The Association Between *HTR2C* Gene Polymorphisms and the Metabolic Syndrome in Patients With Schizophrenia

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Abstract: The use of antipsychotics is associated with metabolic side effects, which put patients with schizophrenia or related disorders at risk for cardiovascular morbidity. The high interindividual variability in antipsychotic-induced metabolic abnormalities suggests that genetic makeup is a possible determinant. In this cross-sectional study, we investigated whether genotypes of the HTR2C receptor are associated with the metabolic syndrome in patients using antipsychotics. Patients were identified from a schizophrenia disease management program. In this program, patients' blood pressure, triglycerides, high-density lipoprotein–cholesterol, and waist circumference are measured regularly during follow-up. The primary end point of our study was the prevalence of the metabolic syndrome as classified by a modified version of the National Cholesterol Education Program's Adult Treatment Panel III. Primary determinants were polymorphisms in the HTR2C receptor gene (HTR2C:c.1–142948[GT]n, rs3813928 [–997 G/A], rs3813929 [–759 C/T], rs518147 [–697 G/C], and rs1414334 [C > G]). The included patients (n = 112) mainly (>80%) used atypical antipsychotics (clozapine, olanzapine, and risperidone). Carriership of the variant alleles of the HTR2C polymorphisms rs518147, rs1414334, and HTR2C:c.1–142948(GT)n was associated with an increased risk of the metabolic syndrome (adjusted odds ratio [OR], 2.62 [95% confidence interval {CI}, 1.00–6.85]; OR, 4.09 [95% CI, 1.41–11.89]; and OR, 3.12 [95% CI, 1.13–8.16]), respectively. Our findings suggest that *HTR2C* genotypes are associated with antincreased risk of metabolic syndrome in patients taking antipsychotics.

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Metabolic side effects of antipsychotic drugs including lipid abnormalities, disturbed glucose metabolism, and weight gain can have a major impact on the treatment of psychiatric patients.[1–4] These metabolic side effects are part of the metabolic syndrome that is increasingly recognized as an independent risk factor for diabetes type 2 and cardiovascular outcomes.[5–7] Although controversy exists about the causal mechanisms, the metabolic syndrome seems to be more prevalent among psychiatric patients treated with antipsychotic drugs compared with the general population.[8,9] The mechanism behind antipsychotic-induced metabolic abnormalities is not entirely clear. The high interindividual differences suggest that genetic makeup is a modulating factor. One of the potential genetic determinants is genetic variation in the serotonin 2C (5-HT2C) receptor encoded by the *HTR2C* gene. The 5-HT2C receptor is of interest because of the increased feeding behavior and obesity observed in 5-HT2C knockout mice and studies in humans showing genetic association with obesity and some eating disorders.[10–12] Furthermore, the antipsychotics that have been associated with the largest risk of weight gain, lipid abnormalities, and glucose intolerance (clozapine and olanzapine) have a relatively high affinity for the 5-HT2C receptor when compared with other antipsychotics.[13]

Yuan et al[14] found that several polymorphisms in the promoter region of the *HTR2C* gene were associated with an increased risk of diabetes and obesity in patients without psychiatric disorders. These findings resulted in several studies investigating the association between antipsychotic-induced weight gain and one of these polymorphisms (–759 C/T; a single nucleotide polymorphism [SNP] with dbSNP database [www.ncbi.nlm.nih.gov/SNP] identifier rs38139 29). Reynolds et al[15,16] and others[17–20] found a positive association between the *HTR2C* rs3813929 (–759 C/T) polymorphism and antipsychotic-induced weight gain. However, other studies could not confirm the association.[21–23] To our knowledge, there are no studies available in which the association between polymorphisms in the *HTR2C* gene and the metabolic syndrome was investigated. The objective of this cross-sectional study was to evaluate whether polymorphisms in the *HTR2C* gene are associated with the metabolic syndrome in psychiatric patients using antipsychotics.

MATERIALS AND METHODS

Setting

Patients were recruited from the Department of Psychotic Disorders of the General Psychiatric Hospital GGZ Drenthe in the Northern part of the Netherlands. The department houses several psychiatric services and treats inpatients and outpatients with schizophrenia and schizoaffective disorder, covering a population of approximately 200,000 persons. Patients were identified from a schizophrenia disease management program developed by the department. Patients taking part in this program are followed over time by regular standardized evaluation of the patient and measurements of blood pressure, body mass index, triglycerides, high-density lipoprotein (HDL)–cholesterol, and waist circumference. For each patient, a prescription file is available listing patient details (age, date of birth, and identification), drug details (name of drug and dosage regimen and start and stop date), and treatment details (diagnosis, compliance, and adverse events). The study protocol was reviewed and approved by an independent medical ethical committee (METIGG, Utrecht, The Netherlands).

Design and Patients

A cross-sectional design was used to assess the relationship between *HTR2C* variants and the metabolic syndrome in psychiatric patients using antipsychotics. Patients were eligible if they participated in the disease management program. The antipsychotic drug used during the first evaluation of the patient had to have been started at least 3 months before this evaluation. This inclusion criterion was used because weight gain occurs mainly during the first 3 months after the first prescription of the drug.[24] We used this criterion to exclude patients in which antipsychotic-induced weight gain did not yet occur. After complete description of the study to the patients, written informed consent was obtained. Patients were included between August 2004 and April 2005.

Outcome Measures

Primary end point of the study was the presence of the metabolic syndrome. The metabolic syndrome was defined according to a modified version of the definition of the National Cholesterol Education Program's Adult Treatment panel III (NCEP:ATP III).[5] A patient was classified as having the metabolic syndrome if 3 or more of the following 4 metabolic parameters were out of the specified range: waist circumference of greater than 102 cm (male patients) or greater than 88 cm (female patient), triglycerides of 1.7 mM or higher, HDL-cholesterol of less than 1.0 mM (male patient) or less than 1.3 mM (female patient), and blood pressure of 135/85 mm Hg or higher or use of antihypertensive medication. Although the NCEP:ATP III definition specifies a fifth metabolic parameter, namely fasting plasma glucose of 6.1 mM or greater, this was not measured in the disease management program. Therefore, the modified definition has a greater emphasis on cardiovascular risk rather than on diabetic risk because of the absence of glucose measurements. Secondary end points were the individual metabolic parameters mentioned above.

Determinants

Primary determinants were genotypes of polymorphisms flanking, or within, the X-linked *HTR2C* gene (genomic structure can be found at www.ensembl.org). In light of the possible impact of findings for psychiatric patients taking antipsychotics and the conflicting results published so far, we decided to genotype all the promoter polymorphisms published by Yuan et al.[14] The following polymorphisms in the promoter region were investigated: rs3813928 (−997 G/A), rs3813929 (−759 C/T), rs518147 (−697 G/C), and a $(GT)_n$ dinucleotide repeat polymorphism 30 nucleotide upstream of rs3813928.[14] This dinucleotide polymorphism has no official symbol in genomic variation databases and will be referred to in this paper as HTR2C: c.1−142948$(GT)_n$. In addition, a frequent SNP in intron 5 of the *HTR2C* gene close to the 3′UTR was investigated (rs1414334 C > G). No other genes or genetic variants were investigated in the cohort. With regard to *HTR2C* polymorphism nomenclature, we use the nomenclature and nucleotide numbering at the genomic level according to the guidelines of the Human Genome Variation Society (www.hgvs.org) and the ''traditional'' nomenclature and numbering used in previous publications for reasons of clarity. The rs1414334 polymorphism allele C is thought to be the ancestral allele (dbSNP database: www.ncbi.nlm.nih.gov/SNP). However, in Western and Northern Europeans, allele G seems to be the major allele. In the analysis, we therefore considered the allele C as the variant allele.

DNA Isolation and Genotyping by Pyrosequencing

Genomic DNA was isolated from EDTA-anticoagulated peripheral blood using standard methods. The *HTR2C* genotypes were determined by pyrosequencing, except for the HTR2C:c.1−142948$(GT)_n$ repeat polymorphism.[25,26] The dinucleotide repeat polymorphism was determined by polymerase chain reaction and subsequent determination of the length of the alleles by direct analysis on an automated capillary sequencer (ABI3730; Applied Biosystems) using standard conditions. Detailed information on genotyping procedures, including primer sequences and reaction conditions, is available upon request. The researcher was blinded to the genotyping results, and results were not available to the treating psychiatrist before data analysis.

Data Analyses and Statistics

Pharmacy records and other patient information were transferred to a database (MS Access) for analysis. The prescribed daily dose (PDD) was defined as the administered dosage divided by the defined daily dose (DDD) (PDD = dosage/DDD) according to the World Health Organization guidelines. Concomitantly used medication that influence weight, lipid levels, or glucose measurements of the included patients were assessed according to available evidence.[1,27]

For all variants, Hardy-Weinberg equilibrium testing was performed. Pairwise linkage disequilibrium was analyzed using the software program Haploview (version 3.31).[28] The association between the metabolic syndrome

and *HTR2C* genotypes (presence or absence of the variant *HTR2C* allele) was investigated with logistic regression. In an exploratory analysis, the individual metabolic parameters were investigated using logistic regression as well. The strength of the associations was expressed as odds ratios (ORs) together with a 95% confidence interval (CI) using the genotype, with only the common allele as a reference. Data were investigated for potential confounding effects of age, sex, type and dosage of the antipsychotic drugs used, polypharmacy (more than 1 antipsychotic drug at the same moment), weight-influencing drugs, lipid-influencing drugs, glucose metabolism–influencing drugs, and whether the patient was hospitalized. We included the variable in the multivariate model if it was univariately associated with the metabolic syndrome at a significance level of $P < 0.20$.[29] Unless stated otherwise, results are expressed as adjusted ORs. Because the *HTR2C* gene is located on the X chromosome, data were investigated for interaction between carriership of variant alleles and sex. Finally, a combined genotype analysis was performed. In female patients, combined genotypes were classified as the combinations of individual *HTR2C* polymorphism genotypes. In male patients, these cosegregating alleles for the individual polymorphisms are in fact haplotypes. A P value of 0.05 or less was regarded as significant. A Bonferroni correction was applied for the analyses of the primary outcome measure (presence of the metabolic syndrome) regarding the individual polymorphisms.[30] Data were analyzed using SPSS 11.0.

RESULTS

In total, 112 hospitalized (n = 27) and nonhospitalized (n = 85) psychiatric patients with a chronic psychiatric disorder (mainly schizophrenia [n = 70 {63%}] or schizoaffective disorder [n = 28 {25%}]) gave informed consent for participation in this study. The included patients were mainly white (>95%) patients with a mean age of 36 years (SD, 10), and 66% (n = 74) were men.

The most frequently used antipsychotics were clozapine (n = 41 [37%]), olanzapine (n = 36 [32%]), and risperidone (n = 24 [21%]). Other antipsychotics used were bromperidol (n = 2), flupentixol (n = 2), haloperidol (n = 2), perphenazine (n = 1), pimozide (n = 1), quetiapine (n = 1), and zuclopenthixol (n = 2). Polypharmacy was present in 16 (14%) of the included patients. Polypharmacy was associated with an increased risk of the metabolic syndrome (OR, 3.40 [95% CI, 1.03–11.24]) compared with patients without polypharmacy.

Genotype distribution of the polymorphisms analyzed in this study did not deviate significantly from Hardy-Weinberg equilibrium (HTR2C:c.1–142948[GT]$_n$ [$P > 0.1$], rs3813928 [–997 G/A] = rs3813929 [–759 C/T] [$P = 0.1888$], rs518147 [–697 G/C] [$P = 1.0$], and rs1414334:C > G [$P = 1.0$]).

The complete linkage disequilibrium ($r^2 = 1$) between the rs3813928 (–997) A allele and the rs3813929 (–759) T allele as described previously was confirmed in this study.[14] The rs518147 C allele and the HTR2C:c.1–142948(GT)$_n$ 13 repeat allele were in complete linkage disequilibrium as well. Linkage disequilibrium r^2 values for other SNP pairs were all

TABLE 1. Primary End Point: Relative Risk of Metabolic Syndrome

Genotype	n	Metabolic Syndrome	Crude OR (95% CI)	Adjusted* OR (95% CI)
Genotype analysis†	112	28 (25%)	—	—
HTR2C:c.1–142948(GT)$_n$13R‡	45	16 (36%)	2.45 (0.99–6.07)	3.12 (1.13–8.16)
rs3813928 A/rs3813929 T	26	7 (27%)	1.14 (0.42–3.09)	1.18 (0.40–3.47)
rs518147 C	48	16 (33%)	2.17 (0.91–5.16)	2.62 (1.00–6.85)§
rs1414334 C‖	21	10 (48%)	3.69 (1.36–10.02)¶	4.09 (1.41–11.89)#
Combined genotype analysis**				
Combined genotype 1††	59	10 (17%)	1.00 (reference)	1.00 (reference)
Combined genotype 2	23	6 (26%)	1.73 (0.55–5.48)	2.06 (0.58–7.35)
Combined genotype 3	18	8 (44%)	3.92 (1.24–12.40)‡‡	4.69 (1.34–16.45)§§

*Data were adjusted for polypharmacy, glucose-lowering comedication, and lipid-lowering drugs.

†Data were analyzed with the common genotype as the reference for all polymorphisms.

‡HTR2C:c.1–142948(GT)$_n$ was analyzed for the most frequent alleles 16 repeat (R) and 13 R (total number of patients n = 104), with 16 R as the reference.

§$P = 0.049$.

‖The Bonferroni correction was applied to the analyses of the individual polymorphisms (4 tests). The result of the rs1414334 C allele remained significant after the correction ($P = 0.042$).

¶$P = 0.011$.

#$P = 0.01$.

**In total, 12 combined genotypes were found only once and are therefore not taken into account in the analysis.

††Combined genotype 1 (absence of variant alleles HTR2C:c.1–142948[GT]$_n$13R, rs3813929 T, rs518147 C, and rs1414334 C), combined genotype 2 (presence of HTR2C:c.1-142948[GT]$_n$13R allele, rs3813929 T, and rs518147 C and absence of the rs1414334 C allele), combined genotype 3 (absence of variant rs3813929 T allele and presence of HTR2C:c.1-142948[GT]$_n$13R allele, rs518147 C, and rs1414334 C).

‡‡$P = 0.02$.

§§$P = 0.016$.

TABLE 2. Individual Metabolic Determinants and HTR2C Polymorphisms

	Genotype*†‡			
Determinant§‖	**$(GT)_n$ 13R**	**−997 A/−759 T**	**−697 C**	**3′UTR C**
HDL	2.02 (0.86–4.76)	2.00 (0.80–5.02)	2.06 (0.91–4.68)	1.72 (0.63–4.70)
Triglyceride	1.92 (0.84–4.37)	0.94 (0.38–2.34)	1.54 (0.70–3.41)	2.11 (0.73–6.05)
Waist	2.57 (1.16–5.73)¶	1.12 (0.46–2.75)	2.24 (1.03–4.88)#	3.76 (1.25–11.29)**
Hypertension	0.92 (0.40–2.10)	1.02 (0.40–2.62)	0.94 (0.42–2.09)	1.12 (0.41–3.06)

*Data were analyzed with the common genotype as the reference for all polymorphisms.

†(GT)n: HTR2C:c.1−142948$(GT)_n$, −997/−759: rs3813928/rs3813929, −697: rs518147, 3′UTR: rs1414334.

Data were adjusted for polypharmacy, use of glucose-lowering comedication, and lipid-lowering drugs.

§HDL = HDL-cholesterol, <1.0 mM (male patient) or <1.3 mM (female patient); Triglyceride = triglycerides, ≥1.7 mM; Waist = Waist circumference, >102 cm (male patient) or >88 cm (female patient); and blood pressure, ≥135/85 mm Hg or use of antihypertensive medication.

‖All analyses were performed with 112 patients except those for the HTR2C:c.1−142948(GT)n polymorphism that were analyzed for the most frequent alleles 16 repeat (R) and 13 R (total number of patients, n = 104), with 16 R as the reference.

¶$P = 0.022$.

#$P = 0.046$.

**$P = 0.018$.

less than 0.4. For the HTR2C:c.1−142948$(GT)_n$ repeat polymorphism, 5 alleles were detected with 13, 15, 16, 17, and 19 repeats, respectively. Genotypes with 15, 17, and 19 repeats were rare (n = 8 [7%]). Therefore, the outcome measures were calculated only for carriers of the alleles with 13 and 16 repeats (n = 104 [93%]), with the 13 repeat allele defined as the variant allele (n = 45 [40%]). Because of differences in the number of patients included in the analysis, the results of the HTR2C:c.1−142948$(GT)_n$ and the rs518147 (−697 G/C) polymorphism are presented separately. The prevalence of the rs3813928 (−997) A/rs3813929 (−759) T allele and the rs518147 (−697) C allele was 23% (n = 26) and 43% (n = 48), respectively. The prevalence of the rs1414334 C allele was 19% (n = 21).

The metabolic syndrome was present in 28 (25%) patients. There was no association between the metabolic syndrome ($P > 0.20$) and the covariates age, sex, type and dosage of antipsychotic drugs used, use of weight-influencing drugs, and whether the patient was hospitalized. Accordingly, the obtained results were adjusted for polypharmacy, use of glucose-lowering comedication, and use of lipid-lowering drugs. The interaction term for *HTR2C* genotype and sex was not significant ($P = 0.11$).

Table 1 shows that *HTR2C* polymorphisms are associated with an increased risk for the metabolic syndrome in carriers of the HTR2C:c.1−142948$(GT)_n$ 13 repeat allele (OR, 3.12 [95% CI, 1.13–8.16]) and the variant alleles rs518147 (−697) C (OR, 2.62 [95% CI, 1.00–6.85]) and rs1414334 C (OR, 4.09 [95% CI, 1.41–11.89]). There was no association between the metabolic syndrome and carriers of the variant rs3813928 (−997) A and rs3813929 (−759) T alleles (OR, 1.18 [95% CI, 0.40–3.47]). In addition, Table 1 shows that the combined genotype with carriers of the HTR2C:c.1−142948$(GT)_n$ 13 repeat allele, the common allele rs3813929 (−759) C, and the variant alleles rs518147 (−697) C and rs1414334 C, which is present in 18% of the patients, is associated with an increased risk (44% vs. 17%) of the metabolic syndrome (OR, 4.69 [95% CI, 1.34–16.45]) compared with the combined genotype with the common alleles.

The association between an increased risk for the metabolic syndrome and the combined genotype of the HTR2C:c.1−142948$(GT)_n$ 13 repeat allele, the common allele rs3813929 (−759) C, and the variant alleles rs518147 (−697) C and rs1414334 C for male patients (OR, 9.84 [95% CI, 1.95–49.68]) compared with female patients (OR, 0.83 [95% CI, 0.06–11.28]) suggests differential effects for male and female patients, although the sex by genotype interaction was not significant.

Table 2 shows the results of an exploratory analysis of the association between the individual items of the modified NCEP:ATP III classification for the metabolic syndrome and *HTR2C* polymorphisms. *HTR2C* polymorphisms were associated with a waist circumference of greater than 102 cm (male patient) or greater than 88 cm (female patients) in carriers of the HTR2C:c.1−142948$(GT)_n$ 13 repeat allele (OR, 2.57 [95% CI, 1.16–5.73]) and the variant alleles rs518147 (−697) C (OR, 2.24 [95% CI, 1.03–4.88]) and rs1414334 C (OR, 3.76 [95% CI, 1.25–11.29]). There was no association between a waist circumference of greater than 102 cm (male patient) or greater than 88 cm (female patient) and carriership of the variant alleles rs3813928 (−997) A and rs3813929 (−759) T (OR, 1.12 [95% CI, 0.46–2.75]). Other metabolic determinants for the metabolic syndrome were not significantly associated with *HTR2C* polymorphisms.

DISCUSSION

In this study, we found that several polymorphisms (HTR2C:c.1−142948$(GT)_n$, rs518147 (−697 G/C), and rs1414334), flanking or within the gene for the HTR2C receptor were associated with an increased risk for metabolic syndrome in patients using antipsychotics. The *HTR2C* polymorphisms rs3813928 (−997 G/A) and rs3813929 (−759 C/T) were not associated with the presence of the metabolic syndrome.

There are some limitations to these results. First, we recognize that the power of our study was limited. The small sample size may have limited the power to detect differences between groups that are only moderate in size. Furthermore, the sample size was too small to investigate the association between *HTR2C* polymorphisms and the metabolic syndrome in patients taking specific antipsychotic drugs. Although the sample size was limited, significance of the findings remained for several of the, quite conservatively, adjusted analyses, making a type I error highly unlikely. Correction for multiple testing was applied to the analysis of the primary outcome measure regarding the individual polymorphisms. The association with the metabolic syndrome in carriers of the variant rs1414334 C allele remained significant after correction for multiple testing. We did not adjust the other results because we believe this would increase the type II error rate too much, and the association with the combined genotype and the individual parameters of the metabolic syndrome are regarded as exploratory.[31] In answer to these limitations, it is important to realize that these results need to be confirmed in a larger independent sample of patients. A second limitation of our study is the fact that data on metabolic parameters of the patients at the initiation of antipsychotic drug treatment were not available to us. Therefore, it was not possible to analyze data for changes in these parameters over time related to the use of antipsychotic drugs. Third, we have used a modified version of the NCEP:ATP III classification of the metabolic syndrome because we had no access to data regarding glucose levels of the patients. Therefore, the increased risk of the metabolic syndrome for specific *HTR2C* genotypes might represent an increased cardiovascular risk profile rather than an increased diabetic risk profile. Finally, apart from genetic factors, several other variables can contribute to the risk of the metabolic syndrome. For example, smoking behavior, diet, and exercise were not taken into account. Future studies should ideally contain these variables to investigate whether these variables are confounding factors in the association between *HTR2C* genotypes and metabolic abnormalities.

The increased risk of the metabolic syndrome is mainly the result of the association between *HTR2C* genotypes and waist circumference. Waist circumference is one of the strongest determinants for insulin resistance and cardiovascular morbidity in the definition of the metabolic syndrome according to NCEP: ATPIII.[32,33] We could not find clear associations between *HTR2C* genotypes and other metabolic determinants. However, there were trends toward increased point estimates for the association between *HTR2C* genotypes and levels of HDL and triglycerides. The power of the analysis with HDL and triglycerides was possibly too low to find significant associations. Pooley et al[34] found that heterozygosity for the rs3813929 (−759 C/T) polymorphism was associated with increased levels of triglycerides in obese women without psychiatric disorders. We could not find other studies about the association between *HTR2C* genotypes and levels of HDL and triglycerides. These data suggest that future research with *HTR2C* genotypes should include levels of HDL and triglycerides, next to body mass index or waist circumference.

The association between *HTR2C* genotype and an increased risk for the metabolic syndrome looks particularly strong for the intragenic SNP rs1414334. As shown by McCarthy et al,[35] the linkage disequilibrium pattern between the promoter SNPs rs3813928 (−997 G/A) and rs3813929 (−759 C/T) and the intragenic region of *HTR2C* is disturbed because of gene conversion (within the promoter) and recombination (between promoter and intragenic region) events. Therefore, *HTR2C* promoter activity probably does not entirely determine the association between *HTR2C* genotypes and the presence of the metabolic syndrome or weight gain, but it may well be that a more downstream alteration affecting *HTR2C* stability, expression, or even function is equally or even more important.

Recently, McEvoy et al[9] found that the prevalence of the metabolic syndrome was significantly increased in schizophrenic patients compared with that in the general population. This study showed that all items of the National Cholesterol Education Program definition of the metabolic syndrome (waist circumference, HDL, triglycerides, blood pressure, and fasting glucose) exceeded the specified range significantly more often in schizophrenic patients compared with the general population, except for the glucose criterion. We found an increased risk for the metabolic syndrome in psychiatric patients taking antipsychotic drugs for certain genotypes. If confirmed, this may help to identify psychiatric patients at risk for the metabolic syndrome.

Zipursky et al[4] showed that weight gain due to antipsychotic drugs will be highest in the first 20 weeks of treatment before reaching a plateau after approximately 30 to 50 weeks of treatment. Identifying ''high-risk'' patients before or just after starting pharmacotherapy can be important for the treatment to be successful. Fast increase in weight will be noticed by the patient, and the risk of noncompliance will be increased. Psychiatric patients consider weight gain as one of the most disturbing adverse events and one of the important reasons to become noncompliant.[36] Preventive genotyping of *HTR2C* polymorphisms can possibly identify some of these high-risk patients.

In conclusion, genotypes of *HTR2C* polymorphisms are associated with the metabolic syndrome in psychiatric patients using antipsychotics. The increased risk of the metabolic syndrome is mainly the result of the association between *HTR2C* polymorphisms and waist circumference. Replication of these results in another sample of patients can have major impact on the treatment of schizophrenic patients.

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