Interaction of Pipamperone Augmentation of Citalopram and Genetic Variables in the Prediction of Antidepressant Response

Elisabeth Binder,[1,2] Charles Nemeroff,[3] Alan Schatzberg,[4] Thomas Schlaepfer,[5] Kees Bol,[6] Ludo Haazen,[7] Didier De Chaffoy,[7] Erik Buntinx[7]

[1]Max-Planck Institute of Psychiatry, Munich, Germany; [2]Emory University School of Medicine, Atlanta, GA, USA; [3]University of Miami Miller School of Medicine, Miami, FL, USA; [4]Stanford School of Medicine, Stanford, CA, USA; [5]University of Bonn, Bonn, Germany, and Johns Hopkins University School of Medicine, Baltimore, MD, USA; [6]Kinesis Pharma BV, Breda, Netherlands; [7]PharmaNeuroBoost N.V., Alken, Belgium

Abstract

Background: Individual variability observed in therapeutic response to antidepressant drug treatment is thought to be -in part- genetically determined. In a search for genetic predictors of antidepressant response in 1953 patients treated with citalopram (CIT) in the STAR*D trial, McMahon et al., reported that variation in the gene encoding the serotonin 2_A receptor ($5HTR_{2A}$) was associated with antidepressant treatment outcome. Pipamperone (PIP) is an antipsychotic drug that is not available in the US, but is widely used in Germany, Belgium and other EU countries. PIP is a highly potent and selective antagonist at the $5-HT_{2A}$ and D_4 receptors when administered at very low doses (5 to 15 mg/day). In a randomized, double-blind proof-of-concept (POC) study in major depression (DSM-IV), PIP at those low doses was found to both accelerate and augment the antidepressant effects of CIT with no additional side effect burden.

Methods: As part of a separate protocol, approved by the responsible IRB, patients participating in the POC study were asked to participate in pharmacogenetic testing. Of the 165 patients enrolled into the POC study, 89 consented to this additional protocol, 44 of them receiving CIT and 45 PIPCIT. Pharmacogenetic assessments included polymorphisms in 2 genes influencing the pharmacokinetics of CIT and PIP: *CYP2D6* and *ABCB1*, as well as polymorphisms in 5 genes known to be related to pharmacodynamic effects of selective serotonin receptor inhibitors: the serotonin transporter, *BDNF, COMT, 5HTR2A* and *FKBP5*. In addition, the analysis included three putatively functional polymorphisms in genes regulating dopaminergic transmission: *DRD4, DRD3* and the dopamine transporter gene. Here we present the results of an exploratory analysis on the relation of the assessed genetic variants and the onset of antidepressant effect, quantified by means of T_{50} values. T_{50} was defined as the time to 50% of the maximum observed antidepressant effect, i.e. 50% of the maximum drop in MADRS score and was obtained by means of population pharmacokinetic/pharmacodynamic (PK/PD) modeling.

Results: In this subsample, augmentation with PIP led to a highly significant reduction of T_{50} ($p<0.001$), with the T_{50} being over 5 days shorter in patients treated with PIPCIT than patients treated with CIT alone. Of the 19 tested polymorphisms, only the *BDNF* Val66Met polymorphism had a significant main effect on T_{50} ($p=0.04$, genotypic model). Using a general linear model, we then tested the interaction of the genetic predictors with the treatment arm on T_{50}, and observed a significant treatment by SNP interaction for the *BDNF* Val66Met polymorphism ($p=0.038$) as well as for rs7997012 within the *5HTR2A* gene ($p=0.024$). In both cases, significant effects of the polymorphisms were only seen in CIT but not the PIPCIT group. In fact, for carriers of the *BDNF* Met risk allele, the improvement of T_{50} by the augmentation was 7.7 days on average vs. 4.2 days for the Val/Val carriers. For carriers of the rs7997012 risk allele, the improvement was 6.6 days, vs 1.6 days for the carriers of the rarer beneficial AA genotype. *CYP2D6* metabolizer status did not have an effect on T_{50} in either treatment group.

Discussion: Augmentation with PIP led to significant reduction in T_{50}. Polymorphisms in *BDNF* and *5HTR2A*, previously reported to be associated with response to antidepressant treatment, predicted T_{50} only in the CIT but not the PIPCIT group. Improvement of T_{50} with PIP augmentation was much more pronounced in carriers of the previously defined non response alleles. This suggests that patients carrying special genetic polymorphisms known to be associated with poorer response to traditional antidepressant drugs would especially profit from PIP augmentation.

Background

- Citalopram (CIT) is a selective serotonin reuptake inhibitor (SSRI) used as a first-line agent for the treatment of major depressive disorder (MDD). A genetic study of phenotypes measuring outcome of CIT treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study detected a significant association with a variant located in the serotonin 2A receptor gene (*HTR2A*).[1]

- Pipamperone (PIP) is a mild antipsychotic used in the treatment of schizophrenia in a number of EU countries. At recommended doses (120–360 mg/d), PIP is only a moderate dopamine D_2-receptor antagonist; at low doses (5–15 mg/d), PIP is a highly selective $5-HT_{2A}$ and D_4 receptor antagonist.

- A randomized, double-blind proof-of-concept study in 165 patients with moderate to severe MDD showed that the addition of low-dose PIP (5 mg twice daily [BID]) augmented and accelerated the antidepressant effect of CIT.

- Patient response is difficult to predict because of the highly variable rates of efficacy and tolerability to antidepressant drugs among individuals.

  - Contributors to this variability include clinical heterogeneity and psychophysiological, psychosocial, and genetic factors.

Objective

- To investigate whether genetic variation predicts the onset of response to PIPCIT combination therapy or CIT monotherapy in patients with MDD

Methods

Patients

- Participants (n=89) were patients with moderate to severe MDD without psychotic symptoms (as defined by *DSM-IV*) who participated in a phase II trial (n=165) that tested the efficacy and tolerability of PIPCIT combination therapy in a randomized, double-blind study (ClinicalTrials.gov identifier: NCT00672659).

- For each participant, 20 mL of whole peripheral blood was obtained by venipuncture.

- Patients received combination treatment with CIT 40 mg once daily (QD) plus PIP 5 mg BID or CIT 40 mg QD plus placebo BID in a fixed-dose titration design.

- The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice; all patients provided written informed consent.

Primary Outcomes

- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) score at 8 weeks

- The onset of antidepressant effect, defined as the time to reach 50% of the maximum decrease in total MADRS score (T_{50}), identified by a population pharmacokinetic (PK)/ pharmacodynamic (PD) model

Genetic Variants and Genotyping

- 25 single nucleotide polymorphisms (SNPs) were selected from 11 genes that were involved in the PK of PIP or CIT (ABCB1 and CYP2D6), the PD effects of SSRIs (BDNF, COMT, FKBP5, HTR2A, and SLC6A4), or the regulation of dopamine transmission (DRD3, DRD4, and SLC6A3), or were reported to be associated with antidepressant treatment outcomes (CRHR1).

- DNA was extracted from whole blood using a BioRobot M48 automated extraction system (QIAGEN, Valencia, CA). Variants were genotyped using Taq-Man® assays on a 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA).

- To distinguish between the long and short alleles of the variant in the promoter of the serotonin receptor (*5HTTLPR*), fluorescent-labeled primers and polymerase chain reaction products were electrophoresed with an ABI Prism 3730 DNA sequencer (Applied Biosystems, Foster City, CA).

- Metabolizer status was inferred from the genotyping of 6 SNPs in the CYP2D6 gene; individuals were classified as extensive, intermediate, or poor metabolizers based on the identified haplotypes.

Statistical Analyses

- A general linear model with T_{50} as the dependent variable was used to measure the main effect of each SNP and the interaction between each SNP and the treatment received.

- Both genotypic and dominant models were tested, combining patients who carried the risk allele for a worse response and noncarriers.

- For 2 significant SNPs, interaction analyses assessed the effect of carrying both the BDNF (Met/Met or Val/Met) and HTR2A risk genotypes (GG or AG) vs beneficial genotypes on T_{50} in each treatment group.

Results

- Demographic and clinical characteristics were similar between groups (**Table 1**).

Table 1. Demographic and Clinical Characteristics of Patients Included in the Pharmacogenetic Study

	Treatment Group	
Characteristics	CIT (n=44)	PIPCIT (n=45)
Mean ± SD age (range)	44.7±11.3 (20–64)	43.3±11.8 (20–68)
Men/Women	11/33	5/40
White, n (%)	44 (100)	44 (100)
Mean ± SD duration of current MDD episode, d (range)	104±44 (12–220)	96±39 (31–188)
Duration >12 wk, n (%)	27 (61)	23 (51)
Mean ± SD MADRS total score (range)	32.8±5.8 (19–44)	32.2±5.0 (21–42)
MADRS ≥30, n (%)	34 (77)	28 (62)
Any previous psychiatric history, n (%)	28 (64)	38 (84)
Any ongoing psychiatric diagnosis in addition to MDD, n (%)	4 (9)	2 (4)

CIT=citalopram; MDD=major depressive disorder; MADRS= Montgomery Åsberg Depression Rating Scale; PIP=pipamperone.

- The time to reach onset of antidepressant action averaged 5.6 days earlier for patients receiving PIPCIT ($P<0.001$).

- All SNPs were successfully genotyped, with a mean call rate of 98.7%, and all of them were in Hardy-Weinberg equilibrium ($P>0.05$).

- There was no significant effect of variants in ABCB1, COMT, FKBP5, DRD3, DRD4, serotonin and dopamine transporters, the CRH receptor 1, or the metabolizer status with the onset of the antidepressant action (T_{50}).

- The SNP associated with T_{50} was the functional Val66Met polymorphism in the BDNF gene (rs6265). Patients carrying the Met allele showed an average delay of 2.6 days in their improvement in T_{50} ($P=0.005$; genotypic model).

- Results from the interaction of each SNP with the treatment group showed that

  - 2 SNPs (rs6265 in BDNF and rs7997012 in HTR2A) modified the mean T_{50} depending on the treatment type ($P=0.038$ and $P=0.024$, respectively).

  - Patients carrying the allele known to be associated with worse antidepressant response (Met for rs6265 and G for rs7997012) had a significantly later onset of antidepressant action when treated with CIT (**Table 2; Figure 1**) but benefited most from the PIP augmentation.

Figure 1. Time to Reach 50% of the Maximum Decrease in Total Montgomery-Åsberg Depression Rating Scale score (T_{50}) as a Function of Treatment Received and Genotype in 2 Significant SNPs: (A) Functional Val66Met Variant in BDNF and (B) HTR2A

CIT=citalopram; PIP=pipamperone.
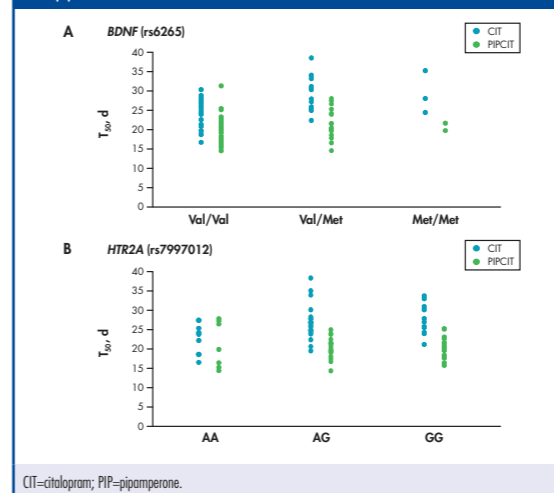
- Patients who received PIP augmentation and carried the Met risk allele in BDNF improved in T_{50} by a mean average of 7.7 days compared with those patients who only received CIT, and by 6.6 days if they were carriers of the G risk allele of rs7997012 in HTR2A (**Table 2**). Patients with other genotypes benefited from the PIP augmentation to a lesser extent (4.3 d earlier response in the case of BDNF and 1.7 d in the case of HTR2A).

- Patients who received PIP augmentation and carried the risk genotypes of both the BDNF and HTR2A SNPs improved 9 days earlier than patients with the same genotype configuration but who received CIT alone (**Table 2; Figure 2**).

Figure 2. Plot of the Time to Reach 50% of the Maximum Decrease in Total Montgomery-Åsberg Depression Rating Scale score (T_{50}) as a Function of Treatment Received and Being a Carrier of Beneficial or Risk Genotypes at Val66Met Variant in BDNF and HTR2A

CIT=citalopram; PIP=pipamperone.
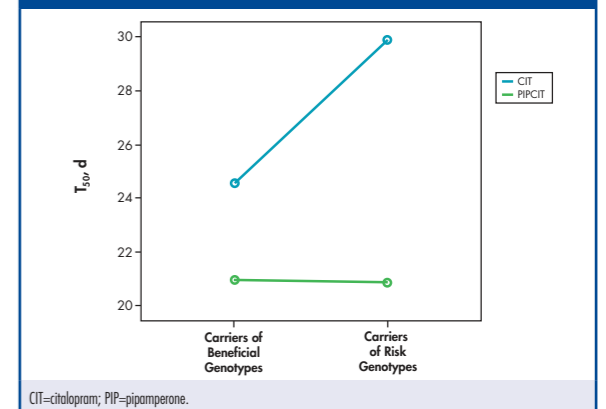
Conclusions

- Both BDNF and HTR2A were previously reported to be associated with response to antidepressant treatment. The rs7997012 AA genotype in HTR2A is associated with a better response to CIT,[2] whereas both the Val and the Met allele in BDNF have been related to a better response to different antidepressants.

- PIPCIT produced overall greater improvements in the clinical response to treatment compared with CIT monotherapy.

- Genetic variants in BDNF and HTR2A can predict a slower response to CIT treatment.

- Patients carrying the nonresponse alleles for these SNPs might benefit most from combination therapy with PIP and CIT.

References

1. McMahon FJ, et al. *Am J Hum Genet.* 2006;78(5):804-14.
2. Horstmann S, Binder EB. *Pharmacol Ther.* 2009;124(1):57-73.

Table 2. Results for the 2 Significant SNPs Modifying the Onset of Antidepressant Response in Each Treatment Group

dbSNP ID	Good Response Allele	Genotype	Number of Patients (CIT/PIPCIT)	Mean T_{50}, d (95% CI) CIT	Mean T_{50}, d (95% CI) PIPCIT	P Value
rs6265	Val	Val/Val	52 (26/26)	24.8 (23.3–26.2)	20.5 (19.0–21.9)	
		Met carriers (Val/Met or Met/Met)	37 (18/19)	29.2 (27.5–31.0)	21.5 (19.8–23.3)	0.038
rs7997012	A	AA	16 (9/7)	23.0 (20.4–25.5)	21.3 (18.4–24.3)	
		G carriers (AG or GG)	72 (34/38)	27.5 (26.1–28.8)	20.9 (19.6–22.1)	0.024
rs6265*rs799012	Val+A	Val/Val + AA, Val/Val + G carriers Met carriers + AA	58 (27/31)	24.6 (23.1–30.0)	21.0 (19.6–22.3)	
		Met carriers and G carriers	30 (16/14)	29.9 (28.0–31.7)	20.9 (18.9–22.8)	0.002

CIT=citalopram; PIP=pipamperone; SNP= single nucleotide polymorphisms; T_{50}=time to reach 50% of the maximum decrease in total Montgomery-Åsberg Depression Rating Scale score. *Interaction.