Pharmacogenomic Analysis Shows Differences in Markers Associated With Response Between Two Atypical Antipsychotics, Iloperidone and Ziprasidone, in the Treatment of Patients With Schizophrenia

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INTRODUCTION

Schizophrenia, a chronic, severe, disabling disorder that affects approximately 1% of the US population, is characterized by hallucinations, delusions, social withdrawal, and cognitive deficits.[1] Considerable evidence indicates that schizophrenia is not caused by a single gene but rather by several interacting susceptibility loci and environmental risk factors. Patients' response to antipsychotic drugs is highly variable,[2,3] and multiple genetic factors are thought to play a role in drug response.[2]

Iloperidone is an investigational mixed D_2/5-HT_2 antagonist antipsychotic that has demonstrated clinical efficacy in a broad range of schizophrenia symptoms and has a reduced potential for extrapyramidal side effects.[4-7]

Through a whole genome association study (WGAS) conducted in a phase 3 clinical trial, we have identified 6 single nucleotide polymorphisms (SNPs) associated with the efficacy of iloperidone measured as change in the Positive and Negative Syndrome Scale Total score (PANSS-T) between baseline and Day 28. One SNP is located within the *NPAS3* (neuronal PAS domain protein 3) gene, close to a translocation breakpoint site previously observed in a family with schizophrenia (Poster #1035/T). The other SNPs are associated with 5 genes: *XKR4* (XK, Kell blood group complex subunit-related family, member 4), *TNR* (tenascin-R), *GRIA4* (glutamate receptor, ionotropic, AMPA 4), *GFRA2* (glial cell line-derived neurotrophic factor receptor-alpha2), and *NUDT9P1* located in the chromosomal region of the serotonin receptor 7 gene (*HTR7*) (Poster #1036/T).

We investigated whether or not the genotypes of these SNPs associated with iloperidone efficacy were also associated with the efficacy of the active comparator, ziprasidone, used in the trial where the WGAS was performed. Our findings suggest that some of the efficacy markers are not common to both antipsychotics, supporting the idea that each drug has its unique combination of genetic markers of response, which reflects its unique efficacy properties and safety profile.

METHODS

The genotypes of 98 patients treated with ziprasidone (80 mg bid for 28 days) were generated using the same microarray set (GeneChip Human Mapping 500K Array Set; Affymetrix, Santa Clara, California) used for the WGAS that led to the discovery of the 6 SNPs associated with iloperidone response (Poster #1036/T). A mixed-model repeated-measures (MMRM) statistical analysis was performed for each SNP.

RESULTS

As expected, genotype frequencies of the 6 SNPs identified in our WGAS were similar between groups of patients treated with iloperidone and the comparator drug (**Table 1**). However, the effect of these genotypes on efficacy response was clearly different between the drugs for PANSS-T, as well as the subscales, PANSS positive (PANSS-P), PANSS negative (PANSS-N), and PANSS general psychopathology (PANSS-GP) (**Figure 1**).

Table 1. Genotype Frequencies of SNPs Associated With Iloperidone Efficacy Response.

SNP	Gene	Genotype Class	Iloperidone-Treated Patients	Ziprasidone-Treated Patients
rs11851892	*NPAS3*	non-GG	31.0%	36.7%
rs964348	*XKR4*	non-GG	77.6%	79.6%
rs875326	*TNR*	non-AG	63.1%	60.8%
rs2513265	*GRIA4*	non-TT	77.1%	81.6%
rs7837682	*GFRA2*	AA	58.6%	61.5%
rs4528226	*NUDT9P1*	GT	47.6%	44.3%

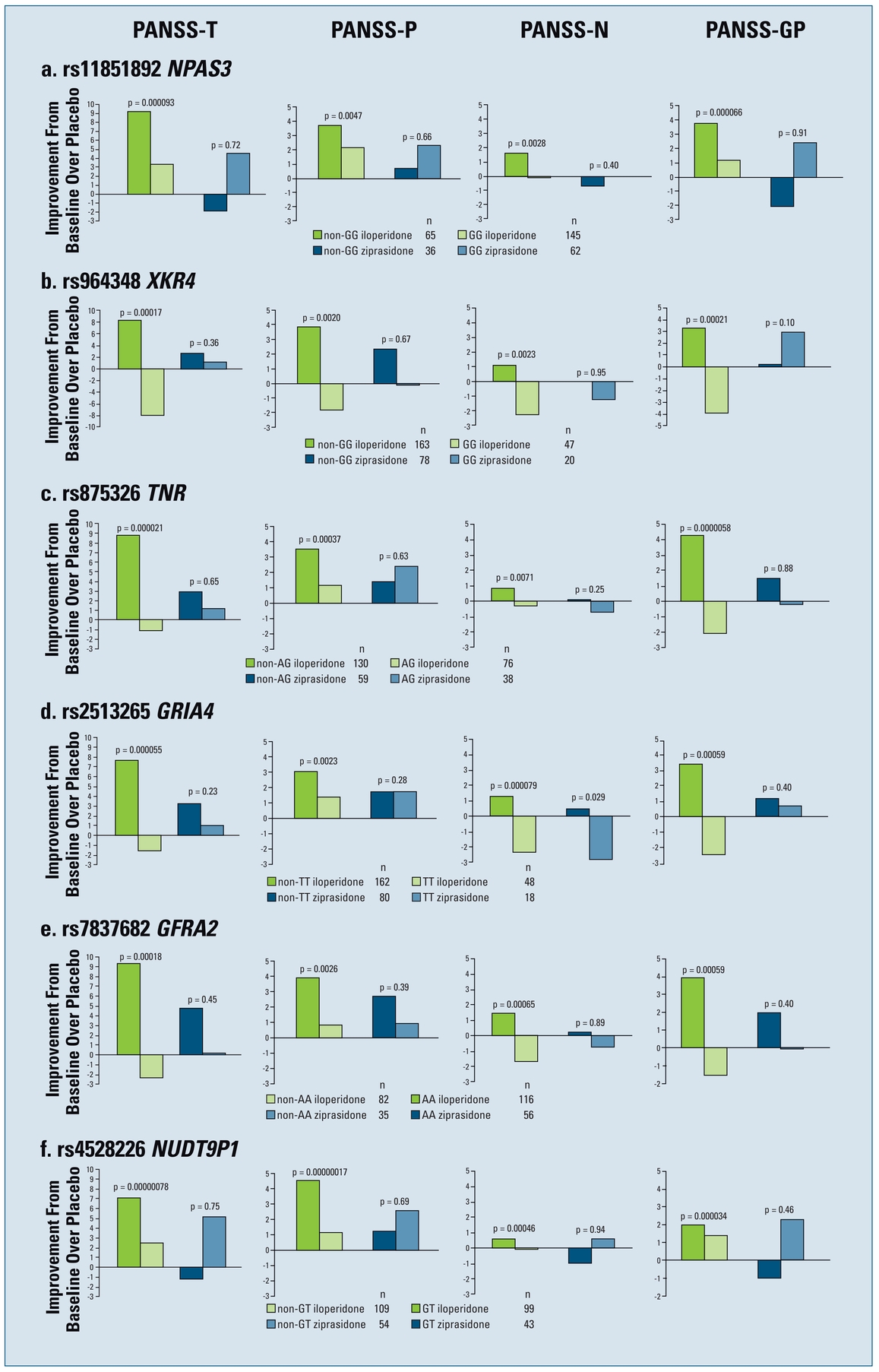
None of the 6 SNPs significantly associated with iloperidone efficacy reached statistical significance for ziprasidone response as measured with PANSS-T. Likewise, we have observed that SNPs in the *CERKL* gene associated with QT-prolongation in iloperidone-treated patients did not correlate with QT-prolongation in the ziprasidone group (see Poster #1039/T).

The lowest p value in the ziprasidone-treated group was obtained for SNP rs2513265 (*GRIA4*) in the PANSS-N subscale (p = 0.029), still not as significant as for the iloperidone-treated patients (p = 0.000079) (**Figure 1d**). The difference in the number of patients in each treatment group could play a role in the level of statistical significance. However, 2 SNPs (rs11851892 and rs4528226) showed an opposite trend toward PANSS-T response between the treatment groups: the non-GG genotype for rs11851892 (*NPAS3*) was associated with higher iloperidone response but lower ziprasidone response than the GG genotype (**Figure 1a**). Similarly, an opposite trend was observed for rs4528226 (*NUDT9P1*) between the 2 treatment groups (**Figure 1f**).

Furthermore, while the association of these 6 SNPs was significant in the iloperidone-treated patients across the different subscales (PANSS-P, PANSS-N, and PANSS-GP), 2 SNPs (rs964348, *XKR4*; rs875326, *TNR*) showed an inconsistent trend across the different subscales in the comparator group (**Figures 1b** and **1c**).

Only 2 SNPs (rs2513265, *GRIA4*; rs7837682, *GFRA2*) showed a similar trend across all subscales for both antipsychotics (**Figures 1d** and **1e**).

Figure 1. Comparison of Genotype Effect on Efficacy Response.



CONCLUSIONS

- None of the 6 SNPs significantly associated with an overall efficacy response to iloperidone were significantly associated with a response to ziprasidone.
- Two SNPs showed a similar trend: rs2513265 (*GRIA4*) and rs7837682(*GFRA2*).
- Two SNPs showed an opposite trend: rs11851892 (*NPAS3*) and rs4528226 (*NUDT9P1*).
- The efficacy signature of an antipsychotic appears to reflect the specificity of each drug, which may be mediated by its unique complex-binding profile, its interaction with other molecules, and its particular metabolism.
- Our findings suggest that pharmacogenomics could lead to differentiation of antipsychotics.

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