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).

• Pramipexole (P) is a weak antipsychotic used in the treatment of schizophrenia in a number of EU countries.

Methods

• Participants (n=89) were patients with moderate to severe MDD without psychosis (as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) who participated in a phase II trial (n=165) that tested the efficacy and tolerability of PIP/CIT combination compared to CIT monotherapy in a randomised, double-blind study (ClinicalTrials.gov identifier: NCT00767259)

• 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).

• Results from the interaction of each SNP with the treatment group showed that 2 SNPs (rs6265 and rs7997012) modified the mean T50, 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 2) but benefited most from the PIP augmentation.

• Patients who received PIP augmentation and carried the Met risk allele in BDNF improved in T50 by a mean of 7.7 days compared with those patients who only received CIT and by 6.6 days if they were carriers of the Val risk allele in BDNF.

Results

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

Both BDNF and HTR2A were previously reported to be associated with response to antidepressant treatment. Treatment with PIP in 2012 (A allele group) and HTR2A is associated with a slower response to CIT, whereas both the Val and the Met allele in BDNF have a better response to different antidepressants.

• PIPECIT produced overall greater improvements in PIP/CIT interaction associated with CIT monotherapy. Patients carrying the nonresponse alleles for these SNPs might benefit most from combination therapy with PIP and CIT.

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

• Differences in the time to reach 50% of the maximum decrease in total Montgomery-Åsberg Depression Rating Scale score (T50) as a Function of Treatment Received and Genotype in 2 Significant SNPs: (A) Functional BDNF Val66Met Variant in BDNF and (B) HTR2A (rs7997012) (Figure 2).

Conclusions

Author’s Disclosures

Dr. Elizabeth Brinder, Dr. Kea Bol, Prof. Dieter de Chaffoy, Dr. Ido Hozo are consultants to PharmaNeuroBoost. Prof. Charles Nemeroff, Prof. Alan Schatzberg, and Prof. Thomas Schlaepfer are members of the Scientific Advisory Board of PharmaNeuroBoost and are also shareholders in the company. Prof. Nemeroff additionally serves on the Scientific Advisory Board of PharmaNeuroBoost and is also a consultant for Lundbeck. Prof.  Schlaepfer is a consultant for Corcept, Pfizer, Lilly, Neuronetics, BrainCells, Aravette, Sanfil, Teleda, CeNeRx, CNS Response, Viva, Bosch, Xytis, Lundbeck, Forest laboratories and GSK. Prof. Schatzberg receives income from Stanford use patents. Prof. Schlaepfer is a consultant for Lundbeck, Prof. De Chaffoy is Chief Scientific Officer and Dr. Hozo is Chief Medical Officer of PharmaNeuroBoost. Dr. Erik Bunton is a psychiatrist, Chief Executive Officer and Managing Director of PharmaNeuroBoost, and is also a shareholder in PharmaNeuroBoost.

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• Both BDNF and HTR2A were previously reported to be associated with response to antidepressant treatment. Treatment with PIP in 2012 (A allele group) and HTR2A is associated with a slower response to CIT, whereas both the Val and the Met allele in BDNF have a better response to different antidepressants. PIPECIT produced overall greater improvements in PIP/CIT interaction associated with CIT monotherapy. Patients carrying the nonresponse alleles for these SNPs might benefit most from combination therapy with PIP and CIT.

References

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