Genetic Variation in KCNH2 and a Unique hERG Isoform in Patients With Schizophrenia: Efficacy-Safety Link

To the Editor: Based on the results of an NIMH double-blind trial and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, Apud et al. (1) have provided support for the hypothesis of Huffaker et al. (2) that a genetic variation in the hERG1 protein, the KCNH2 3.1 isoform, may be related to treatment response. Could this hypothesis be extended to personalized medicine to minimize the risk of dysrhythmias related to QTc prolongation by giving antipsychotics only to those who will benefit from them? Or better, could we de-risk compounds by developing more targeted drugs that only bind to brain KCNH2 3.1?

The patient samples in the NIMH (N=54) and the CATIE study (N=364) are too small to predict with any statistical certainty whether or not individuals with the KCNH2 3.1 isoform were more likely to experience QT/QTc prolongation and related events, since torsade de pointes is extremely rare (3). In phase 1 of the CATIE study (4), 0/231 QTc prolongation events were reported in the olanzapine group, 6/214 (3%) in the quetiapine group, 7/218 (3%) in the risperidone group, 2/172 (1%) in the perphenazine group, and 2/148 (1%) in the ziprasidone group; these values were not statistically different, and there were no instances of torsade de pointes. Citrome and Stroup (5) calculated the number needed to harm based on these data and found it was between 31.1 and 86. Were these patients with QTc prolongation treatment responders? Did they carry the isoform KCNH2 3.1?

Extending this inquiry, might it be valuable to perform genotyping on patients in antipsychotic drug clinical trials who experience QTc prolongation or its sequelae?

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Response to Warner Letter

To the Editor: The letter from Dr. Warner concerning our article on the KCNH2 3.1 isoform and antipsychotic response in patients with schizophrenia (1) raises a very interesting question: Do patients with QTc prolongation respond differently (better or worse?) to antipsychotic drugs, and do they have risk-associated genotypes in KCNH2? Our study results show that risk-associated KCNH2 genotypes, which also predict greater expression in the brain of the novel, brain-selective KCNH2 3.1 isoform, responded better to antipsychotic drugs in both the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) outpatient study and in our NIMH inpatient placebo-controlled trial. As noted by Dr. Warner, the frequency of potentially clinically significant QTc prolongation in the CATIE study was too rare for us to test her question based on this qualitative untoward outcome. However, we could address the question of whether the KCNH2 risk-associated genotypes that predict better treatment response are associated with prolongation of the QTc interval measured on clinical ECGs, which are in the CATIE database. Among the 364 patients used in our treatment response data analysis, 340 had at least one measure of the QTc interval during phase 1/1A of the CATIE study (Table 1). We performed a general linear model analysis while controlling for sex, age, drug clearance, years of antipsychotic treatment, duration of disease, and mean chlorpromazine equivalents from change in QTc based on the last available ECG compared with baseline. We found no significant association of any of the three single-nucleotide polymorphisms (SNPs) in KCNH2 with change in QTc (Table 2). We also tested possible interactions of these SNPs with specific treatments, and again no significant interactions were found between treatment and any of the SNPs on QTc duration. While this sample is clearly underpowered to address this question more conclusively, the negative results are consistent with the evidence from earlier research (2)—the KCNH2 3.1 isoform associated with genotypes that predict better treatment response is a relatively brain-specific potassium channel with negligible expression in the heart.

In conclusion, recently identified schizophrenia risk-associated SNPs in KCNH2 that affect the processing of a brain-specific 3.1 isoform with unique physiologic properties do not appear to affect hERG1 potassium channel function in the heart and are

TABLE 1. Descriptive Statistics of Change in QTc From Baseline to Last ECG in Phase 1/1A of the CATIE Study by rs1036145 Genotype

Genotype	N	Mean	SD	Minimum	Maximum
CC	139	1.97	26.28	–62	62
TC	141	0.61	29.28	–80	119
TT	51	2.28	25.63	–53	63

TABLE 2. Association Analysis of QTc Change With Three Single-Nucleotide Polymorphisms at KCNH2: Genotypic Model

Source	df	F	p
rs3800779	2	0.49	0.61
rs748693	2	0.64	0.53
rs1036145	2	0.03	0.97

not likely to be related to antipsychotic drug-induced QTc prolongation. Dr. Warner's prescient question about whether the 3.1 isoform might be a target for the development of new antipsychotic agents is the subject of ongoing research.

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Unplanned Pregnancies in Adolescents With Bipolar Disorder

TO THE EDITOR: We conducted a naturalistic longitudinal study that prospectively assessed adolescents with bipolar disorder after their first manic episode. Each participant's legal guardian was given a complete description of the study, and they provided written informed consent; adolescents also provided written assent. The study was approved by the institutional review boards of the University of Cincinnati and Cincinnati Children's Hospital Medical Center.

In our study, 83% (19/23) of the adolescent girls (ages 15–19 years) were sexually active, and 30% (7/23) experienced an unplanned pregnancy at least once during the follow-up period (median weeks in study=105; median weeks to first pregnancy=59) while they were still under the age of 20. Additionally, six of eight pregnancies (one of the seven girls became pregnant twice as a teen) resulted in live births. To put this 26% (6/23) birth rate in context, local birth rates ranged from 0.46%–0.54% in the 15- to 19-year-old age group during the years over which the data were collected (1999–2006) (1). The high rate of teen pregnancy we observed is consistent with findings from a larger study (N=249) of bipolar adolescents, which reported a 5% 12-month prevalence of pregnancy, with higher rates in girls with substance use disorders (20%) than in those without (1%) (2).

Teens with bipolar disorder require treatment that proactively addresses the risks of unprotected sex as well as factors that may influence decisions about sexual behavior, such as substance use and psychiatric symptoms. Notably, 57% (4/7) of the pregnant teens in our study also had a substance use disorder, and 83% (5/6 with complete data) were experiencing at least subthreshold affective episodes at the time of conception, with two girls (33%) meeting full criteria for mania (N=1) or depression (N=1).

The high rates of unplanned pregnancies we observed also suggest that teratogenicity should be considered when prescribing psychotropic medications to adolescent girls, as exposure could harm a developing fetus during a critical period of development (i.e., the first trimester), before the pregnancy is discovered. In one-half (N=4) of the pregnancies in our sample, psychotropic medications were being taken around the time of conception. In each case, the medications were discontinued at varying points during the first trimester: almost immediately (N=1), after 1 month (N=2), and after 3 months (N=1). Three of the four pregnancies resulted in live births, with no gross anomalies noted in the newborns. The other pregnancy, in which medication was discontinued almost immediately, resulted in a spontaneous abortion after 2 months. Further study of pregnancy outcomes in these adolescents is needed to understand the risks associated with prescribing teratogenic medications to at-risk teenage girls with bipolar disorder.

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