Pharmacogenomic Associations With Weight Gain in Olanzapine Treatment of Patients Without Schizophrenia

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ABSTRACT

Objective: Pharmacogenomic analyses of weight gain during treatment with second-generation antipsychotics have resulted in a number of associations with variants in ankyrin repeat and kinase domain containing 1 (*ANKK1*)/dopamine D2 receptor (*DRD2*) and serotonin 2C receptor (*HTR2C*) genes. These studies primarily assessed subjects with schizophrenia who had prior antipsychotic exposure that may have influenced the amount of weight gained from subsequent therapies. We assessed the relationships between single-nucleotide polymorphisms (SNPs) in these genes with weight gain during treatment with olanzapine in a predominantly antipsychotic-naive population.

Method: The association between 5 *ANKK1*, 54 *DRD2*, and 11 *HTR2C* SNPs and weight change during 8 weeks of olanzapine treatment was assessed in 4 pooled studies of 205 white patients with diagnoses other than schizophrenia who were generally likely to have had limited previous antipsychotic exposure.

Results: The A allele of *DRD2* rs2440390(A/G) was associated with greater weight gain in the entire study sample ($P = .0473$). Three *HTR2C* SNPs in strong linkage disequilibrium, rs6318, rs2497538, and rs1414334, were associated with greater weight gain in women but not in men ($P = .0032$, .0012, and .0031, respectively). A significant association with weight gain for 2 *HTR2C* SNPs previously reported associated with weight gain, −759C/T (rs3813929) and −697G/C (rs518147), was not found.

Conclusions: Associations between weight gain and *HTR2C* and *DRD2* variants in whites newly exposed to olanzapine may present opportunities for the individualization of medication selection and development based on differences in adverse events observed across genotype groups.

Trial Registration: ClinicalTrials.gov identifiers: Study A: NCT00088036, Study B: NCT00091650, Study C: NCT00094549, Study D: NCT00035321

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Weight gain is common during treatment with antipsychotics, including olanzapine. The mechanism(s) remain unclear, and weight gain is frequently reported as a reason for discontinuation. However, not all patients gain weight during treatment; therefore, genetic biomarkers predicting susceptibility to weight gain may help inform clinical decisions and drive drug discovery efforts.

Receptors antagonized by many antipsychotics are thought to be involved with weight gain through the regulation of appetite, energy homeostasis, and addiction/reward pathways.[1–4] Binding to serotonin (eg, 5-HT_{2C}, 5-HT_6), histamine (eg, H_1), and dopamine (eg, D_2) receptors has been associated with weight gain in antipsychotic use.[5–10] In addition, based on monozygotic twin and sibling pair studies, genetic factors are estimated to account for 60% to 80% of weight-gain variance during treatment with antipsychotics.[11] Genetic variations in the serotonin 2C receptor (*HTR2C)* and the dopamine D2 receptor (*DRD2*) genes are important to study in hypothesis-driven candidate gene studies, due to the affinity of the widely prescribed antipsychotic olanzapine for both of these receptors,[12] the relatively common allele frequencies in these 2 genes with consequences for receptor expression/function, and the biological contributions of these gene variants to appetite regulation.

Serotonin receptor genes are primary pharmacogenetic candidates to assess, due to the role of serotonin in eating behavior.[13,14] Among these, 5-HT_{2C} receptors, encoded by *HTR2C* on chromosome Xq24,[15] are of particular interest in the context of treatment with olanzapine, which has high affinity for these receptors.[12] Additionally, its location on chromosome X may be pertinent to greater weight gain reported for women treated with antipsychotic medication.[16–18] In mice, knocking out the *HTR2C* gene results in hyperphagia and obesity.[19] In humans, polymorphisms in *HTR2C* are associated with weight gain during treatment with olanzapine and clozapine.[7,8,10] Furthermore, administration of a 5-HT_{2C} receptor agonist resulted in decreased appetite and weight loss in 18 moderately obese subjects.[14] Investigating polymorphisms in *HTR2C*, Yuan et al[10] identified a haplotype of 3 single-nucleotide polymorphisms (SNPs) (−697G/C, −759C/T, and −995G/A) and a $(GT)_n$ dinucleotide repeat locus at −1027 (Z-6) that were collectively associated with lower body weight gain and absence of type 2 diabetes. Several studies[7,8,20–24] have reported a protective effect of the −759T allele on weight gain. However, several other studies[25–28] found no association with weight gain. Functional studies have identified that the −759T allele is associated with greater 5-HT_{2C} receptor expression.

A second pharmacogenetic candidate gene of interest in olanzapine studies of weight gain is *DRD2*, due to the role of dopamine in appetite, food intake, and reward association.[5,29,30] Drugs that increase dopamine are known to suppress appetite and decrease body weight.[5] Olanzapine has moderate-to-high affinity for D_2 receptors.[31] Genetic variants of D_2 receptors associated with prolactin changes and response during antipsychotic treatment may also be associated with weight gain. D_2 receptor variants have recently been associated with striatal activation

and eating behavior, underscoring the importance of investigating *DRD2* SNPs in pharmacogenetic studies of weight gain during treatment with olanzapine.[4] The 3′ region of the *DRD2* gene has been shown to be associated with schizophrenia and physically overlaps the ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene.[32,33] Notably, the *ANKK1* missense mutation Taq1A is potentially associated with a reduction in *DRD2* density[32] and is in linkage disequilibrium (LD) with regions of *DRD2* up to 25 kb away.[34] However, SNPs in *ANKK1*/*DRD2* have been investigated for an association with weight gain in Chinese patients with inconclusive findings; specifically, significant associations[9] with rs4456378 but lack of association with rs1800497 (Taq1A, a nonsynonymous SNP encoding Glu713Lys within an ankyrin repeat)[35] and unclear association ($P = .09$) with rs1801028 (Ser311Cys).[36]

We conducted a pharmacogenetic study limited to 3 genes (due to limitations in statistical power) previously associated with weight gain during antipsychotic treatment in study samples from subjects believed to have minimal prior antipsychotic exposure. To minimize the potential effects of ethnicity and previous antipsychotic exposure on weight, we examined the association of *ANKK1*/*DRD2* and *HTR2C* SNPs with weight gain in olanzapine-treated white patients from 4 studies of treatment for borderline personality disorder, treatment-resistant depression, and bipolar disorder. (It should be noted that olanzapine is not approved to treat borderline personality disorder and olanzapine monotherapy is not approved to treat treatment-resistant depression.) The reasoning was that these patients generally would have had limited previous antipsychotic exposure in comparison to patients with schizophrenia, who typically have been treated with antipsychotics for many years. We believed that patients in our analysis would very likely have a stronger genetic association with weight gain in association with olanzapine treatment, since they would have less weight increase in association with previous antipsychotic treatment. Patients were not specifically excluded from our analysis based on previous antipsychotic exposure, since we felt that the potential effects of limited previous exposure were outweighed by loss of power from excluding these patients. Overall, antipsychotics to which 5% or more of patients had prior exposure were risperidone (7.1%) in Study A, olanzapine (7.0%) and risperidone (5.1%) in Study B, and no antipsychotics in Study D. We were unable to readily determine the level of exposure for Study C.

METHOD

Analysis Population

All clinical trial participants provided informed consent. All studies were approved by investigational review boards for all sites and conducted in accordance with the Declaration of Helsinki. Only data from participants who consented to genetic analyses were used in this study.

Clinical Points

- Individual single-nucleotide polymorphism (SNP) variations in *DRD2* and *HTR2C* showed significant associations with weight gain in patients with diagnoses other than schizophrenia treated with olanzapine. These variants may prove useful for individualized medicine and the development of new medications with a lower risk of treatment-emergent adverse events.
- Weight gain with second-generation antipsychotics has been associated with variants in the ankyrin repeat and kinase domain containing 1 gene, the adjacent dopamine D2 receptor gene (*DRD2*), and the serotonin 2C receptor gene (*HTR2C*) in patients with schizophrenia.
- In a cohort of patients with other diagnoses, weight change during olanzapine treatment was associated with 3 *HTR2C* SNPs, including Cys23Ser, in females and with a *DRD2* SNP in all patients.

The primary objective of this study was to characterize the relationship between genetic variation in *ANKK1*/*DRD2* and *HTR2C* with weight change after olanzapine treatment using 4 combined clinical trials (ClinicalTrials.gov identifiers: Study A: NCT00088036; Study B: NCT00091650; Study C: NCT00094549; Study D: NCT00035321). Details regarding these 4 clinical trials are described elsewhere.[37–40] The inclusion criteria for the pharmacogenomic analysis population were as follows: self-reported white, mean dose over 8 weeks > 5 mg, no prior exposure to olanzapine, and at least 1 measurement of weight postbaseline.

Genotyping

DRD2 SNPs were assayed to provide comprehensive coverage of the gene, surrounding promoter, and 3-untranslated region (UTR). *ANKK1* SNPs proximal to and sharing an LD block with *DRD2* were also selected, including a Taq1A previously associated with body weight[4] and prolactin increase[41] during antipsychotic treatment. *HTR2C* SNPs were selected primarily based on previously published assessments for association with medication-induced weight gain. Genotyping was performed by a central laboratory (Cogenics, Newton, Massachusetts) using MassArray (Sequenom, San Diego, California). Single-nucleotide polymorphisms in *ANKK1*/*DRD2* (n = 56) and *HTR2C* (n = 11) that passed quality control with call rate > 90%, minor allele frequency > 1%, and exact Hardy-Weinberg equilibrium P value > 10^{-4} were analyzed.

Statistical Methods

Mixed-model repeated measures (calculated with SAS v 9.2; SAS Institute Inc, Cary, North Carolina), including all observations up to 8 weeks on treatment, were used to test for association between individual SNPs and change in weight from baseline after adjustment for study, baseline body mass index (BMI), and mean dose over 8 weeks

as fixed effects. Significance of the SNP-by-week interaction term was assessed based on a type III test of sums of squares (ie, an *F* test). Individual SNPs were coded under the additive genetic model as 0, 1, or 2 (continuous) corresponding to the number of minor alleles present. To present a graphical representation of change in weight over time, the least-squares (LS) means by genotype, by week, were generated for each SNP using a categorical genotypic model (ie, significance was not assessed in this model). *ANKK1*/*DRD2* association testing was conducted on the overall pharmacogenomic population, and *HTR2C* analyses were conducted on the overall pharmacogenomic population and also stratified by sex.

Haplo.stats v1.3.8 package (Mayo Clinic, Rochester, Minnesota) run in R v2.7.2 (function haplo.em) was used to calculate the posterior probabilities for the set of all possible diplotypes within a specific genomic region (ie, haplotype block) for each patient. The specific 3-SNP block in *HTR2C* comprising –759C/T (rs3813929), –697G/C (rs518147), and Cys23Ser (rs6318) was tested based on previously reported evidence.[42] Patients were classified under the additive genetic model as having 0, 1, or 2 copies of the C-C-C haplotype. Mixed-model repeated measures (SAS) were conducted on the *HTR2C* haplotype variable using the same methods as described above for individual SNP variation.

As a secondary outcome, weight gain on olanzapine treatment (a continuous variable) was dichotomized in order to assess the diagnostic utility of individual SNPs (ie, to provide some insight into how a clinician might go about using a biomarker to make diagnoses). A weight gain of 7% from baseline was used as the criterion in order to be consistent with Eli Lilly–sponsored studies on olanzapine, olanzapine labeling, and US Food and Drug Administration–accepted practice. Logistic regression was performed on all SNPs, with *HTR2C* testing further stratified by sex.

Multiple Comparison Adjustment

Linkage disequilibrium, as measured by the pairwise r^2 correlation, was calculated for all SNPs using Haploview v4.2 (Broad Institute of Harvard and Massachusetts Institute of Technology Cambridge, Massachusetts)[43] with positions relative to National Center for Biotechnology Information build 36.3. The SimpleM method[44] was implemented in SAS to approximate the effective number of tests (M_{eff}) from a principal components analysis given the composite LD correlation matrix. The M_{eff} for the primary outcome of change in weight was 11, resulting in a multiple-test, corrected, 2-sided α of .00455, controlling the experiment-wise type I error rate at 5%.

HTR2C SNPs were stratified by sex for further analysis based on the potential of female-specific weight gain from antipsychotics and on evidence observed in modeling *HTR2C* SNPs in the overall pharmacogenomic population in which the heterozygote group showed separation from common and rare homozygotes (in which homozygotes had similar effect). To ensure that the type I error rate was maintained at 5% after performing the additional tests within the female subgroup, the effective number of tests was doubled, and the multitest corrected 2-sided α was set at .00227 (.05/22).

RESULTS

This study included 205 white patients with nonschizophrenia diagnoses. Supplementary eTable 1, available at PSYCHIATRIST.COM, shows demographic and baseline clinical characteristics, including weight and BMI, for Studies A to D for the overall trial cohorts and the pharmacogenomic analysis population.

Table 1 summarizes the LS mean changes in weight at 8 weeks by genotype for SNPs that had *P* values < .05 from additive modeling or either were SNPs previously assessed for associations with weight gain during antipsychotic treatment or were SNPs proximal to SNPs reported as associated with weight gain for *ANKK1/DRD2* or *HTR2C*. Given an experiment-wise corrected α of .00455, the A allele of *DRD2* intron 4 SNP rs2440390 was associated with increased weight gain over time (*P* = .0043) (Figure 1). In addition, *HTR2C* SNPs rs6318G (Cys23Ser), rs2497538C, and rs1414334G (Table 1) were associated with increased weight gain over time in women (*P* = .0001, *P* = .000052, and *P* = .0001, respectively) but not in men (illustrated for rs6318 in Figure 2).

Six SNPs in intron 1 of *DRD2* surrounding rs4436578 previously reported as associated with weight gain on atypical antipsychotics[9] had *P* values < .05, and upstream SNP rs12364283 had a *P* value of .0571. *ANKK1* rs1800497 (Taq1A) had a *P* value of .0265; however, no *HTR2C* SNPs (–997G/A, –759C/T, or –697G/C) previously evaluated for an association with weight gain during antipsychotic treatment had *P* values < .05.

Figures 3 and 4 present the LD plots for *HTR2C* and *ANKK1/DRD2* for SNPs in this study, with the SNP-by-week interaction term *P* values from the mixed-model repeated measures analysis overlaid. In *HTR2C* (Figure 3), 4 of 11 SNPs, all in the same LD block, returned *P* values < .05 in the overall study sample, and 3 SNPs (rs6318, rs2497538, and rs1414334) were statistically significant after correction for multiple comparisons in females, with no evidence of a significant effect in males. Not surprisingly, the LD among the top 3 *HTR2C* SNPs is high, with a minimum r^2 of 0.89 for pairwise comparisons among this group. In *ANKK1*/*DRD2* (Figure 4), 14 of 56 SNPs had *P* values < .05, with rs2440390 (*P* = .0043) being less than the experiment-wise corrected α. Single-nucleotide polymorphism rs6278, which showed significant association in previous genetic studies of weight gain during olanzapine treatment, was only suggestive here (*P* = .0100).

In this study, the C-C-C haplotype tested by Gunes et al[42] was modeled under the additive genetic model, returning as significant only in females (*P* = .0003) and as nonsignificant overall (*P* = .057) and in males (*P* = .311). While the C-C-C haplotype in *HTR2C* showed significance in females, it was less significant than the individual SNP variation at rs6318 (Cys23Ser) (*P* = .0001). The other 2 SNPs composing this

Table 1. Least Squares Mean (SE) Change in Weight From Baseline to Week 8 of Olanzapine Treatment in Patients With *ANKK1/DRD2* and *HTR2C* SNPs With Uncorrected Overall *P* Values < .05 or That Were Previous Candidates for Association With Weight Gain During Treatment With Antipsychotics[a]

SNP	Position	Region	Sex	Uncorrected *P* Value	Corrected *P* Value	LS Mean (SE) Change in Weight (kg) at Week 8 and No. of Patients With Genotype		
						AA	AB	BB
ANKK1								
rs2734848(T/C) (Tyr561Tyr)	112775584	Exon 8	Both	.0128	.1406	3.24 (0.29) 71	4.08 (0.37) 40	4.81 (0.86) 7
rs1800497(G/A) (Taq1A,Glu713Lys)	112776038	Exon 8	Both	.0265	.2920	3.86 (0.27) 74	3.13 (0.39) 41	2.03 (1.07) 4
rs11214601(C/T)	112777972	Downstream	Both	.0061	.0669	3.89 (0.27) 79	3.00 (0.44) 30	2.18 (1.11) 4
DRD2								
rs2242593(A/G)	112781475	Downstream	Both	.0131	.1439	3.87 (0.27) 80	3.02 (0.42) 33	2.18 (1.11) 4
rs2242591(G/A)	112785131	Downstream	Both	.0169	.1862	3.83 (0.26) 81	3.11 (0.42) 34	2.16 (1.11) 4
rs6278(G/T)	112785934	3′UTR	Both	.0100	.1096	3.87 (0.27) 78	3.16 (0.43) 33	1.49 (1.25) 3
rs1801028(C/G) (Ser311Cys)	112788694	Exon 7	Both	.9939	1.0000	3.62 (0.24) 113	3.94 (0.96) 5	NA, 0
rs2440390(G/A)	112792088	Intron 4	Both	.0043	.0473	3.27 (0.27) 82	3.89 (0.41) 30	5.78 (1.04) 5
rs2075654(G/A)	112794276	Intron 2	Both	.0441	.4850	3.83 (0.27) 77	3.31 (0.46) 29	2.16 (1.13) 4
rs1079598(T/C)	112801484	Intron 1	Both	.0201	.2216	3.84 (0.28) 77	3.33 (0.46) 29	1.35 (1.09) 4
rs1079596(G/A)	112801829	Intron 1	Both	.0361	.3970	3.76 (0.26) 83	3.26 (0.43) 31	2.17 (1.11) 4
rs1125394(A/G)	112802395	Intron 1	Both	.0267	.2934	3.76 (0.27) 80	3.35 (0.45) 28	1.53 (1.25) 3
rs1125393(G/A)	112802559	Intron 1	Both	.0292	.3213	3.78 (0.26) 83	3.17 (0.43) 32	2.18 (1.11) 4
rs7103679(G/A)[c]	112808884	Intron 1	Both	.0077	.0843	3.79 (0.27) 83	2.88 (0.48) 25	2.15 (1.12) 4
rs4648319(C/T)	112819573	Intron 1	Both	.0480	.5276	3.78 (0.26) 84	3.09 (0.43) 31	2.79 (1.07) 4
rs12364283(T/C)[d]	112852165	Upstream	Both	.0571	.6276	3.71 (0.24) 107	2.37 (0.64) 12	NA, 0
HTR2C								
rs521018(A/C)	113724164	Upstream	Both	.0474	.5210	3.63 (0.33) 54	3.89 (0.38) 41	3.17 (0.49) 21
			Female	.1921	1.0000	3.89 (0.47) 24	3.87 (0.37) 41	2.38 (0.79) 9
			Male	.2029	—[b]	3.63 (0.51) 30	NA, 0	3.53 (0.66) 12
rs3813928(G/A) (−997G/A)	113724538	Upstream	Both	.5409	1.0000	3.38 (0.28) 78	4.28 (0.46) 27	3.34 (0.65) 13
			Female	.5959	1.0000	3.35 (0.36) 42	4.20 (0.47) 27	3.51 (1.05) 5
			Male	.2474	—[b]	3.61 (0.46) 36	NA, 0	3.11 (0.87) 8
rs3813929(C/T) (−759C/T)	113724776	Upstream	Both	.5338	1.0000	3.38 (0.27) 79	4.28 (0.46) 27	3.34 (0.65) 13
			Female	.5903	1.0000	3.35 (0.36) 43	4.20 (0.46) 27	3.52 (1.05) 5
			Male	.2474	—[b]	3.61 (0.46) 36	NA, 0	3.11 (0.87) 8
rs518147(G/C) (−697G/C)	113724838	5′UTR	Both	.0606	.6669	3.58 (0.33) 55	3.80 (0.37) 42	3.16 (0.48) 22
			Female	.1755	1.0000	3.85 (0.46) 24	3.76 (0.37) 42	2.42 (0.79) 9
			Male	.2236	—[b]	3.60 (0.50) 31	NA, 0	3.50 (0.65) 13
rs6318(G/C) (69G/C; Cys23Ser)	113871991	Exon 5	Both	.0374	.4110	3.88 (0.26) 95	2.50 (0.58) 17	3.15 (0.88) 5
			Female	.0001	.0032	4.22 (0.32) 55	2.28 (0.57) 17	0.13 (2.07) 1
			Male	.3112	—[b]	3.49 (0.47) 40	NA, 0	3.71 (1.01) 4
rs2497538(C/A)	113874597	Intron 6	Both	.0146	.1610	3.83 (0.25) 96	2.30 (0.55) 18	3.22 (0.86) 5
			Female	.000052	.0012	4.16 (0.31) 56	2.10 (0.54) 18	0.07 (2.06) 1
			Male	.1594	—[b]	3.50 (0.45) 40	NA, 0	3.79 (0.99) 4
rs1414334(G/C)	114044400	Intron 7	Both	.0115	.1262	3.81 (0.25) 98	2.40 (0.57) 17	2.81 (0.95) 4
			Female	.0001	.0031	4.09 (0.31) 57	2.23 (0.56) 17	0.13 (2.07) 1
			Male	.1685	—[b]	3.55 (0.45) 41	NA, 0	3.36 (1.11) 3

[a]SNP-by-week interaction term *P* values for select *ANKK1/DRD2* SNPs from a mixed-model repeated measures analysis on change in weight from baseline, using all observations up to 8 weeks in the olanzapine analysis population. Two-tailed *P* values as obtained from Model 1 are presented for SNPs under the additive genetic model, with and without correction for multiple comparisons. SNP-by-week interaction term *P* values for select *HTR2C* SNPs from a mixed-model repeated measures analysis of change in weight from baseline, using all observations up to 8 weeks in the olanzapine analysis population. Two-tailed *P* values as obtained from Model 1 are presented for SNPs under the additive genetic model, with and without correction for multiple comparisons. (Model 1: Change in Weight from Bsl = Study + Mean Dose + Bsl_BMI + Week + SNP + SNP-by-week.)
[b]Corrected *P* values for *HTR2C* SNPs (on the X chromosome) were not calculated for men, since none of the uncorrected *P* values were less than .05 and consequently corrected values would also be nonsignificant.
[c]3091 bases from intron 1 SNP rs4436578.
[d]702 bases from upstream SNP rs1799732.
Abbreviations: *ANKK1* = ankyrin repeat and kinase domain containing 1, Bsl = baseline, BMI = body mass index, *DRD2* = dopamine D2, *HTR2C* = serotonin 2C, LS = least squares, Mean Dose = mean dose of olanzapine over 8 weeks, NA = not applicable, SNP = single-nucleotide polymorphism, Study = study identifier, UTR = untranslated region.

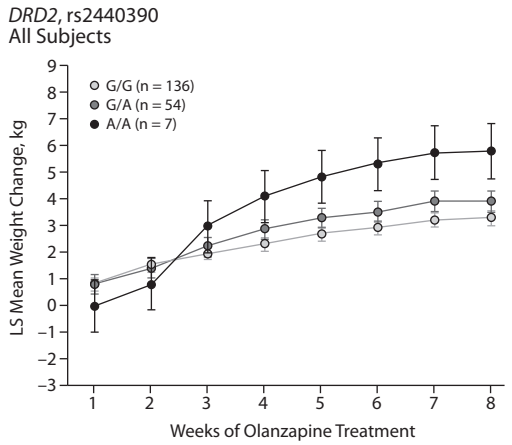
block, rs3813929 and rs518147, were nonsignificant individually (*P* = .59 and *P* = .18, respectively).

The predictive utility of *DRD2* and *HTR2C* SNPs associated with a change in weight from baseline over 8 weeks was assessed with logistic regression performed on a binary outcome defined as 7% weight gain from baseline. No *DRD2* SNP was significantly associated with a 7% gain in weight. *HTR2C* SNPs showed nominal association, but for females with 1 or more C alleles at rs6318, only 11.5% (3 of 26) had 7% weight gain versus 30.4% (28 of 92) for women homozygous for the G allele (*P* = .07).

DISCUSSION

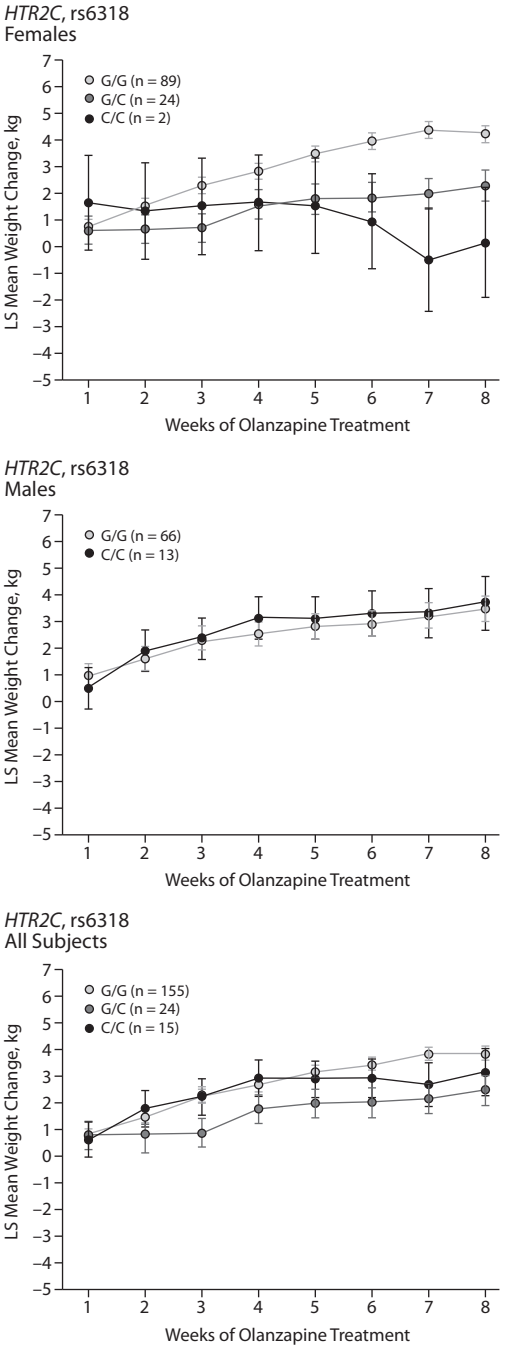
HTR2C and *DRD2* are primary pharmacogenetic candidate genes of interest in weight gain and metabolic syndrome during antipsychotic treatment. In the present study of nonschizophrenia patients treated with olanzapine,

Figure 1. Least Squares Means for *DRD2* Allele rs2440390 by Week of Olanzapine Treatment



Abbreviations: *DRD2* = dopamine D2, LS = least squares.

Figure 2. Least Squares Means for *HTR2C* Allele rs6318 by Week of Olanzapine Treatment



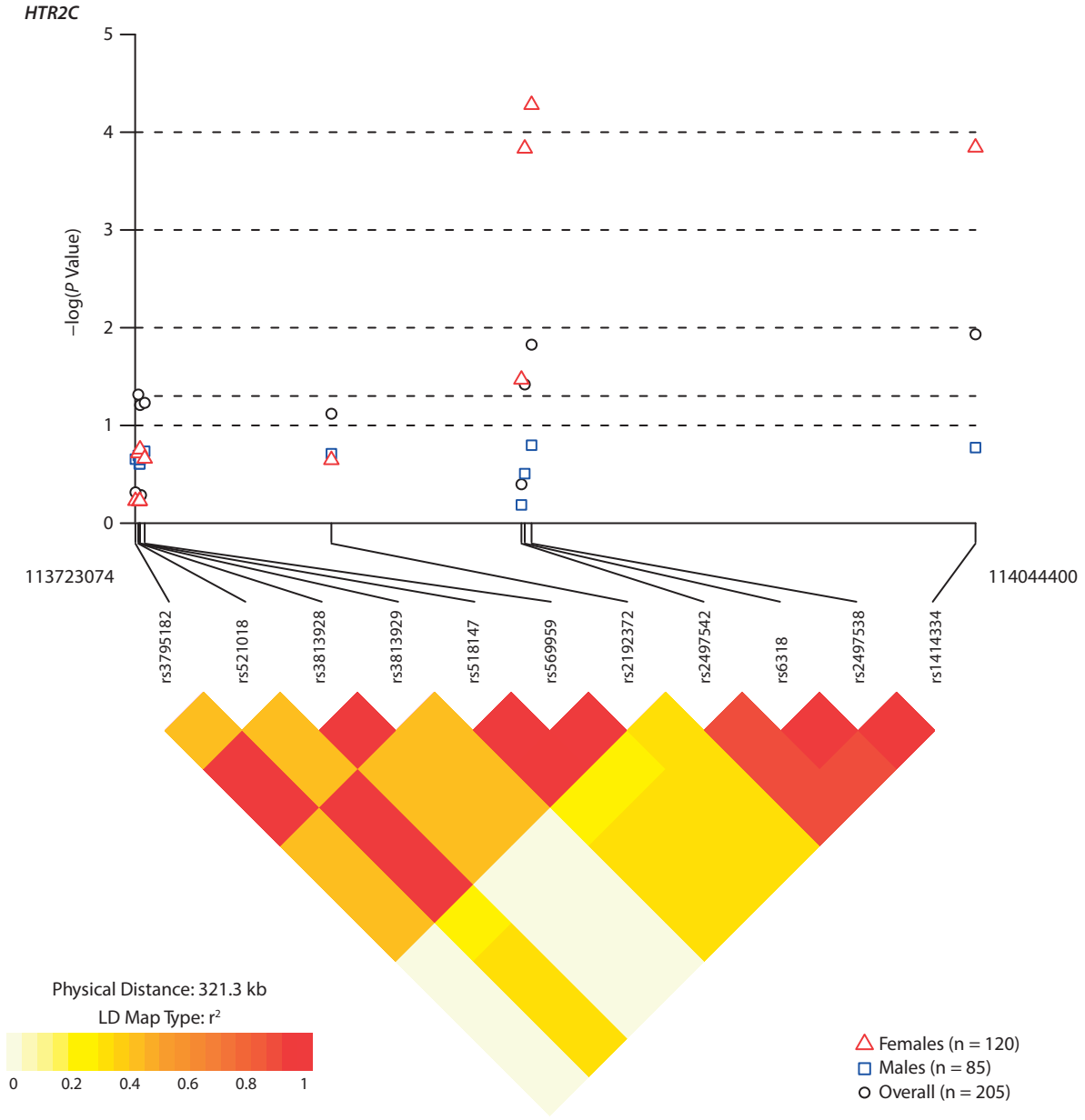
Abbreviations: *HTR2C* = serotonin 2C, LS = least squares.

we observed significant associations between weight change over 8 weeks and genetic variation in *HTR2C* and *DRD2*. In the *DRD2* gene, rs2440390(G/A) showed experiment-wise significance in the overall pharmacogenomic population, with the A allele associated with increased risk of weight gain. No other variant was significant in the overall pharmacogenomic population; however, in the *HTR2C* gene, rs6318G (Cys23Ser), rs2497538C, and rs1414334G showed experiment-wise significance for association with increased weight gain over time in women ($P = .0001$, $P = .000052$, and $P = .0001$, respectively) but not in men.

Gunes et al[42] suggested an association between haplotypic variation in *HTR2C*, specifically the 3-SNP block comprising −759C/T (rs3813929), −697G/C (rs518147), and Cys23Ser (rs6318) and metabolic changes in patients treated with olanzapine and clozapine. In particular, patients carrying the C-C-C haplotype were observed to have higher BMI and C peptide levels. Another study, involving patients with schizophrenia treated with atypical antipsychotics, failed to show an association between this haplotype and weight gain over time.[45] Therefore, we performed a haplotype analysis on this region to investigate potential association between the *HTR2C* haplotype and weight change during olanzapine treatment. Here, we observed no association between the C-C-C haplotype in the overall pharmacogenomic population; however, this haplotype was significantly associated with weight change in females only ($P = .0003$). Notably, Cys23Ser (rs6318) was also individually significant in females ($P = .0001$), while the other 2 SNPs comprising this block were nonsignificant on their own (both P values $> .05$).

Numerous studies have examined the *individual* SNPs comprising this *HTR2C* haplotype. A meta-analysis of 8 studies is consistent with a protective effect of the −759T allele on weight gain during olanzapine treatment[24]; more recently, another study reported an association with weight change during olanzapine treatment for polymorphisms −697C (rs518147) and −759T (rs3813929) in patients with schizophrenia.[23] While both rs518147 and rs3813929 have potential consequences for gene regulation, neither has an expected effect on protein structure, whereas the variation at rs6318 is a missense mutation resulting in an amino acid change in the protein. This suggests the Cys-to-Ser residue change in the serotonin 2C receptor may provide an informative target in the development of antipsychotic therapeutics, and it is known that this substitution has a differential effect on the affinity for certain ligands, including serotonin.[46] This SNP is in strong LD with the other 2 statistically significant *HTR2C* SNPs, which have no known direct functional

Figure 3. Linkage Disequilibrium Map Showing Associations Between *HTR2C* Polymorphisms Investigated in This Study[a,b]



[a]*P* values for *HTR2C* SNPs indicate significance of the SNP-by-week interaction term from mixed-model repeated measures analysis of change in weight from baseline over 8 weeks, after adjustment for study, baseline BMI, and mean dose over 8 weeks. SNPs were coded under the additive genetic model as 0, 1, or 2 (continuous) corresponding to the number of minor alleles present based on frequency. Significance was assessed based on a type III test of sums of squares. The line between the graph and the LD map represents the relative gene position between 113723074 and 114044400.
[b]The color scale indicates strength of LD, with white indicating no LD and deep red indicating the strongest LD.
Abbreviations: BMI = body mass index, *HTR2C* = serotonin 2C, LD = linkage disequilibrium, SNP = single-nucleotide polymorphism.

effects. However, Mulder et al[45,47] identified a strong association of rs1414334 with obesity and metabolic syndrome in patients receiving antipsychotic therapy. Risselada et al[48] reported the association of rs1414334 with eating behavior and weight gain in patients receiving mirtazapine.

Reports of sex differences in weight gain during treatment with atypical antipsychotics are somewhat limited. However, greater weight gain in women has been reported over 2 years of clozapine treatment,[16] in patients treated with antipsychotics over extended periods,[17] and in olanzapine/fluoxetine combination treatment.[18] The striking difference in the strength of association patterns for females compared to males is intriguing, and our results are consistent with previous reports associating weight gain with rs6318 (Cys23Ser) and rs1414334. Our nonschizophrenia patient population included a higher proportion of females than males, which is quite different from previous pharmacogenetic studies of olanzapine. Thus, we may have identified sex effects not detectible in prior male-dominated studies. Additionally, diagnostic differences in previously conducted schizophrenia studies may have influenced the genetic composition of these patient populations (ie, the underlying distribution

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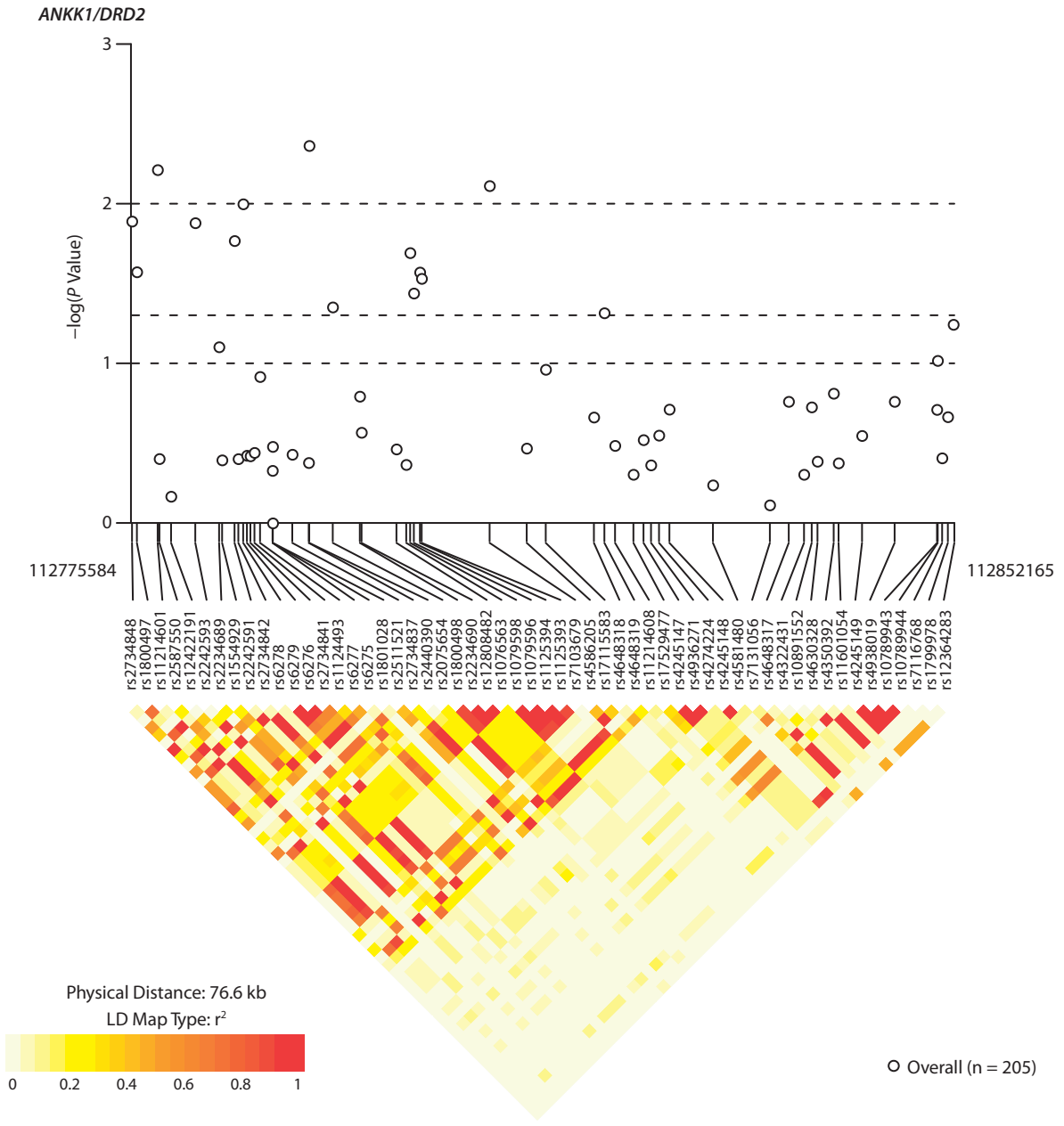
Figure 4. Linkage Disequilibrium Maps Showing Associations Between *ANKK1/DRD2* Polymorphisms Investigated in This Study[a,b]



[a]*P* values for *ANKK1/DRD2* SNPs indicate significance of the SNP-by-week interaction term from mixed-model repeated measures analysis of change in weight from baseline over 8 weeks, after adjustment for study, baseline BMI, and mean dose over 8 weeks. SNPs were coded under the additive genetic model as 0, 1, or 2 (continuous) corresponding to the number of minor alleles present based on frequency. Significance was assessed based on a type III test of sums of squares. The negative log *P* values are presented overall (circle). The line between the graph and the LD map represents the relative gene position between 112775584 and 112852165.

[b]The color scale indicates strength of LD, with white indicating no LD and deep red indicating the strongest LD.

Abbreviations: *ANKK1* = ankyrin repeat and kinase domain containing 1, BMI = body mass index, *DRD2* = dopamine D2, kb = kilobase pair, LD = linkage disequilibrium, SNP = single-nucleotide polymorphism.

of haplotype and/or allele frequencies may vary by patient population). In a report of healthy subjects, low body weight was shown to be associated with the Cys23Ser variant, and increased body weight was associated with absence of the T allele at −759C/T, particularly in women.[49]

The role of dopamine function is less well-characterized with respect to weight gain during antipsychotic treatment.[9] D_2 receptor agonists decrease food intake and body weight in rats and genetically obese mice.[50,51] *DRD2* intronic SNP rs2440390, statistically significant in our analysis, has no known functional significance. In humans, decreased D_2 receptor expression levels are associated with a corresponding decrease in BMI.[52] Hong et al[9] have reported on a genetic case-control study involving 479 Chinese Han schizophrenia

patients, genotyping 13 polymorphisms representative of *DRD2* variations observed in the Chinese population treated with clozapine, risperidone, or olanzapine. They identified 1 *DRD2* variant, rs4436578, not assayed in our analysis, with an association for weight gain during antipsychotic treatment. Interestingly, this intron 1 SNP is proximal to rs7103679 and several other intron 1 SNPs assessed in our study with uncorrected *P* values < .05. The rs12364283 (*P* = .0571), located outside the LD block containing all *ANKK1/DRD2* SNPs nominally associated with weight gain in our analysis, is close to the SNP reported by Lencz et al.[53]

We have previously replicated an association of several *ANKK1/DRD2* SNPs with prolactin increase during olanzapine treatment.[41,54] Additionally, there have been literature reports of associations between SNPs in these genes and weight gain.[9,35,36] In turn, variants in this region or proximal to this region of *ANKK1/DRD2* might be expected to have an impact on both weight gain and prolactin increases.

While this study presents novel and supporting evidence for genetic associations between weight change during antipsychotic treatment and *HTR2C* and *DRD2*, characterizing the contributions of variants within the *HTR2C* and *DRD2* genes on changes in metabolic parameters during antipsychotic treatment has been difficult due to heterogeneity of phenotypes and study designs. Another limitation of the study is that previous use of medications was not controlled for. The choice of subject population helped to minimize the number of subjects who were previously exposed to antipsychotics, but no attempt was made to take into account the previous use of antidepressants or anxiolytics in the present study. The strength of this study derives from its assessment of the genetic contribution to weight change during olanzapine treatment in a homogenous study population (ie, whites only) while minimizing the potential effects of previous antipsychotics, given the general expectations of diagnoses in this set of clinical trials. Our patient population was heterogeneous with respect to disease state compared with previous association analyses, which have predominantly assessed patients with schizophrenia. Whether our findings, in a set of patients with different diagnoses, can be applied to patients with schizophrenia needs further evaluation. Similarly, these results may not extend into nonwhite populations. Other parameters not considered were smoking behavior, diet, exercise, and alcohol consumption, due to difficulty in their interpretation relative to genetic factors. Insulin resistance, lipid profiles, and other metabolic syndrome measures were not available. The extent to which the present results can be extended to other second-generation antipsychotics is limited by the differences in their receptor binding profiles. However, there is considerable overlap among them, especially with regard to *HTR2C* and *DRD2*. Weight gain has been linked with, for example, a *DRD2* polymorphism (rs4436578) in patients taking clozapine or risperidone.[9] Also, clozapine is associated with weight gain in patients with the *HTR2C* −759C/T polymorphism.[21]

An inherent limitation to this study is limited sample size. Efforts toward evaluating 2 or more top candidates in either a multimarker modeling approach or using derived conditional variables were limited by the frequency of variants of interest and availability of patients (data not shown). In turn, no definitive statements can be made regarding the additive or synergistic effects of these genetic variants on change in weight after olanzapine treatment. Additionally, coverage of potential candidate genes was limited in scope, focusing on *HTR2C* and *DRD2*, without consideration of other gene-by-gene interactions. There are other interesting lines of research which we did not pursue. For example, variations in genes for the histamine H_1 receptor, α_2-adrenergic receptor, and possibly drug metabolizing enzymes are additional important targets for potential research.

In summary, individual SNP variation in *DRD2* showed significant association with change in weight from baseline in the overall pharmacogenomic population after treatment with olanzapine, whereas individual SNP variations in *HTR2C* also showed significant association, except this effect was limited to the female subgroup of the pharmacogenomic population. Future studies investigating the relationship between metabolic markers may be informative in determining the underlying mechanisms and pathways influenced by polymorphisms in dopamine and serotonin genes.

Drug names: clozapine (Clozaril, FazaClo, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), risperidone (Risperdal and others).

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Potential conflicts of interest: **Drs Conley, Fijal**, and **Zhao** are employees of and minor stockholders in Eli Lilly. **Drs Houston** and **Hoffmann** are employees of Lilly USA and minor stockholders in Eli Lilly. **Dr Bishop** has received an honorarium from Eli Lilly and grant funding from Ortho-McNeil-Janssen. **Dr Kohler** and **Ms Ostbye** are employees of BioStat Solutions, Inc, which received funding from Eli Lilly to support the work presented in this article. **Dr Ellingrod** has served on an advisory board for Eli Lilly.

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Supplementary Material

Article Title: Pharmacogenomic Associations With Weight Gain in Olanzapine Treatment of Patients Without Schizophrenia

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List of Supplementary Material for the article

1. eTable 1 — Basic Demographics for the Olanzapine Cohorts And All Subjects Who Received Olanzapine Treatment

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Supplementary Material

eTable 1. Basic Demographics for the Olanzapine Genetic Cohorts and All Subjects Who Received Olanzapine Treatment[a]

	Olanzapine Overall					Olanzapine Genetic				
Variable	**Study A 2.5 mg**	**Study A 5-10 mg**	**Study B**	**Study C**	**Study D**	**Study A 2.5 mg**	**Study A 5-10 mg**	**Study B**	**Study C**	**Study D**
Number of Patients	150	148	155	201	199	52	44	70	139	73
Age, mean ± SD	32.6 ± 11.2	32.9 ± 10.0	31.8 ± 9.4	39.5 ± 12.0	44.3 ± 10.8	33.3 ± 11.9	33.4 ± 10.1	32.6 ± 8.9	38.2 ± 12.0	43.4 ± 9.8
Sex, Female, n (%)	109 (72.7%)	106 (71.6%)	113 (72.9%)	109 (54.2%)	123 (61.8%)	41 (78.8%)	29 (65.9%)	49 (70%)	70 (50.4%)	44 (60.3%)
Ethnicity, %										
Caucasian	68%	58.8%	87.7%	79.6%	92.4%	59.6%	40.9%	87.1%	80.6%	76.7%
African	4.7%	7.4%	6.5%	13.9%	9.5%	5.8%	13.6%	5.7%	13.7%	9.6%
Hispanic	24%	30.4%	1.3%	5%	6%	28.8%	45.5%	0%	5.8%	8.2%
East/Southeast Asian	0.7%	2.7%	1.3%	0.5%	0.5%	0%	0%	1.4%	0%	1.4%
Western Asian	0.7%	0%	0.6%	0%	0%	0%	0%	4.3%	0%	0%
Other	2%	0.7%	2.6%	0%	1.5%	5.8%	0%	1.4%	0%	4.1%
Country, % US (n/total)	56.0% (84/150)	60.8% (90/148)	25.2% (39/155)	59.2% (119/201)	N/A	73.1% (38/52)	68.2% (30/44)	38.6% (27/70)	71.2% (99/139)	87.7% (64/73)
Baseline weight (kg), mean ± SD	70.8 ± 18.7	71.4 ± 18.4	71.5 ± 19.2	82.5 ± 21.6	86.2 ± 21.9	75.4 ± 20.3	78.7 ± 17.4	78.8 ± 24.2	82.0 ± 23.3	88.5 ± 21.6
Baseline BMI (kg/m^2), mean ± SD	N/A	N/A	N/A	28.2 ± 7.3	30.4 ± 7.1	27.3 ± 6.0	27.4 ± 4.6	27.08 ± 6.5	28.2 ± 7.7	31.1 ± 6.4
Mean weight change (kg)	2.1	3.2	2.9	1.3	5.53	1.57	2.76	2.45	2.3	4.7
Rate of 7% weight increase, %	20.3%	30.6%	34.2%	22.9	22.2%	17.3%	31.8%	27.1%	20.9%	15.1%
OLZ dose (mg), mean ± SD	2.5	6.66 ± 2.91	7.1 ± 5.1	11.4 ± 5.0	8.1 ± 3.5	2.97 ± 1.17	5.6 ± 2.02	6.7 ± 4.49	12.4 ± 3.8	7.6 ± 3.04
OLZ dose over 8 weeks (mg), mean ± SD	N/A	N/A	N/A	N/A	N/A	2.4 ± 0.34	5.5 ± 1.7	6.5 ± 4.1	12.6 ± 3.7	7.6 ± 3.0

Abbreviations: BMI = body mass index; n = number; N/A = not applicable; OLZ = olanzapine; SD = standard deviation; US = United States.
[a] Patient diagnoses: Study A and B, Borderline Personality Disorder; Study C, Mania, Bipolar I Disorder; Study D, Treatment-Resistant Major Depressive Disorder.