

The catechol-O-methyltransferase Val^{108/158}Met polymorphism affects short-term treatment response to mirtazapine, but not to paroxetine in major depression

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Received: 18 March 2004
Revised: 17 September 2004
Accepted: 27 September 2004
Published online 2 November 2004

ABSTRACT

The catechol-O-methyltransferase (COMT) is a major degrading enzyme in the metabolic pathways of catecholaminergic neurotransmitters such as dopamine and norepinephrine. This study investigated whether the functionally relevant Val^{108/158}Met gene variant is associated with differential antidepressant response to mirtazapine and/or paroxetine in 102 patients with major depression (DSM-IV criteria) participating in a randomized clinical trial with both drugs. In patients treated with mirtazapine, but not paroxetine, allelic variations in the COMT gene were associated with differential response. COMT^{VAL/VAL} and COMT^{VAL/MET} genotype carriers showed a better response than COMT^{MET/MET}-bearing patients in the mirtazapine group. Moreover, carriers of the COMT^{VAL/VAL} or COMT^{VAL/MET} genotype had significantly greater HAMD-17 (Hamilton Rating Scale for Depression 17 item version) score reductions than COMT^{MET/MET} homozygotes from week 2 to 6, respectively, in the mirtazapine group. Time course of response and antidepressant efficacy of mirtazapine, but not paroxetine, seem to be influenced in a clinically relevant manner by this allelic variation within the COMT gene.

The Pharmacogenomics Journal (2005) 5, 49–53. doi:10.1038/sj.tpj.6500289
Published online 2 November 2004

Keywords: pharmacogenetics; antidepressant; response; COMT; mirtazapine; paroxetine

INTRODUCTION

Identification of pharmacogenetic factors influencing drug response seems a promising strategy in the search for predictors of response to psychopharmacological drugs. Recent study results provide evidence for the influence of gene variants of the serotonin transporter on response to selective serotonin reuptake inhibitors like paroxetine or fluvoxamine.^{1–4} The antidepressant effect of SSRI has also been found to be influenced by gene variants of tryptophan hydroxylase (TPH),^{5,6} whereas variants of MAO-A and 5-HT_{2A} did not seem to modulate SSRI effects.⁷

Mirtazapine is an antidepressant drug with a unique pharmacological profile, consisting of potent antagonism of central α_2 -adrenergic autoreceptors and heteroreceptors as well as an antagonism of both 5-HT₂ and 5-HT₃ receptors.^{8,9}

As a result, mirtazapine seems to enhance both the neurotransmission of serotonin and norepinephrine (NE). So far, there are no reports of an influence of genetic variants on a clinical response to mirtazapine.

The catechol-*O*-methyltransferase (COMT) plays a crucial role in the degradation of NE,¹⁰ thereby regulating availability of central NE and presumably consecutively affecting NE/5-HT interactions. The COMT gene, which codes for both the membrane-bound (MB-COMT) and soluble (S-COMT) form of the enzyme, is therefore a candidate for a possible genetic influence on antidepressant response. Within the gene, a transition of guanine to adenine at codon 158 leads to a substitution of Val¹⁰⁸ by Met¹⁰⁸ in the S-COMT (or the corresponding amino acids at position 158 in the MB-COMT). This single-nucleotide polymorphism (SNP) affects the level of enzyme activity in human tissues with a trimodal distribution of low (COMT^{LL}; COMT^{MET/MET}), intermediate (COMT^{HL}; COMT^{VAL/MET}) and high (COMT^{HH}; COMT^{VAL/VAL}) activities with three- to fourfold differences between COMT^{MET/MET} and COMT^{VAL/VAL}.¹⁰

So far, pharmacogenetic studies on the influence of variations in the COMT gene are scarce and limited to drugs for the treatment of Parkinson's disease. COMT genotype did not appear to influence treatment response neither to levodopa¹¹ nor to the COMT inhibitor tolcapone.¹² Whether COMT genotype affects antidepressant drug response has not been investigated so far. From a theoretical point of view one could hypothesize that drugs primarily modulating noradrenergic neurotransmission might be affected by the functionally active polymorphism of COMT, whereas SSRI treatment response should not be affected.

The aim of the present study was to investigate the possible effect of the functional COMT Val^{108/158}Met gene variant on the outcome of mirtazapine and paroxetine antidepressant treatment in patients with major depression.

RESULTS

Of 116 patients who gave written informed consent for DNA genotyping, $n=14$ had to be excluded because of missing complete Hamilton Rating Scale for Depression 17 item version (HAMD-17) data at baseline ($n=12$) or missing

genotyping ($n=2$). Thus, the sample consisted of $n=102$ patients (mean age = 48.6 ± 11.0 years; female/male: $n=74/28$). Analyses were performed for the intention-to-treat sample. A description of clinical and demographic characteristics as well as genotype frequencies of our sample is shown in Table 1. There were no significant differences between groups in any of the variables investigated. Baseline HAMD-17 scores were comparable in all treatment or genotype groups.

The mean values of the HAMD-17 total scores for the genotype groups COMT^{VAL/VAL}, COMT^{VAL/MET} and COMT^{MET/MET} are plotted in Figure 1a for the patients treated with mirtazapine, the respective values for the paroxetine-treated patients are shown in Figure 1b. Patients with COMT^{MET/MET} appeared to respond less pronouncedly to mirtazapine than patients with COMT^{VAL/VAL} or COMT^{VAL/MET} genotype. In patients treated with mirtazapine, the global comparison of HAMD change scores across the treatment course revealed a significant interaction of genotype (VAL ($n=35$) vs MET ($n=8$)) and time course (ANCOVA, baseline-adjusted main effects: time course $P=0.045$; $F=2.47$; $df=4.2, 167.2$; genotype $P=0.011$; $F=7.19$; $df=1, 40$; interaction: $P=0.039$; $F=2.55$; $df=4.2, 167.2$). In the paroxetine group, no significant differences between VAL ($n=34$) and MET ($n=9$) were found (ANCOVA, baseline-adjusted main effects: time course $P=0.63$; $F=0.66$; $df=4.9, 194.9$; genotype $P=0.35$; $F=0.91$; $df=1, 40$; interaction: $P=0.12$; $F=1.78$; $df=4.9, 194.9$).

The analysis of differences between VAL and MET at particular time points revealed that in the mirtazapine group the difference was statistically significant from week 2 to 6 of treatment (week 2: $T=-2.54$, $df=46$, $P=0.015$; week 3: $T=-2.18$, $df=45$, $P=0.034$; week 4: $T=-2.30$, $df=44$, $P=0.026$; week 6: $T=-2.28$, $df=40$, $P=0.028$), while in the paroxetine group there were no statistically significant differences.

Comparing the decrease of HAMD-17 total score during the whole study period, we found that in the mirtazapine group COMT^{MET/MET} patients had a mean decrease of 9.4 (± 7.2 SD) points, while patients with COMT^{VAL/VAL} or COMT^{VAL/MET} decreased by a mean of 13.8 (± 6.0 SD) points. This difference approached statistical significance (T -test,

Table 1 Clinical and demographic characteristics of our sample

COMT genotype	Mirtazapine ($n=53$)			Paroxetine ($n=49$)		
	VAL/VAL	VAL/MET	MET/MET	VAL/VAL	VAL/MET	MET/MET
Number (%)	11 (20.8)	26 (49.1)	16 (30.2)	14 (28.6)	21 (42.9)	14 (28.6)
Sex (male/female)	3/8	7/19	3/13	3/11	10/11	2/12
Age (years)	48.5 ± 11.5	47.3 ± 11.6	50.5 ± 10.2	51.0 ± 9.5	47.0 ± 12.6	49.2 ± 10.0
HAMD-17 at baseline	22.4 ± 2.9	22.4 ± 2.8	23.3 ± 3.2	22.6 ± 3.0	23.4 ± 4.3	23.4 ± 3.1
Mean HAMD-17 score decrease at week 6	12.9 ± 8.3	14.1 ± 5.2	9.4 ± 7.2	14.5 ± 5.9	12.0 ± 5.3	11.5 ± 7.0
Duration of current episode (weeks)	10.3 ± 10.5	13.6 ± 11.9	11.7 ± 7.7	16.4 ± 13.1	17.9 ± 14.6	11.2 ± 10.2
Episodes in the last 5 years (number)	1.9 ± 0.9	2.9 ± 2.0	1.6 ± 0.7	2.6 ± 1.8	2.5 ± 1.3	2.0 ± 1.3

The three COMT genotype groups did not differ significantly in both treatment groups.

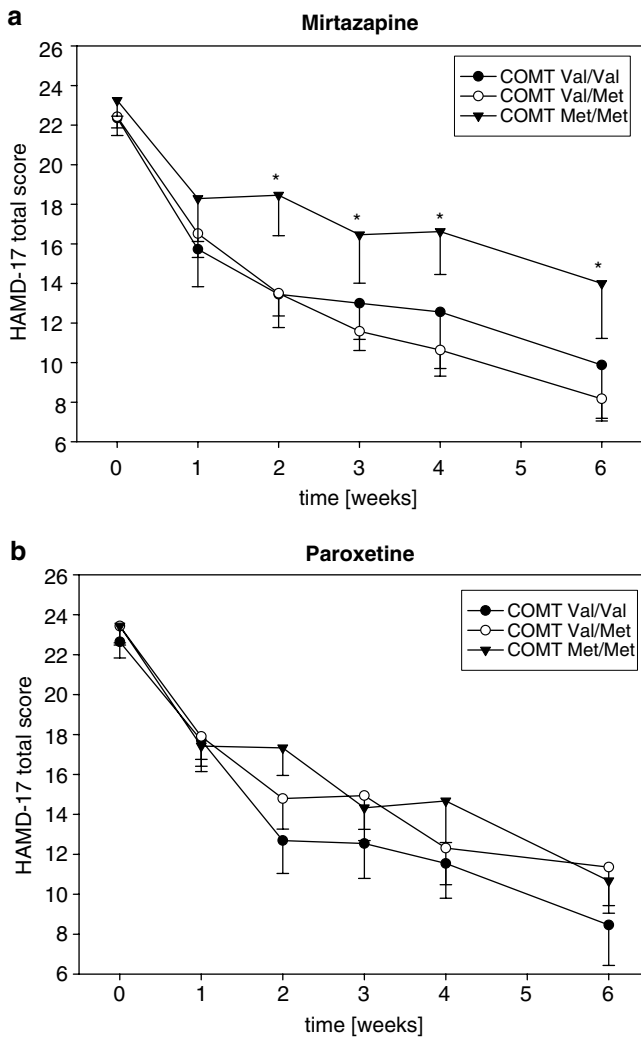


Figure 1 Time course of changes in HAMD-17 score during treatment stratified by genotype groups. *COMT^{MET/MET} vs COMT^{VAL/VAL} or COMT^{VAL/MET}, $P < 0.05$. In the mirtazapine-treated group (a) subjects with COMT^{MET/MET} showed a slower and less pronounced decrease of symptoms compared to subjects bearing the COMT^{VAL/VAL} or COMT^{VAL/MET} gene variant. This effect was not present in the paroxetine-treated group (b).

$P = 0.054$). In the paroxetine group, the respective values were 12.0 (± 5.3 SD) points for the patients with COMT^{MET/MET} and 12.9 (± 6.5 SD) points for the patients with COMT^{VAL/VAL} or COMT^{VAL/MET} ($P = 0.668$).

We performed global tests across the course of treatment (6 weeks) for categorical response rates (ie proportion of patients with at least 50% improvement in HAMD scores) and dimensional changes in HAMD scores. For the global evaluation of response rates between different genotypes, we calculated Kaplan–Meier curve analyses similar to survival analyses (‘survival time’ = time to first occurrence of response and no change in responder status later on or time of last observation in case of nonresponse) for both treatment

groups (MIR, PAR). The commonly used overall statistical test (log-rank test) for comparing the responder curves (‘survival curves’) of different genotype groups was applied. A significant effect indicates that the grouping variable has a significant effect on responder rates during the course of treatment. In the mirtazapine group, overall comparison of response rates during the treatment course using Kaplan–Meier curves revealed a significant difference between patients with VAL and MET (log-rank test, $\chi^2 = 3.99$, $df = 1$, $P = 0.045$). In the paroxetine group, no significant difference between VAL and MET groups was found (log-rank test, $\chi^2 = 0.04$, $df = 1$, $P = 0.84$).

We performed further responder analyses defining treatment response as a reduction of $\geq 50\%$ of HAMD-17 baseline score. In the mirtazapine-treated group, at day 14 only two patients bearing the COMT^{MET/MET} genotype were found to meet the responder criterion. Testing COMT^{MET/MET} vs the pooled data of COMT^{VAL/MET} and COMT^{VAL/VAL}, the differences showed a trend toward statistical significance at week 2 (Pearson’s $\chi^2 = 3.13$; $df = 1$; $P = 0.077$) and reached significance at end point (Pearson’s $\chi^2 = 5.94$; $df = 1$; $P = 0.015$).

In the paroxetine-treated group, analysis of responders showed no significant differences between COMT genotype groups at all time points of assessment.

A *post hoc* power analysis yielded a power of approximately 80% ($1 - \beta = 0.77$) to detect estimated differences in responder rates of 70% (group 1, $n = 34$) and 30% (group 2, $n = 12$) in the paroxetine group ($N = 46$) with $\alpha = 0.05$ and an overall responder rate of 50%. Thus, although sample sizes were rather restricted, differences of the size as observed in the mirtazapine group could have been revealed with sufficient statistical power also in the paroxetine group.

DISCUSSION

Our results provide suggestive evidence that allelic variation of the COMT Val^{108/158}Met polymorphism affects the response to mirtazapine, but not to paroxetine in major depression. This conclusion is derived from the finding that mirtazapine-treated patients with the COMT^{MET/MET} genotype showed a slower and poorer response than patients with the COMT^{VAL/VAL} or COMT^{VAL/MET} genotype. In contrast, we did not find such differences in the paroxetine-treated patients.

Mirtazapine affects the neurotransmission of NE¹³ and COMT plays a crucial role in the degradation of NE.¹⁰ Therefore, COMT activity may be partly responsible for the observed differences in treatment response. The mechanisms that lead to the observed differences in antidepressant response are largely unknown. Such mechanisms might be related to adaptive downregulation of central α_2 -autoreceptor function following increased NE availability.^{14,15} Hypothetically, subjects with COMT^{MET/MET} genotype could have a higher central NE availability and, consecutively, a relatively lower density of (downregulated) α_2 -autoreceptors compared to subjects with the COMT^{VAL/VAL} and COMT^{VAL/MET} allele variants. Treatment with mirtazapine, which exerts pharmacologic effects via present α_2 -receptors, could result

in a reduced responsiveness of α_2 -autoreceptors and consequently in reduced antidepressive effects.

COMT is not involved in the metabolism of serotonin. Consequently, it is not really surprising that we found no association between the functional COMT polymorphisms and paroxetine treatment efficacy. Therefore, our finding is also plausible from the pathophysiological point of view. For SSRI, allelic variations in TPH or/and serotonin transporter (5-HTT) genes seem to be more important, because TPH and 5-HTT are crucial protein structures in the metabolic pathways of serotonin. Functionally different gene variants may therefore affect treatment outcomes after SSRI administration in major depression. Recent pharmacogenetic studies on SSRI treatment response indeed found that the antidepressant activity of fluvoxamine was related to allelic variation in TPH gene⁶ and in the promoter of 5-HTT gene.¹ The same polymorphisms were also associated with differential response to paroxetine treatment in various studies.²⁻⁵

Our results are to some extent preliminary, because this pilot study did not allow us to control for unknown population stratification and gender effects. For example, the possible influence of comorbid personality disorders needs to be addressed in future studies. Moreover, the relatively small sample size in this study as well as the fact that our patients were outpatients may limit the generalizability of our results.

METHODS

Patients

There were 272 outpatients who participated in a multicenter, randomized, double-blind comparison of mirtazapine and paroxetine conducted at 50 centers in Germany. Of these patients, 116 gave written informed consent for the asservation of blood samples for DNA genotyping and the analyses of possible associations between genotypes and clinical data (eg response to treatment). All study components had been approved by the local ethics committees.

A detailed description of the recruitment procedure, treatment schedule and clinical assessments has been reported separately in a previous paper.¹⁶ Patients of both sexes, aged from 18 to 70 years and fulfilling DSM-IV criteria for major depressive episode with a sum score ≥ 18 on HAMD-17 at the start and end of a placebo washout period were eligible for the study. Diagnosis of major depressive episode according to DSM-IV criteria was ascertained by a total of 11 clinically experienced research assistants, who had been trained in several rater trainings prior to the start of the study. Rater trainings were performed in order to improve inter-rater reliabilities for HAMD-17. These trainings included joint ratings of five different videotapes from patients with major depressive disorder, with the requirement that HAMD-17 total scores should not differ more than ± 2 points from an independent expert rating.

Exclusion criteria were the presence of a current depressive episode of more than 12 months duration, lack of response to at least two adequate antidepressant treatments during the current episode, more than three previous

episodes that did not respond to adequate treatment, a reduction of $\geq 25\%$ in the HAMD-17 sum score during placebo washout period, suicide risk defined as a score of 4 to 6 on item 10 of the Montgomery-Asberg Depression Rating Scale (MADRS), history of bipolar affective disorder, depressive disorder not otherwise specified, panic disorder (with or without agoraphobia), agoraphobia without a history of panic disorder, schizophrenia, organic mental disorder, eating disorder, specific phobia, social phobia or generalized anxiety disorder.

After a 3- to 7-day washout period, patients were randomly assigned to either mirtazapine or paroxetine treatment for six weeks. Mirtazapine was first administered at 15 mg (days 1 and 2), from day 3 onward at 30 mg/day; after 2 weeks, an increased dose of 45 mg/day was given to nonresponders, defined by Clinical Global Impression Scale (CGI) ratings in the efficacy index of 'slight' or 'unchanged/worsened' and no 'outweighs therapeutic efficacy' ratings in the tolerability index. Paroxetine dose was 20 mg/day and could be increased to 40 mg/day after 2 weeks in nonresponders according to the same prespecified CGI criterion. No concomitant benzodiazepine treatment was allowed during the study.

All patients were assessed at baseline (day 0) and on days 7, 14, 21, 28 and 42 of active treatment using the HAMD-17.

DNA Analysis

Genotyping was performed blind to treatment and clinical course of the illness. Genomic DNA was prepared from 10 ml blood using the Quiagen Maxi DNA Extraction Kit (Hilden, Germany). Two primers (5'-ACT GTG GCT ACT CAG CTG TG-3' and 5'-CCT TTT TCC AGG TCT GAC AA-3') were used to amplify a 169-bp fragment of the target sequence within the COMT gene. The 50 μ l reactions contained 50 nmol genomic DNA, 0.2 mM/l dNTPs, 15 mM/l ammonium sulfate, 60 mM/l Tris-HCl (pH 9.0), 2 mM/l MgCl₂, 0.3 μ M/l of each primer and 1 U *Taq* polymerase (Life Technologies, Karlsruhe, Germany). Following an initial denaturation step at 95°C for 3 min, DNA was amplified in 35 PCR cycles (94°C for 30 s; 66°C for 30 s; 72°C for 1 min). The final extension step was 72°C for 5 min. A measure of 30 μ l of the PCR product were digested with 6 U *Nla*III (New England Biolabs, Frankfurt, Germany), analyzed by gel electrophoresis in a 3% agarose gel containing ethidium bromide and visualized under UV light. When adenine is present at codon 108/158 (ATG/Met/low activity allele), digestion of the 169 bp PCR product results in fragments of 96, 26, 29 and 18 bp, whereas the presence of guanine at codon 108/158 (GTG/Val/high activity allele) lacks the additional *Nla*III recognition site, resulting in fragments of 114, 26 and 29 bp.

Data Analysis

The SPSS statistical software package was used for data analyses (version 11.0). Within treatment groups, HAMD-17 total score differences between genotype groups were analyzed by repeated measurement ANCOVA controlling for baseline values. Huynh-Feldt's correction of degrees of freedom was applied for deviation from sphericity. Patients

with valid HAMD scores for at least 2 weeks of treatment (and baseline) were included ($n=43$ in both groups, MIR and PAR). A linear regression approach (SPSS) was used to handle missing data (in both groups, 3.5% of data were missing). Unpaired *T*-tests were applied as *post hoc* tests.

For the global evaluation of response rates between different genotypes, we calculated Kaplan–Meier curve analyses with log-rank tests in both treatment groups (mirtazapine, paroxetine) separately. Time to first occurrence of response and no change in responder status later on or time of the last observation in case of nonresponse was used as ‘survival time’. Additionally, HAMD-17 total score differences between genotype groups were analyzed at each time point with one-way analysis of variance or *T*-tests, if appropriate. For each assessment day, analysis of genotype distribution between responders and nonresponders was performed using χ^2 test. The level of significance was set at 0.05 (two-tailed). A correction for multiple testing was not performed because of the exploratory nature of the study.

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