Applicability of a Genetic Signature for Enhanced Iloperidone Efficacy in the Treatment of Schizophrenia

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Objective: To demonstrate how several polymorphisms previously associated with the efficacy of the novel antipsychotic iloperidone could be used together to predict clinical response and provide practical information for individualized treatment.

Method: This inpatient randomized, double-blind, placebo- and ziprasidone-controlled, 28-day study of the efficacy of iloperidone was conducted from November 2005 to September 2006. Likelihood ratios, predicted probabilities of response, and number needed to treat were calculated for patients with schizophrenia (DSM-IV criteria) using 6 genetic markers of iloperidone response as measured by change in the Positive and Negative Syndrome Scale-Total (PANSS-T) score. Data analysis was performed on 409 patients of various ethnic origins.

Results: The 6-marker genotype combinations defined 4 groups of patients with distinct probabilities of response. More than 75% of iloperidone-treated patients in the group with the optimal genotype combinations showed a 20% or greater improvement, compared with 37% for patients with other genotypes. These patients had a significant response by the first week of treatment, which was earlier than for patients with other genotype combinations. The odds of responding to iloperidone treatment with at least 20% improvement ranged from 2.4 to 3.6 for patients with 1 of the 6 favorable single-marker genotypes. The odds increased to 9.5 or greater for patients with the most favorable 6-marker combinations. The difference in PANSS-T score improvement observed between the genotype groups was also seen for the positive, negative, and general psychopathology PANSS subscales. The relationship between treatment efficacy and genotype combinations was not observed for patients treated with ziprasidone.

Conclusion: These results illustrate the combined use of genetic markers to predict enhanced response to iloperidone and support the application of pharmacogenetics to differentiate medication options and improve individualized treatments for schizophrenia.

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Schizophrenia is a severe psychotic disorder affecting approximately 1% of the population.[1] The disease carries a high rate of mortality, with approximately 10% of patients committing suicide.[2] A number of drugs are available to treat this chronic illness, which is characterized by positive symptoms (e.g., delusions, hallucinations, thought disorganization), negative symptoms (e.g., social withdrawal, lack of pleasure in everyday life), and impaired cognitive functions (e.g., memory and learning, planning, information processing). However, patient response to treatment remains unpredictable and highly variable. Consequently, the discontinuation rate for antipsychotic treatment is high, with approximately 74% of patients discontinuing medication in the first 18 months.[3–5]

Although individual differences in drug response can be due to the nature and severity of the disease being treated, the individual's age, sex, race, concomitant illnesses and therapies, and genetic makeup might also play a role. Even though there are data linking genetic factors

to disease progression and severity, little is known about the genetic impact on drug efficacy and the occurrence of adverse events. However, it has become more evident that genetic factors influence both the effectiveness of a drug and the likelihood of experiencing an adverse event.[6,7] The field of pharmacogenetics has rapidly evolved since the completion of the Human Genome Project and is now providing opportunities to identify patients with the greatest chance of benefiting from a particular treatment while minimizing the risk for unwanted side effects.

In psychiatry, numerous advances have been made to identify genetic factors associated with drug response, in particular for antipsychotics.[5,8–11] Treatment response is a complex phenomenon resulting from a multitude of elements that most likely include various genetic factors. It is important to note that these genetic factors may individually contribute to only a small portion of the observed variability in interindividual drug response, which makes not only their discovery but also their clinical application challenging. The acceptance of predictive genetic markers in clinical practice will necessitate the validation of their clinical value, as well as the practical utilization of the comprehensive information they provide.

Currently, there is no standard approach to determine the effect of multiple genetic markers in the pathophysiology of a disease or in the response of a drug treatment. As a result, it has become crucial to develop methods to combine the information gathered from all relevant biomarkers. This approach will provide a clear interpretation and therefore an easier implementation in clinical practice of the genetic information that may otherwise be viewed as too complex or impractical.

We report here on the application of several methods to evaluate and combine the information provided by multiple genetic factors associated with drug response. We have used the information of 6 single nucleotide polymorphisms (SNPs) recently associated with the efficacy of a novel antipsychotic, iloperidone,[11] in order to calculate the expected treatment response of patients with schizophrenia and discuss how this information could, if validated, be used in clinical practice.

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.[12–18] In a recent whole genome association study,[11] 6 SNPs associated with iloperidone efficacy were identified. They include rs11851892 in the neuronal PAS domain protein 3 gene (*NPAS3*); rs9643483 upstream of the XK, Kell blood group complex subunit-related family member 4 gene (*XKR4*); rs875326 near the tenascin-R gene (*TNR*); rs2513265 upstream of the ionotropic glutamate receptor, AMPA 4 gene (*GRIA4*); rs7837682 close to the glial cell line-derived neurotrophic factor receptor-α 2 gene (*GFRA2*); and rs4528226 between the *NUDT9P1* pseudogene and the serotonin receptor 7 gene (*HTR7*). It was shown that patients treated with iloperidone who carried a specific genotype for 1 of these markers experienced between 25% and 68% greater improvement in the Positive and Negative Syndrome Scale-Total (PANSS-T) score than the mean response of all iloperidone-treated patients.[11] Patients affected with schizophrenia who carried a genotype associated with better iloperidone response were approximately 2.4 to 3.6 times more likely to experience a 20% or greater improvement in PANSS-T score than patients who carried the alternate genotype.[11]

While the association of these specific SNPs still needs to be reproduced in future studies, the approach described herein is applicable to any therapy for which multiple predictive markers of response should be taken into consideration to optimize individualized treatment.

METHOD

Ethical Conduct of the Study

The study was conducted from November 2005 to September 2006. The study protocol and informed consent forms were approved by institutional review boards or independent ethics committees. Each patient signed an informed consent before participating. This study was conducted in accordance with the Declaration of Helsinki, the U.S. Code of Federal Regulations governing the protection of human subjects and obligations of clinical investigators, and Good Clinical Practice and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. The design and overall results of this study have been reported previously.[15]

Patients and Study Design

Patients 18 to 65 years of age with a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition were eligible to participate in an inpatient randomized, double-blind, placebo- and ziprasidone-controlled, 28-day study of the efficacy and safety of iloperidone. Patients who consented to the optional pharmacogenetic study were treated with iloperidone 12 mg twice a day (n = 218), ziprasidone 80 mg twice a day (n = 103, active control), or placebo (n = 105). Data analysis was performed on 409 samples from 326 men (80%) and 83 women (20%) of various ethnic origins: Asian (n = 35, 8%), black (n = 207, 51%), white (n = 147, 36%), or other (n = 20, 5%).

Pharmacokinetic Data of Iloperidone

Single-point pharmacokinetic samples were taken at days 7, 14, 21, and 28. Iloperidone and its primary metabolites (P88, P95) were measured using a validated liquid chromatographic-mass spectrometric analytic method (Aptuit, Riccarton Edinburgh, United Kingdom).[19,20] The

(iloperidone +P88)/P95 ratio, which measures the amount of biologically active (iloperidone +P88) versus inactive (P95) compounds, was calculated and used in our statistical analysis.

Statistical Analysis

Analysis of the genotype effect on efficacy of the 6 SNPs previously reported was conducted using the general linear model with baseline value as a covariate. The PANSS-T and the PANSS positive (PANSS-P), negative (PANSS-N), and general psychopathology (PANSS-GP) subscales were analyzed at days 7, 10, 14, 21, and 28 as improvement from baseline using the last observation carried forward. Improvement from baseline was defined as follows: change from baseline/(baseline value–n), wherein n = number of items in the scale (n = 30, 7, and 16 for PANSS-T, PANSS-P/N, and PANSS-GP, respectively). The mean PANSS-T score at baseline was approximately 92 points.

For calculation of improvement of schizophrenia symptoms, we first used a threshold of 20% change from baseline in PANSS-T score; this level of clinical improvement has been previously used in other studies.[21,22] Additional analyses with thresholds up to 50% improvement were also conducted to compare posttest probabilities obtained by the likelihood ratio method (see below). For each marker, we calculated the true positive (TP) and false positive (FP) values: number of patients who carry the genotype associated with high response and experienced (TP) or did not experience (FP) a 20% or greater improvement. We also determined the number of true negative (TN) and false negative (FN) cases: number of patients who did not carry the genotype associated with high response and experienced (FN) or did not experience (TN) a 20% or greater improvement. Sensitivity (Sn) and specificity (Sp) were calculated as follows: Sn = TP/(TP + FN) and Sp = TN/(TN + FP).

Likelihood ratios (LR), which can be used to combine information from several genetic tests and compute, for example, the probability of developing a multifactorial disease,[23,24] were calculated for a positive test (LR+) and for a negative test (LR–) as follows: LR+ = Sn/1 – Sp and LR– = 1 – Sn/Sp. The likelihood ratio of each 6-marker genotype combination [L(f)] was the product of individual LR+ and LR–.[24] The likelihood that a patient would experience an improvement of at least 20% a priori without knowing the genotype (pretest odd) was calculated as follows: pretest odd = pretest probability/(1 – pretest probability). Posttest odds and posttest probabilities were calculated as follows: posttest odd = LR(f) × pretest odd and posttest probability = posttest odd/(1 + posttest odd).

The number needed to treat (NNT) was calculated as the reciprocal of the absolute risk reduction (1/ARR). The ARR was defined by the formula ARR = (CER – EER), for which CER is the control event rate and EER is the experimental event rate.[25,26] The 95% confidence interval (CI) was calculated using publicly available GraphPad QuickCalcs software.[27]

A linear regression analysis was conducted to analyze the additive effect of each of the 6 efficacy markers on response to iloperidone. To develop our regression model, we first estimated a "full model" that included several potential clinical and laboratory predictors (e.g., baseline PANSS-T score, drug blood exposure at day 28) and the 6 genetic markers. Terms were excluded from this full model if they did not significantly contribute to the model ($p > .05$). It was previously shown that the significant association of the 6 individual markers with iloperidone efficacy was not attributable to a bias resulting from the race heterogeneity of the patient population.[11] We, however, evaluated race in this regression model and confirmed that, despite differences in genotype frequencies, race was not a significant predictor of response to iloperidone ($p = .19$). Using a step-down approach, we evaluated the potential contribution of each single marker, and based on this model, odds ratios and R^2 statistic, which measures the proportion of the total variability explained by the model, were calculated. We further adjusted the R^2 statistic for the number of parameters used (R^2_{adj}). Generalized linear model was used for the prediction of PANSS-T score improvements for each patient based on his or her baseline PANSS-T score, drug blood exposure, and genotype.

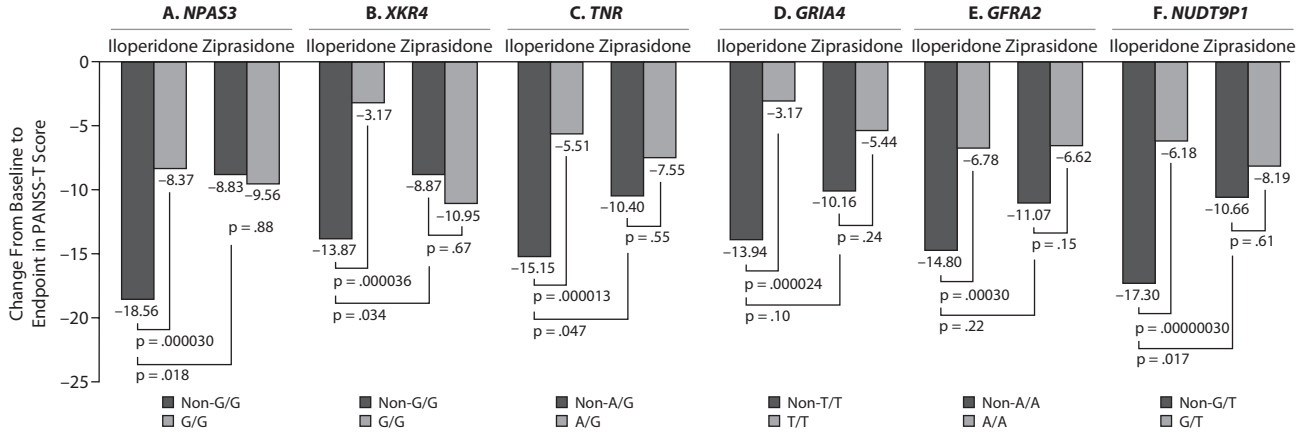
RESULTS

The Effect of Individual SNPs on Iloperidone and Ziprasidone Efficacy

We previously identified specific genotypes for 6 SNPs associated with 25% to 68% greater iloperidone efficacy than the mean response of all iloperidone-treated patients.[11]

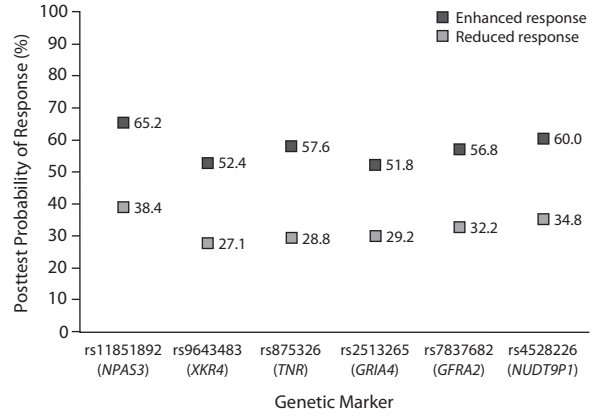
The effect of these genotypes on efficacy response, as measured with the PANSS-T score, was observed to be different between iloperidone- and ziprasidone-treated patients (Figure 1). None of the 6 SNPs significantly associated with iloperidone efficacy reached statistical significance for ziprasidone response. Furthermore, the improvement of symptoms for patients who carried the genotype associated with enhanced iloperidone efficacy was significantly greater ($p < .05$) in the iloperidone group than in the ziprasidone group for rs11851892 (*NPAS3*), rs9643483 (*XKR4*), rs875326 (*TNR*), and rs4528226 (*NUDT9P1*). Two of these SNPs, rs11851892 (*NPAS3*) and rs9643483 (*XKR4*), showed an opposite trend toward PANSS-T response between the treatment groups, in which the genotype associated with higher response to iloperidone (non-G/G) coincide with a slightly lower response to ziprasidone (Figure 1A and 1B). The

Figure 1. Genotype Effect of Individual SNPs on Treatment Efficacy[a]



[a]The change in PANSS-T score from baseline for iloperidone and ziprasidone is graphed by genotype for SNPs of the *NPAS3* (A), *XKR4* (B), *TNR* (C), *GRIA4* (D), *GFRA2* (E), and *NUDT9P1* (F) genes. The p values of the genotype effect within each treatment group, and between iloperidone- and ziprasidone-treated patients for the genotype associated with high response to iloperidone treatment, are shown.
Abbreviations: A = adenosine, C = cytidine, G = guanosine, PANSS-T = Positive and Negative Syndrome Scale-Total, SNP = single nucleotide polymorphisms, T = thymidine.

Figure 2. Genotype Effect of Iloperidone Efficacy Markers on Probability of Treatment Response[a]



[a]Effect of individual iloperidone efficacy markers (horizontal axis) on predicted probability of response (vertical axis) is shown by genotype. Squares represent probability of response for the genotypes associated with an enhanced or reduced response to iloperidone.

other 4 SNPs showed a similar trend for both antipsychotics (Figure 1C–1F). For each of the 6 SNPs, the difference of response between the genotype groups was consistently higher in iloperidone-treated patients (8.0 to 11.1 points improvement) than in patients who received ziprasidone (–2.1 to 4.7 points improvement).

The Probability of Iloperidone Response Based on Likelihood Ratio of Single Genetic Markers

Using single SNP genotyping data, we calculated the LR, which incorporates both the sensitivity and specificity of the genetic test for each marker. The LR provides a direct estimate of how much the test result changes the odds of responding to drug treatment.

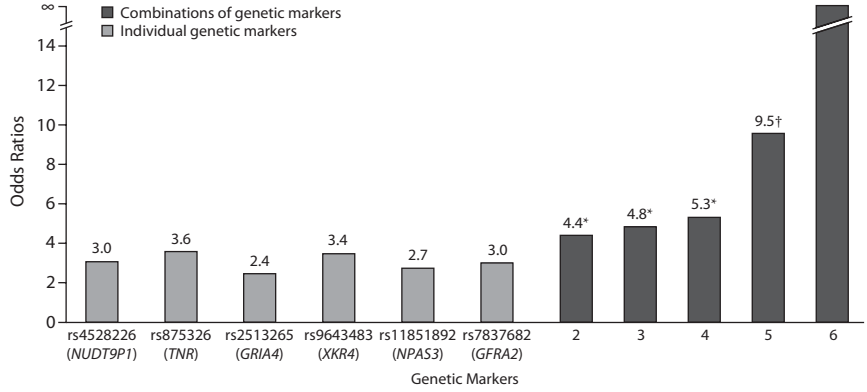
In the absence of genotype information, the proportion of patients treated with iloperidone who experienced a 20% or greater improvement was 46.7%. However, this proportion was predicted to increase for patients who carry a genotype associated with enhanced iloperidone response, from 51.8% for rs2513265 (*GRIA4*) to 65.2% for rs11851892 (*NPAS3*), depending on the marker tested (Figure 2). In contrast, posttest probabilities for the genotypes associated with lower iloperidone response ranged from 27.1% (rs9643483, *XKR4*) to 38.4% (rs11851892, *NPAS3*) (Figure 2).

The Additive Effect of Individual SNPs on Iloperidone Efficacy

In order to evaluate the individual contribution of the 6 markers associated with iloperidone efficacy, we performed a logistic regression analysis using a "full model" approach that included baseline PANSS-T values and blood drug exposure at day 28 because of their possible effect on treatment response. Both baseline PANSS-T score and blood drug exposure values had a limited but statistically significant effect ($R^2_{adj} = 0.046$, $p = .0016$). All SNPs tested with the exception of rs7837682 (*GFRA2*) contributed significantly to the model. A step-down approach with the remaining 5 genetic markers provides a predictive model for PANSS-T improvement, with an R^2_{adj} that increases from 4.6% (baseline and drug exposure effect alone, $p = .0016$) to 41.7% ($p < .0001$).

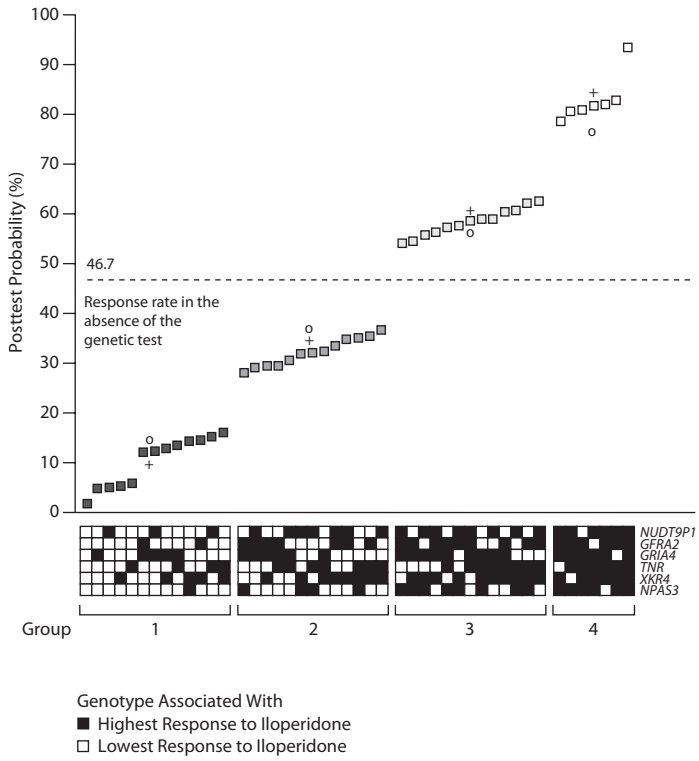
Odds ratio calculations estimated that, for each individual SNP, patients who carried the genotype associ-

Figure 3. Odds of Iloperidone Response for Single and Combined Genetic Markers[a,b]



[a]Odds ratios of response (≥ 20% improvement in PANSS-T score from baseline) for genotypes associated with enhanced iloperidone response are shown for individual genetic markers and for combinations of 2, 3, 4, 5, or 6 markers.
[b]The unfeasibility to calculate a specific odds ratio with the addition of the last genetic marker is represented by the infinity symbol.
*p < .0001.
†p < .005.
Abbreviation: PANSS-T = Positive and Negative Syndrome Scale-Total.

Figure 4. Iloperidone Efficacy per Genotype Group[a]



[a]Each genotype combination observed in the study is shown (horizontal axis) ordered by the predicted probability of ≥ 20% improvement (vertical axis). Groups of patients, 1 to 4, respectively, contain 0–2, 3, 4, and 5–6 genotypes associated with an enhanced response to iloperidone.
Symbols: + = the mean of the predicted posttest probability, 0 = the observed mean for each group.

ated with higher iloperidone efficacy were about 3 times more likely to experience a ≥ 20% improvement (from 2.4 for rs2513265 [*GRIA4*] to 3.6 for rs875326 [*TNR*]) than patients who carried the genotype associated with lower iloperidone efficacy (Figure 3). The likelihood increased with the number of genetic markers added, from 4.4 to 9.5 when the genotypes for rs875326 (*TNR*), rs2513265 (*GRIA4)*, rs9643483 (*XKR4*), and rs11851892 (*NPAS3*) associated with higher response were sequentially added to the model (Figure 3). With the addition of the last genetic marker, rs7837682 (*GFRA2*), no specific odds ratio could be calculated, since all patients with the optimal genotype combination (n = 11) improved by more than 20%.

The Combined Effect of Iloperidone Efficacy Markers

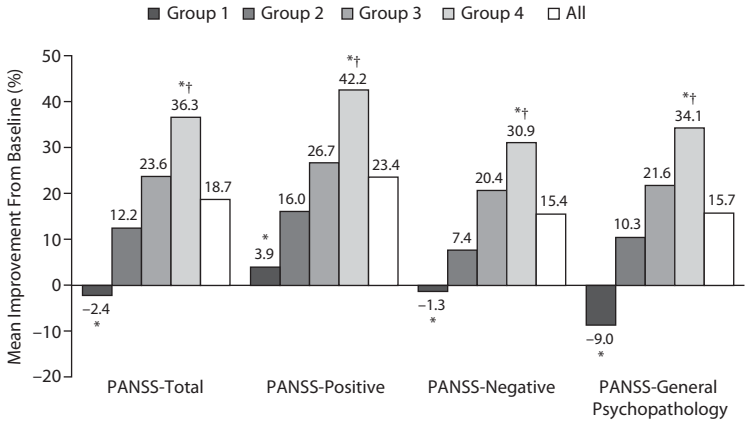
Since a patient can carry any genotype combination of the 6 efficacy markers, we investigated the effect of the various genotype combinations on the response to iloperidone treatment. Forty-six of the 64 possible 6-marker genotype combinations were observed in the iloperidone-treated group (Figure 4); based on the allele frequencies in this study, the other 18 combinations were expected to be rare (< 2% each). We defined 4 groups of genotype combinations (groups 1 to 4) based on the number of genotypes associated with enhanced response. Group 1 contained patients with 0 to 2 genotypes associated with enhanced response. Patients in group 2 had 3 genotypes associated with enhanced

Table 1. Patients With Improvement of Schizophrenia Symptoms Measured By Change in PANSS-T Scores

		Improvement From Baseline, %											
		≥ 20			≥ 30			≥ 40			≥ 50		
Group	N	Observed	Predicted	|O–P|[a]	Observed	Predicted	|O–P|[b]	Observed	Predicted	|O–P|[c]	Observed	Predicted	|O–P|[d]
1	45	15.6	10.2	5.4	6.7	3.9	2.8	2.2	2.1	0.1	2.2	0.5	1.7
2	53	34.0	31.8	2.2	17.0	14.1	2.9	13.2	9.0	4.2	3.8	3.0	0.8
3	56	57.1	57.3	0.2	32.1	33.4	1.3	23.2	22.5	0.7	7.1	10.0	2.9
4	58	75.9	81.5	5.6	60.3	63.8	3.5	46.6	50.3	3.7	34.5	33.3	1.2

[a]Mean = 3.4%.
[b]Mean = 2.6%.
[c]Mean = 2.2%.
[d]Mean = 1.0%.
Abbreviations: |O–P| = absolute value of the difference between observed and predicted values, PANSS-T = Positive and Negative Syndrome Scale-Total.

Figure 5. Improvement of Schizophrenia Symptoms per Genotype Group in Patients Treated With Iloperidone[a]



[a]The percentage of mean improvement is shown for PANSS-T and PANSS subscales by genotype group.
*Statistical difference ($p < .01$) from the overall iloperidone-treated group.
†Indicates statistical difference ($p < .01$) of a particular group when compared to the mean improvement of patients in the other 3 groups.
Abbreviation: PANSS-T = Positive and Negative Syndrome Scale-Total.

response, while patients in group 3 had 4. Group 4 included only patients with 5 or 6 genotypes associated with enhanced response (Figure 4). The proportion of patients in groups 1, 2, 3, and 4 was 21.2%, 25.0%, 26.4%, and 27.4%, respectively.

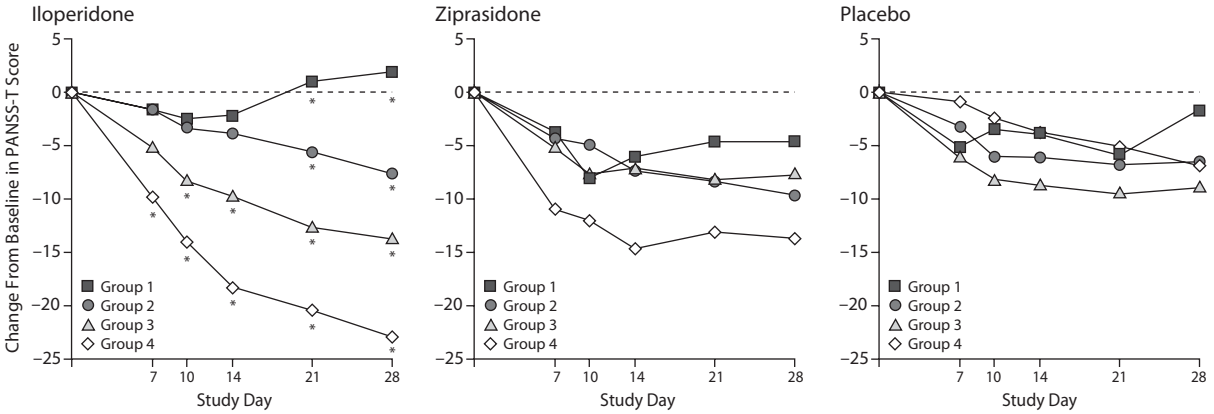
In this analysis, we observed that the probability of response to iloperidone treatment increases with the number of individual genotypes associated with efficacy carried by a patient (Figure 4). The mean of the posttest probability for ≥ 20% improvement was 10.2%, 31.8%, 57.3%, and 81.5% in groups 1, 2, 3, and 4, respectively. The greatest likelihood of response (92%) was achieved for patients in group 4 carrying all 6 genotypes associated with higher response to iloperidone. Indeed, the 11 patients with this optimal genotype combination improved by 30.5 points (or 51.7%) on average, almost 3 times higher than all other patients. Conversely, none of the 6 patients who carried the 6 genotypes associated with low response experienced an improvement of at least 20%, in agreement with a predicted rate of 1.9%. The probability of responding to treatment based on genotype data was comparable to the results observed in the clinical trial. This was consistent across all 4 groups, regardless of the improvement threshold used (Table 1).

The differences between observed and predicted values for the individual genotype groups varied from 0.1% to 5.6%. The mean differences across the 4 genotype groups decreased as the threshold increased, from 3.4% for a 20% improvement threshold down to 1.7% for a 50% threshold (Table 1). These results also indicate that the predicted values were not inflated by a bias in the LR method, which assumes independence of the genetic markers. The 6 markers tested herein are not molecularly or genetically linked. However, while it is possible that they have some level of dependence, the increased accuracy of prediction with increasing number of markers (Figures 3 and 4) strongly supports an additive value of each of the 6 markers.

Number Needed to Treat

The NNT describes the difference between treatment and control in achieving a particular clinical outcome. When using individual genetic markers, the NNT for patients who carried the genotype associated with higher iloperidone response ranged from 8 (95% CI = 3.8 to 468.2) for rs2513265 (*GRIA4*) to 4 (95% CI = 2.5 to 9.3) for rs7837682 (*GFRA2*). The NNT was reduced to 3 (95% CI = 1.7 to 6.4) for patients with the optimal 6-marker combinations (group 4). This small NNT indicates that a positive outcome occurs in nearly every patient with a favorable genotype who receives iloperidone as compared with placebo.

Figure 6. Time Course of Treatment Response per Genotype Group[a]



[a]Mean changes from baseline in PANSS-T score over time for iloperidone, ziprasidone, and placebo are shown for the different genotype groups (1–4).
*For each study day, differences in change from baseline are indicated for individual genotype groups by an asterisk when statistical significance ($p < .05$) was observed for all pairwise comparisons with the other 3 genotype groups.
Abbreviation: PANSS-T = Positive and Negative Syndrome Scale-Total.

Genotype Effect Across PANSS Subscales

The actual mean improvement in PANSS-T score of iloperidone-treated patients in group 4 was 3 times that of the patients in the other 3 groups (36.3% versus 12.1%, Figure 5). Patients in group 3 showed an improvement greater than the mean response of all 4 groups, but this did not reach statistical significance. Similarly, patients in group 2 had a slightly lower improvement than the mean response of all 4 groups. Patients in group 1 did not, on average, improve when compared with the patients in the other 3 groups (–2.4% versus 24.4%, $p = 2.6\ 10^{-10}$ for PANSS-T, Figure 5). The significant differences in improvement seen across the groups were also observed for the PANSS-P, PANSS-N, and PANSS-GP subscales (Figure 5).

The Effect of Iloperidone Efficacy Markers on the Rate of Improvement of Schizophrenia Symptoms

In our phase 3 clinical study, a 7-day titration schedule was used to reach the target dose of 24 mg/day. Time course analysis showed that the improvement of symptoms was gradual for iloperidone-treated patients in groups 2, 3, and 4. The efficacy response for iloperidone-treated patients in groups 3 and 4 was already statistically significant by day 7 ($p < .0001$), with further improvement throughout the remaining 28-day study (Figure 6). The efficacy response was statistically significant for patients in group 2 by day 10 ($p = .046$), with further improvement throughout the remainder of the study; patients in group 1 did not, on average, improve when compared to baseline. In addition, groups 3 and 4 started to significantly differentiate from the other genotype groups by days 10 and 7, respectively (Figure 6).

Drug Specificity of the Genotype Effect

Interestingly, the mean improvement for patients in group 4 treated with ziprasidone or placebo was not statistically different from that of patients in groups 1, 2, or 3 (Figure 6). The mean change in baseline score at day 28 for group 4 was –23.0 with iloperidone but only –13.8 with ziprasidone and –6.9 with placebo (Figure 6).

DISCUSSION

Similar to other complex diseases, schizophrenia is multifactorial in origin, with both genetic and environmental factors contributing to the manifestation of the symptoms. The heterogeneity of the nature, severity, onset, and course of the different symptoms indicates that a single genetic marker cannot accurately predict treatment outcome. We have presented several statistical methods that take advantage of various clinical and nonclinical parameters (i.e., severity of symptoms, drug exposure, and genotype data) to predict response to treatment. Furthermore, we showed the advantage of combining data from several genetic markers over using only individual marker information. In the case of the 6 genetic markers presented here, we have identified 4 groups of patients whose response to iloperidone is variable. We showed that the probability of response to treatment increased with the number of individual genotypes associated with efficacy carried by a patient, similar to what had been observed in our clinical trial. Of particular interest are the 27% of patients who carry 1 of the optimal genotype combinations (group 4). These patients experienced an improvement 3 times greater than that of other iloperidone-treated patients, with more than 75% reaching at least

20% improvement. Additionally, 34.5% of these patients achieved a 50% or greater improvement within 28 days (Table 1).

The 6 SNPs analyzed in our studies are associated with genes that are neither physically nor genetically linked and have no known direct biological connection. In the likelihood ratio analysis, we assumed that the 6 genetic markers were independent. Indeed, based on allele and genotype frequencies, the proportion of the genotype combinations observed was in agreement with that of independent SNPs (data not shown). Consequently, the fact that the differences between actual and predicted number of patients responding to treatment were limited (Table 1) indicates that each marker contributed to the treatment response, while some possible interrelated effect cannot be excluded.

We also showed how a time course analysis can provide information of when clinical benefit is expected for patients with specific genotypes. Physicians could share this information with patients when deciding on the best treatment for them. In our study, the beneficial response of patients in group 4 was significantly higher, even after only 1 week of treatment. Our data also suggest that these patients are likely to further respond to treatment throughout the following weeks. The relevance of early response or lack of response on the outcome of treatment of schizophrenia symptoms has been described previously.[28–31] The ability to identify patients who will respond quickly to treatment and who will have a sustainable improvement may be of importance in improving compliance with medication; it will also ensure an adequate trial in subjects who are likely to benefit. Those patients, whose genotypes are associated with a low rate of response, may be directed to alternative treatments.

Moreover, the difference in treatment efficacy between genotype groups was consistent across the positive, negative, and general PANSS subscales. Patients with different symptoms of schizophrenia may be able to benefit from a pharmacogenetic test that would determine their chance of responding to iloperidone. Genotyping, in combination with relevant clinical information, will be expected to offer a more accurate prediction of efficacy and side effects than the current standard of care's empirical trial-and-error approach.

Interestingly, the 6 genetic markers associated with iloperidone efficacy did not appear to predict response to ziprasidone (Figure 1). It is possible that the limited number of patients treated with ziprasidone in this study was not sufficient to reach statistical significance between genotypes or genotype groups. However, data analysis of individual SNPs (Figure 1) and genotype combinations (Figure 6) suggest that the genetic signature of iloperidone may not be applicable to ziprasidone, and possibly not to other antipsychotics. This finding may reflect differences in receptor binding profiles, chemical and metabolic characteristics between drugs that could be more or less susceptible to polymorphisms in proteins involved in their mechanism of action (i.e., neurotransmitter pathways) or their metabolism (i.e., cytochrome P450 enzymes). Indeed, findings of genetic associations with treatment effect of specific antipsychotics, such as efficacy or adverse events (i.e., weight gain), observed in a given population have not always been replicated in different populations or with alternative antipsychotics.

In conclusion, we have combined the genetic information of 6 genetic markers to predict and to evaluate the improvement of psychotic symptoms of patients with schizophrenia treated with iloperidone. Pharmacogenetics is likely to improve the ability of psychiatrists and their patients to choose the best available treatment option and ultimately improve the life of those affected with this severe chronic illness.

Drug names: iloperidone (Fanapt), ziprasidone (Geodon).

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