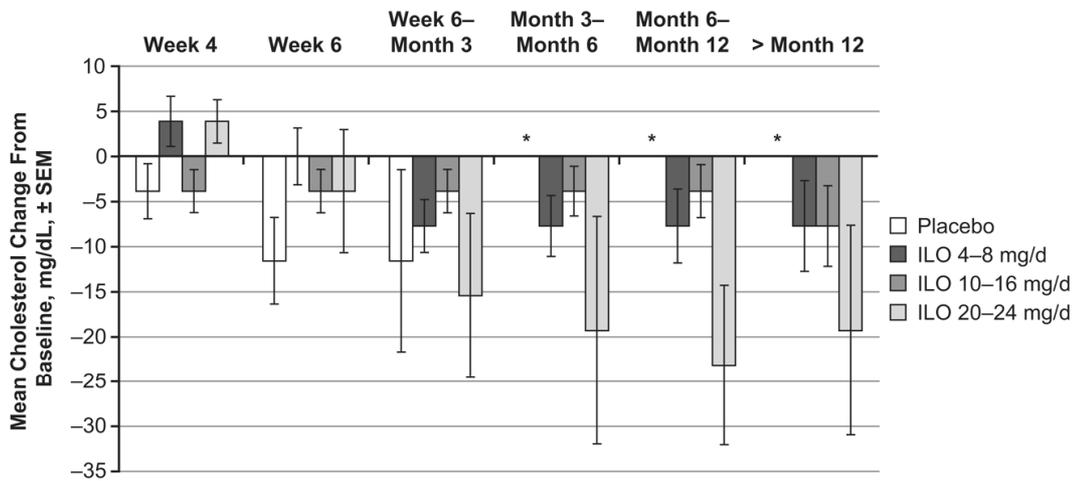
After 3 - 6 months of treatment, iloperidone in all studies was associated with a mean (SD) weight change from baseline of 2.8 (6.4) kg for the 4 - 8 mg/d dose group (n = 495), 3.0 (6.2) kg with 10 - 16 mg/d (n = 850), and 2.8 (7.2) kg with 20 - 24 mg/d (n = 33). From baseline to 6 - 12 months, weight changes were 3.1 (8.9) kg (n = 394), 3.4 (8.4) kg (n = 725), and 1.8 (9.6) kg (n = 31) for the 3 respective dose groups. From baseline to greater than 1 year of treatment, weight changes were 3.2 (10.4) kg (n = 231), 3.0 (9.3) kg (n = 425), and 1.5 (10.0) kg (n = 20) for these 3 respective dose groups.

3.2. Lipid Level Changes

During the first 4 weeks of the studies, mean cholesterol levels increased slightly from baseline (by less than 5 mg/dL) in the iloperidone 4 - 8 mg/d and 20 - 24 mg/d dose groups; however, at time points after Week 4, cholesterol levels were unchanged or decreased from baseline levels for all iloperidone dose groups (**Figure 1(a)**).

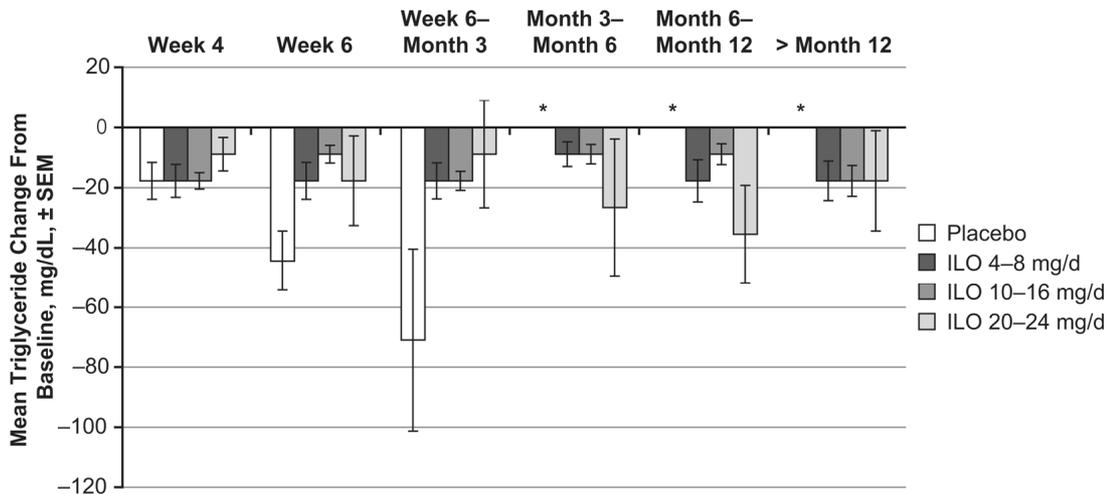
During the first 3 months of the studies (for which period placebo measurements were available), mean cholesterol changes from baseline were generally similar between iloperidone and placebo (-7.7 to 0.0 mg/dL for the combined iloperidone groups and -11.6 to -3.9 mg/dL for placebo). Mean triglycerides in the placebo group decreased from baseline between 17.7 and 70.9 mg/dL (**Figure 1(b)**). Mean triglyceride levels also decreased from baseline to all time points following iloperidone administration (-8.9 to -17.7 mg/dL for the combined iloperidone groups), and these changes were not dose dependent (**Figure 1(b)**).

In addition, fasting lipid levels were examined separately: these were available only for patients in the 4-week double-blind Study 3101 who received iloperidone 24 mg/d. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels were also measured in this study. Among patients receiving placebo in Study 3101, mean fasting total, LDL and HDL cholesterol levels were slightly decreased from baseline to end of study (2.2, 1.4 and 3.4 mg/dL, respectively), while mean triglyceride levels increased 16.5 mg/dL



Treatment	Baseline cholesterol, mg/dL	Patients, n					
		Week 4	Week 6	Week 6–Month 3	Month 3–Month 6	Month 6–Month 12	> Month 12
Placebo	108.4	293	142	29	0	0	0
ILO 4–8 mg/d	104.5	591	481	539	455	389	232
ILO 10–16 mg/d	112.2	985	860	940	783	726	428
ILO 20–24 mg/d	158.7	248	51	41	34	31	20

(a)



Treatment	Baseline triglycerides, mg/dL	Patients, n					
		Week 4	Week 6	Week 6–Month 3	Month 3–Month 6	Month 6–Month 12	> Month 12
Placebo	141.8	293	142	29	0	0	0
ILO 4–8 mg/d	124.0	591	481	538	455	388	232
ILO 10–16 mg/d	115.2	985	860	939	783	726	428
ILO 20–24 mg/d	150.6	248	51	41	34	31	20

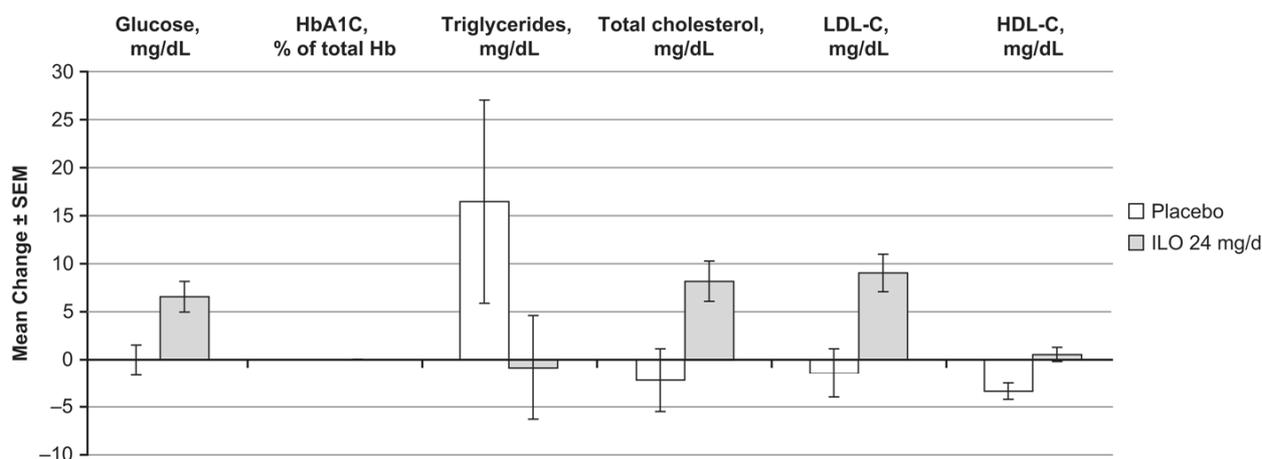
*Placebo data not available for these time points.
ILO, iloperidone; SEM, standard error of the mean.

(b)

Figure 1. Mean changes following iloperidone treatment in (a) cholesterol and (b) triglyceride levels from 9 pooled clinical trials.

(Figure 2). Among iloperidone recipients, fasting mean cholesterol and triglyceride level changes from baseline to end of study (8.2 mg/dL and -0.83 mg/dL, respectively) showed trends similar to those reported from baseline to Week 4 in fasting and nonfasting patients who received iloperidone 20 - 24 mg/d in all 9 studies (3.9 mg/dL and -8.9 mg/dL, respectively; Figures 1(a) and (b)). Mean LDL cholesterol levels increased from baseline to endpoint by 9.0 mg/dL, while mean HDL cholesterol levels increased by 0.55 mg/dL (Figure 2). An analysis of patients who shifted during the study from

normal to high total cholesterol, LDL cholesterol, or triglyceride levels, or from normal to low HDL cholesterol levels, was also performed (Table 4). The percentage of patients with a shift in total cholesterol levels was greater with iloperidone than with placebo but remained below 4%. About half as many patients experienced shifts in mean LDL and HDL cholesterol levels with iloperidone treatment compared with placebo treatment, while similar percentages of patients given iloperidone and placebo had an increase in triglyceride levels (Table 4).



Treatment	Baseline parameter, mean (SD)											
	n	Glucose, mg/dL	n	HbA1C, % of total Hb	n	Triglycerides, mg/dL	n	Total cholesterol, mg/dL	n	LDL cholesterol mg/dL	n	HDL cholesterol mg/dL
Placebo	114	96.0 (12.8)	98	5.8 (0.7)	114	139.9 (74.2)	114	188.3 (41.8)	109	111.8 (34.6)	114	47.5 (13.4)
ILO 24 mg/d	228	94.1 (12.9)	199	5.7 (0.6)	228	158.5 (108.7)	228	190.7 (45.1)	217	110.0 (37.9)	228	49.3 (16.2)

HbA1C = glycosylated hemoglobin A1C; HDL-C = high-density lipoprotein cholesterol; ILO = iloperidone; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation; SEM = standard error of the mean.

Figure 2. Endpoint changes in fasting mean glucose and lipid levels in Study 3101.

Table 4. Proportion of patients shifting from normal to high/low mean fasting laboratory values in Study 3101.

Laboratory parameter	Patients with shift n/n (%)	
	Iloperidone 24 mg/d	Placebo
Total cholesterol		
Normal (<200 mg/dL) to high (≥240 mg/dL)	5/141 (3.6)	1/72 (1.4)
LDL cholesterol		
Normal (<100 mg/dL) to high (≥160 mg/dL)	1/90 (1.1)	1/42 (2.4)
HDL cholesterol		
Normal (≥40 mg/dL) to low (<40 mg/dL)	20/166 (12.1)	19/80 (23.8)
Triglycerides		
Normal (<150 mg/dL) to high (≥200 g/dL)	15/148 (10.1)	6/72 (8.3)
Serum glucose		
Normal (<100 mg/dL) to high (≥126 mg/dL)	18/169 (10.7)	2/80 (2.5)

3.3. Glucose Level Changes

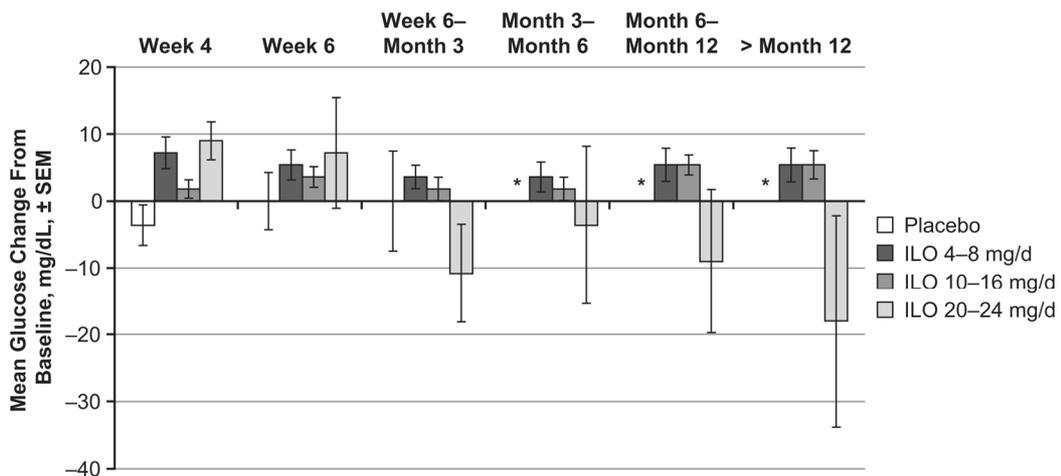
Patients receiving placebo experienced a decrease in fasting and nonfasting mean glucose of 3.6 mg/dL from baseline to Week 4 and no change from baseline at Week 6 and at 3 - 6 months (**Figure 3**). Among iloperidone-treated patients, mean glucose levels increased 5.4 mg/dL from baseline to Week 4 and between 1.8 and 5.4 mg/dL from baseline to time points after Week 6. Mean glucose levels for the iloperidone 20 - 24 mg/d group were increased 9.0 mg/dL from baseline to Week 4 then decreased between 3.6 and 18.0 mg/dL from baseline to time points after Week 6 (**Figure 3**).

Mean fasting glucose levels did not change from baseline to end of study (-0.05 mg/dL) in patients who received placebo. Patients who received iloperidone 24 mg/d experienced mean changes for fasting glucose from baseline to end of study similar to those changes experienced by patients who received iloperidone 20 - 24 mg/d across all 9 studies (6.6 and 9.0 mg/dL, respectively) (**Figures 2 and 3**). Mean glycosylated hemoglobin (hemoglobin A1C) levels (measured only in Study 3101) did not change from baseline to end of study (**Figure 2**). Shifts in mean fasting glucose levels from normal to high were experienced by 10.7% of patients on iloperidone 24 mg/d and by 2.5% of patients on placebo (**Table 4**).

4. DISCUSSION

Among more than 3200 patients participating in 9 Phase II and Phase III trials, iloperidone led to an average weight gain of about 2 kg following treatment for greater than 1 year, and most weight gain occurred within the first 6 weeks of the studies. Clinical study experience with iloperidone places it in the mid-range category for weight gain among atypical antipsychotic agents [5,7,9]. Weight gain in the placebo-controlled studies was lower than in long-term, comparator-controlled studies (2.0 kg versus 3.8 kg) (Data on file, Novartis) [10,11]. The mechanistic basis of weight gain with iloperidone is unknown, however iloperidone binds to serotonin 5-HT_{2A}, 5-HT_{2C}, and histamine H₁ receptors [15-18], which have been implicated in antipsychotic-associated weight gain [19].

Weight gain is often linked to changes in lipids and glucose, however, in this analysis the mid-range weight gain seen with iloperidone was accompanied by less substantial lipid and glucose changes. The uncoupling of changes in body weight or body mass index to changes in lipid levels has been observed in other studies [20-22]. A retrospective study of 94 patients on risperidone or olanzapine found that despite statistically significant increases in weight in both treatment groups, only pa-



Treatment	Baseline glucose, mg/dL	Patients, n					
		Week 4	Week 6	Week 6-Month 3	Month 3-Month 6	Month 6-Month 12	> Month 12
Placebo	111.6	288	141	29	0	0	0
ILO 4-8 mg/d	108.0	585	477	534	453	386	231
ILO 10-16 mg/d	106.2	963	853	933	773	723	425
ILO 20-24 mg/d	99.0	245	48	41	34	31	20

*Placebo data not available for these time points.
ILO, iloperidone; SEM, standard error of the mean.

Figure 3. Changes in fasting and nonfasting mean glucose levels in 9 pooled clinical trials of iloperidone.

tients on olanzapine showed significant increases in glucose and total cholesterol levels [22]. Weight gain was not correlated with change in glucose or lipids for either treatment group, on monotherapy with antipsychotics including olanzapine, clozapine, and sulpiride [20,22]. Data from the Study of Second-generation Antipsychotic Treatment Indications, Effectiveness, and Tolerability in Youth (SATIETY) also showed a contrast for patients, a finding shared by a study of Taiwanese inpatients on aripiprazole between worsening of body composition measurements and stability of metabolic parameters [21]. The physiologic basis for this disconnect remains unknown.

A limitation of the studies used in this analysis is that not all blood samples were taken at a fasting stage, thus the most abundant data are a mix of fasting and nonfasting values. Some clinicians have questioned the necessity of obtaining blood parameters at fasting, especially given that most people consume food throughout the day and are thus postprandial the majority of the time [23]. A study of lipid profiles over time in over 33,000 patients in the Copenhagen General Population Study indicated that maximum mean postprandial lipid changes were -0.2 mmol/L (-7.7 mg/dL) for total and LDL cholesterol, -0.1 mmol/L (-3.9 mg/dL) for HDL cholesterol, and 0.3 mmol/L (26.7 mg/dL) for triglycerides. Nonfasting lipids were predictive of later risk for cardiovascular disease [24].

Nonfasting total cholesterol and HDL cholesterol levels are considered acceptable for determination of risk for cardiovascular complications by the National Cholesterol Education Program Adult Treatment Panel (ATP) III, which recommends keeping fasting total cholesterol levels to below 200 mg/dL [25]. Although mean changes in fasting cholesterol of 8 mg/dL were observed during the 4-week study, nonfasting cholesterol measurements showed decreases from baseline to time points after Week 4, and neither short-term nor long-term treatment with iloperidone lead to development of high or borderline high cholesterol for the overall study population. Baseline fasting LDL and HDL cholesterol levels in Study 3101 were within normal limits and mean levels changed by 5 - 10 mg/dL following 4 weeks of treatment. With longer-term treatment (fasting or nonfasting) these levels continued to improve or remain the same. The magnitude of cholesterol change from baseline to Week 4 for nonfasted patients was similar to that for fasted patients. Although about 3.6% of patients on iloperidone experienced an increase from normal to high levels of fasting total cholesterol compared with 1.4% of patients on placebo, a lower frequency of patients on iloperidone versus placebo experienced low HDL cholesterol levels. In addition, 1.1% of patients on iloperidone shifted from normal to high levels of LDL cholesterol, a lower per-

centage than the 2.4% of patients whose LDL levels increased on placebo. High LDL cholesterol levels are considered the most reliable indicator of lifetime cardiovascular disease risk [25].

Fasting triglyceride levels <150 mg/dL are considered normal [25]. Mean fasting triglyceride levels were above normal at baseline (159 mg/dL) for the iloperidone group (though this group had a large amount of variation, with a standard deviation of 109 mg/dL) but not for the placebo group (140 mg/dL). Mean fasting triglyceride levels in the double-blind portion of Study 3101 and random fasting and nonfasting triglyceride levels in the 9 pooled trials decreased from baseline to all time points, indicating no impact in these populations. In addition, the percentage of patients who experienced an increase from normal to high triglyceride levels while taking iloperidone was similar to that observed among patients given placebo.

Development of type 2 diabetes remains a concern with second generation antipsychotics [26,27]. Approximately 11% of patients treated with iloperidone 24 mg/d in Study 3101 experienced an increase in fasting serum glucose levels from normal to high, compared with 3% of patients receiving placebo. Baseline random mean glucose levels (99 - 112 mg/dL) and baseline fasting mean glucose levels (94 mg/dL) were normal for all iloperidone-treatment groups, and mean increases from baseline of about 5 mg/dL in both the fasting and random glucose groups did not indicate an overall shift to diabetic levels. Similarly, mean levels of glycosylated hemoglobin were unchanged over the 4-week Study 3101.

5. CONCLUSION

These data indicate a metabolic profile for iloperidone of modest weight gain that was not associated with substantial changes in lipids and glucose.

6. ACKNOWLEDGEMENTS

The authors acknowledge Oxford PharmaGenesis, Inc., for editorial assistance with this manuscript, the funding for which was supported by Novartis Pharmaceuticals Corporation.

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