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**ORIGINAL INVESTIGATION**

# Cytochrome P450 1A2 co-determines neuroleptic load and may diminish tardive dyskinesia by increased inducibility

SVETLANA A. IVANOVA[1,5], VALENTINA A. TOSHCHAKOVA[1], MAXIM L. FILIPENKO[3], OLGA YU FEDORENKO[1,5], EVGENIA G. BOYARKO[1], ANASTASIA S. BOIKO[1], ARKADIY V. SEMKE[1], NIKOLAY A. BOKHAN[1,6], LYUBOMIR I. AFTANAS[4] & ANTON J.M. LOONEN[2]

[1]*Mental Health Research Institute, Siberian Branch of RAMSc, Tomsk, Russian Federation,* [2]*Department of Pharmacy, University of Groningen, Groningen, The Netherlands,* [3]*Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russian Federation,* [4]*Scientific Research Institute of Physiology and Basic Medicine, Siberian Branch of RAMSc, Novosibirsk, Russian Federation,* [5]*National Research Tomsk Polytechnic University, Tomsk, Russian Federation, and* [6]*National Research Tomsk State University, Tomsk, Siberia, Russian Federation*

**Abstract**

*Objectives.* The aim of this study was to investigate a possible association between tardive dyskinesia (TD) and *CYP1A2* (*1F, -163C>A, rs762551) polymorphism in Russian psychiatric inpatients. *Methods.* TD was assessed cross-sectionally using the Abnormal Involuntary Movement Scale (AIMS). Orofacial and limb-truncal dyskinesia were assessed with AIMS 1–4 and 5–7, respectively. Standard protocols were applied for genotyping. Analysis of covariance (ANCOVA) was used to compare the mean AIMS scores for each of the genotypic classes. *Results.* A total of 319 Caucasian patients from West Siberia with schizophrenia and 117 healthy volunteers were investigated. No significant differences between the patients and the controls in genotype frequencies were found. Analysis of covariance (ANCOVA) with age, sex, duration of disease, chlorpromazine equivalent (CPZEQ) incorporated as covariates showed that limb-truncal, but not orofacial TD, is associated with *CYP1A2* (−163C>A, rs762551) polymorphism ($F = 3.27$, $P = 0.039$). Patients with the C/C genotype had a higher mean AIMS 5–7 score than those with the A/C or the A/A genotype. *Conclusions.* Our results support the hypothesis that not only with clozapine, but also with other classical and atypical antipsychotics, smoking may decrease plasma levels; this is most extensively expressed in carriers of the CYP1A2*1F (-163C>A) polymorphism.

**Key words:** *tardive dyskinesia, schizophrenia, CYP1A2 gene, tobacco smoking, enzyme induction*

## Introduction

The movement disorder tardive dyskinesia (TD) is a late occurring adverse consequence of long-term treatment with antipsychotic drugs (Loonen and Van Praag 2007; Loonen and Ivanova 2013). TD occurs with an annual incidence of about 5.5% with first-generation antipsychotic drugs, and of about 3.9% with second-generation antipsychotics (Correll and Schenk 2008). Clozapine is the only antipsychotic drug having a very low potential to induce TD, and may be suitable to treat this disorder (Hazari et al. 2013). This incidence is increased by age, and also by the total cumulative dose of antipsychotics (Latimer 1995). Phenotypically, TD can be dissected into two distinct subsyndromes, characterized by orofaciolingual (orofacial) and limb-truncal dyskinesia. Orofacial TD involves movements of mouth and face muscles, and may impair eating and swallowing, whereas limb-truncal TD involves purposeless choreiform movements of trunk and/or limbs, and may cause gait disturbances and falls. Accumulating evidence suggest that orofacial and limb-truncal TD are two distinct clinical entities with different clinical features, different risk factors, different prognoses, and probably even different genetic liability (Gureje 1988; Al Hadithy et al. 2009).

The cytochrome P450 enzyme debrisoquine/sparteine hydroxylase system plays an important role

Correspondence: Professor A.J.M. Loonen, MD, PharmD, PhD, GGZWNB chair of Pharmacotherapy of Psychiatric Patients, Antonius Deusinglaan 1, 9713AV Groningen, The Netherlands. Tel: +31 50 363 7576. Fax: +31 50 363 2772. E-mail: a.j.m.loonen@rug.nl

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in the metabolism of antipsychotic drugs (Brosen 1996). This system consists of a collection of isoenzymes with different abundances within the primary metabolizing organs, and with different affinities for exogenous and endogenous substances. Most antipsychotic drugs are primarily metabolized by CYP2D6, but clozapine, olanzapine and haloperidol are (also) important substrates of CYP1A2 (Flockhart 2007). However, specific xenobiotics are usually substrates of several CYP isoforms. Because CYP2D6 and CYP1A2 account for about 2 and 13%, respectively of the total CYP content in the human liver (Shimada et al. 1994), it has been suggested that CYP2D6 can be considered a high-affinity, but low-capacity metabolic clearance pathway for most typical antipsychotic drugs, whereas CYP1A2 would be a low-affinity, high-capacity metabolic clearance pathway (Fu et al. 2006). An important characteristic of CYP1A2 is its inducibility by several drugs, coffee consumption and tobacco smoking (Mookhoek and Loonen 2004; Flockhart 2007). Tobacco smoking may result in a large increase of CYP1A2 metabolic capacity, which results in increased clearance of typical substrates like clozapine, for example (Taylor 1997). Many patients with mental disorders smoke, and exceptionally high smoking rates (60–90%) are reported in patients suffering from schizophrenia (D'Souza and Markou 2012). This induction of CYP1A2 metabolism may also be relevant for all antipsychotic drugs due to the limited capacity of CYP2D6. The inducibility of CYP1A2 is also under genetic control. For example, −163C>A allele is associated with increased enzyme inducibility (Gunes et al. 2009; Zhou et al. 2009; Djordjevic et al. 2010; Wang et al. 2013). Some investigations suggest that CYP1A2 may contribute to the development of TD by influencing the typical antipsychotics metabolism and acting as a low-affinity high-capacity metabolizing enzyme (Basile et al. 2000; Özdemir et al. 2001; Tiwari et al. 2007). Genetic differences in cytochrome P450 enzyme may mean that some patients have significantly more active enzymatic forms, resulting in lower plasma levels of their medication, and this may also allow the prediction of poor response and lower propensity to side-effects (Meyer 1994).

In the present study we have tried to test the hypothesis that the less inducible polymorphism of the CYP1A2 isoform is more often associated with TD in Caucasian patients from Siberia than the wildtype form.

## Methods

### *Participants*

After obtaining approval of the study protocol by the Institutional Medical Review Board, patients were recruited from four psychiatric centres in West Siberia (Russia). All participants gave written informed consent after being given a proper explanation of the study. We included patients with clinical diagnosis of schizophrenia (ICD-10: F20) or schizotypal disorder (ICD-10: F21), and excluded participants with a non-Caucasian physical appearance (e.g., Mongoloid, Buryats, Tyvans, or Khakassians), clinically relevant withdrawal symptoms, or those with organic or neurological disorders. Patients using clozapine who did not suffer from TD were excluded, as clozapine may suppress the symptoms of TD.

Clinical and demographic data were extracted from patients' medical files. TD was assessed cross-sectionally by the use of the Abnormal Involuntary Movement Scale (AIMS) (Loonen et al. 2000, 2001). The presence of orofacial dyskinesia and limb-truncal dyskinesia was established by a cut-off score of 2 (mild but definite) on any of the items 1 through to 4 and 5 through to 7 of AIMS, respectively. The sum of the first four items was used as a proxy for the severity of orofacial TD, while the sum of items 5 through to 7 was used as a proxy for the severity of limb-truncal TD. The dose of the antipsychotic medication was converted into chlorpromazine equivalents (CPZEQ), as described by Andreasen et al. (2009). The control group consisted of 117 healthy volunteers.

### *Objective*

The aim of this study was to investigate the possible association between orofacial and limb-truncal TD and *CYP1A2* (-163C>A, rs762551) polymorphism in Russian psychiatric inpatients.

### *Genotyping*

DNA was extracted using phenol-chloroform. The *CYP1A2* (-163C>A, rs762551) polymorphism was genotyped after PCR according to standard protocols using an amplifier Real-Time PCR System (StepOnePlus, Applied Biosystems) and blind to the clinical status of the participants.

### *Statistics*

The Hardy–Weinberg (HW) equilibrium of genotypic frequencies was tested by the chi-square test. Statistical analyses were performed using SPSS software, release 17 for Windows: $P$ values less than 0.05 were considered as significant. Analysis of covariance (ANCOVA) was used to compare the mean AIMS scores for each of the genotypic classes, with age, sex, duration of disease and chlorpromazine equivalent (CPZEQ) incorporated as covariates.

Table I. Characteristics of the studied patient group.

| | All (319) | Male (196) | Female (123) |
|---|---|---|---|
| Age | 43 ± 0.9 | 39.3 ± 1 | 48.9 ± 1 |
| Daily dose of antipsychotics | 733.6 ± 40 | 731.9 ± 48 | 736 ± 73 |
| Patients using anticholinergics. *n* (%)* | 251(78.6) | 153 (48) | 98 (31) |
| Daily dose of anticholinergics among users* | 4.6 + 0.2 | 4.5 ± 0.2 | 4.9 ± 0.3 |
| Orofaciolingual AIMS-score | 2.7 ± 0.2 | 2.7 ± 0.2 | 2.7 ± 0.3 |
| Limb-truncal AIMS-score | 1.6 ± 0.1 | 1.5 ± 0.2 | 1.9 ± 0.2 |
| Total AIMS-score | 4.3 ± 0.3 | 4.2 ± 0.4 | 4.5 ± 0.5 |
| Patients with ≥ 2 points on any of AIMS items 1–4, *n* (%) | 169 (53) | 107 (33.5) | 62 (19.4) |
| Patients with ≥ 2 points on any of AIMS items 5–7, *n* (%) | 119 (37.3) | 67 (21) | 52 (16.3) |
| Patients with ≥ 2 points on any of AIMS items 1–7, *n* (%) | 206 (64.6) | 167 (52.4) | 39 (12.2) |

## Results

Table I presents the main demographic and clinical features of the studied population. A total of 319 patients were recruited. The mean disease duration was 17 ± 14 years. The control group consisted of 67 male (age 36 ± 3.5 year) and 50 female (age 34.7 ± 1.7 year) healthy volunteers.

All but five patients were using antipsychotics as monotherapy or combinations of several drugs. Thirty-five patients (11 %) were utilizing depot antipsychotics on the day of assessment (haloperidol decanoate, flupenthixole decanoate and zuclopenthixole decanoate). Oral conventional (typical) antipsychotics were chlorpromazine, haloperidol, trifluoperazine, chlorprothixene, zuclopenthixole. 34.9% of the patients took atypical antipsychotics (sertindole, risperidone, amisulpride, clozapine, quetiapine, olanzapine). Nine patients using clozapine, who nevertheless demonstrated symptoms of TD, were included.

The genotype distribution of *CYP1A2* (A-163A, rs762551) polymorphism were in agreement with the Hardy–Weinberg Equilibrium in both the control and the patient groups (Table II). No significant differences in genotype frequencies between the two groups were found. We also found no differences in genotype distribution between patients with and without TD, limb-truncal TD and orofacial TD (Table III). Analysis of covariance (ANCOVA) with age, sex, duration of disease and chlorpromazine equivalent (CPZEQ) incorporated as covariates showed that limb-truncal TD, but not orofacial TD, is an association with *CYP1A2* (−163C>A, rs762551) polymorphism ($F = 3.27$, $P = 0.039$). Patients with the C/C genotype had a higher mean AIMS items 5–7 score (2(0–3.5)) (median (25–75% percentiles)) than those with the A/C (1(0–3)) or the A/A (0(0–2)) genotype (Figure 1).

## Discussion

The observation that the less inducible variant of CYP1A2 (-163C> , rs762551) is more often associated with limb-truncal TD supports the hypothesis that this cytochrome P450 isoform may become important in antipsychotic metabolism following CYP2D6 saturation at high substrate concentrations during long-term treatment. As such, CYP1A2 may be considered a "low affinity-higher capacity" metabolic clearance pathway for antipsychotics.

Genetic and/or environmental variation in drug metabolism is a pivotal factor contributing to marked variability in pharmacokinetics and in the therapeutic/adverse effects of psychotropic medications. In our population, the difference probably largely depends upon the environmental factor of smoking. In our study, 79% schizophrenic patients are (often heavy) smokers, and therefore may have an increased CYP1A2-dependent pathway of metabolism for the antipsychotics used by them. These findings are well in agreement with those described by Basile et al. (2000) and Fu et al. (2006). Basile et al. (2000) analysed the data of 85 patients with schizophrenia, and showed that the mean AIMS score in patients with the (C/C) genotype (associated with reduced CYP1A2 inducibility) was 2.7- and 3.4-fold greater than in those with the (A/C) or (A/A) genotype, respectively ($F[2,82] = 7.4$, $P = 0.0007$). Also, Fu

Table II. Genotype distribution in control and patients group.

| | *N* | AA | AC | CC | $\chi^2$ (HWE) | *P* (HWE) | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|---|---|
| Control, *n* (%) | 117 | 57 (48.7%) | 51 (43.6%) | 9 (7.7%) | 0.27206 | 0.82 | 0.826 | 0.66 |
| Patients with schizophrenia, *n* (%) | 319 | 143 (44.8%) | 144 (45.2%) | 32 (10%) | 1.093835 | 0.7 | | |

Table III. Genotype distribution in patients with and without dyskinesia.

| Group | | Genotype (%) AA | AC | CC | HWE $\chi^2$ (*P*) values | Allele frequency (%) A | C | $\chi^2$ (*P*) values |
|---|---|---|---|---|---|---|---|---|
| Total | with | 38 (41) | 45 (49) | 9 (10) | 1.1 (0.49) | 0.64 | 0.36 | 0.9 (0.63) |
| dyskinesia | without | 105 (47) | 97 (43) | 23 (10) | 0.007 (0.779) | 0.68 | 0.32 | |
| Orofaciolingual | with | 28 (40) | 35 (50) | 7 (10) | 0.68 (0.59) | 0.65 | 0.35 | 1.1 (0.6) |
| dyskinesia | without | 115 (47) | 107 (43) | 25 (10) | 0.0002 (0.998) | 0.68 | 0.32 | |
| Limb-truncal | with | 17 (36) | 23 (49) | 7 (15) | 0.03 (0.992) | 0.61 | 0.39 | 2.5 (0.3) |
| dyskinesia | without | 126 (47) | 119 (44) | 25 (9) | 0.16 (0.776) | 0.69 | 0.31 | |

et al. (2006) demonstrated that in Chinese patients with schizophrenia, the frequency of the CYP1A2 C allele in patients with TD was significantly higher than that in those without TD ($\chi^2 = 6.38$, $P < 0.05$). In the present study, we did not find significant differences in genotype distribution between patients with and without TD, limb-truncal TD and orofacial TD. However, we found an increased limb-truncal TD severity in patients with the C/C genotype for CYP1A2.

Increased enzyme inducibility associated with CYP1A2*1F (-163C>A) has been demonstrated in patients of different ethnicity. Djordjevic et al. (2010) found an increasing effect of -163C>A on CYP1A2 inducibility in both 64 Serbian ($P = 0.022$) and 114 Swedish ($P = 0.016$) non-smoking heavy coffee consumers. Gunes et al. (2009) studied 146 healthy Turkish volunteers, and found the -163C>A polymorphism correlated with enzyme induction only in the smokers ($P = 0.006$), which suggests increased inducibility in carriers of the A allele. Wang et al. (2013) studied 4 polymorphisms CYP1A2 in 238 unrelated, non-smoking, healthy male Chinese volunteers. CYP1A2*1F (-163C>A) polymorphisms was associated with increased CYP1A2 activity, but CYP1A2 gene polymorphisms appeared to have limited influence.

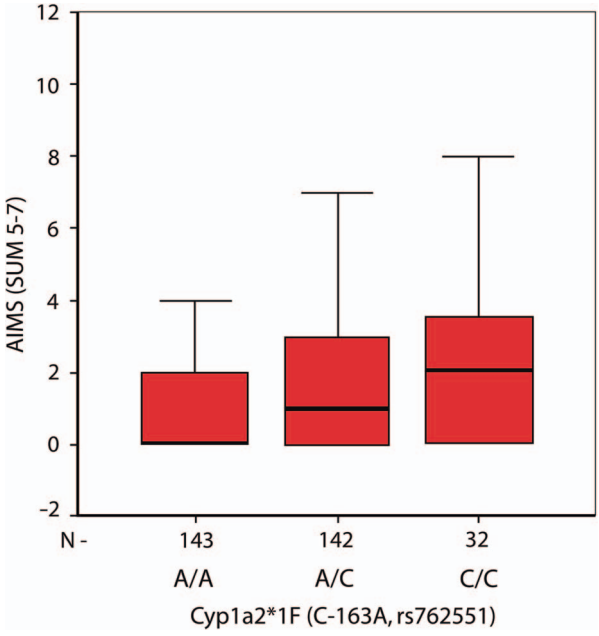


Figure 1. Box-and-Whisker plots showing AIMS scores in patients with different CYP1A2 (-163C>A) genotypes. AIMS (SUM 5–7) - the sum of items 5 through 7 of the Abnormal Involuntary Movement Scale used as a proxy for the severity of limb-truncal dyskinesia. A/A, A/C, C/C – carriers of different genotypes of Cyp1a2*1F( C-163A, rs762551) polymorphism.

We found a similar genotype frequencies in the control group and the patients with schizophrenia: 48.7% were homozygous AA, 43.6% were heterozygous, and 7.70% were homozygous CC in the group of healthy people, while 44.8% were homozygous AA, 45.2% were heterozygous, and 10% were homozygous CC in the patient group. Djordjevic et al. (2009) found a SNP frequency of 0.611.

Our findings seem to contrast those of Koola et al. (2014), who studied the association of TD with variations in CYP2D6 enzyme activity. These authors found an increased risk of TD being associated with an increase in the number of functional CYP2D6 genes. This can be attributed to increased oxidative stress within the brain due to higher activity of this oxidative cytochrome P450 enzyme system. TD is possibly related to neurotoxicity of striatal indirect pathway medium spiny neurons (Loonen and Ivanova 2013), and factors which increase the vulnerability to metabolic stress have been found to increase the likelihood of TD (Al Hadithy et al. 2010; Ivanova et al. 2012a, 2012b, 2014). The variation is possibly related to a difference of enzyme inducibility of cerebral CYP1A2 and CYP2D6. Both cytochrome P450 enzymes are functional within the brain (Gervasini et al. 2004), but CYP2D6 is readily inducible by both alcohol and nicotine (Miller et al. 2014), while CYP1A2 appears not to react on treatment with classical hepatic enzyme inducers (Stamou et al. 2014). So, tobacco smoking may increase CYP2D6 activity within the brain, causing extra oxidative stress and

at the same time lowering the antipsychotic blood and brain levels by inducing hepatic CYP1A2 activity.

Taken together with previous knowledge, our findings suggest that CYP1A2 can play a significant role in the metabolism of typical antipsychotics which are primarily a substrate of CYP2D6. This is in spite of the fact that CYP1A2 is directly involved in only a minor group of antipsychotics, such as clozapine and olanzapine. This is in accordance with the hypothesis, that CYP1A2 is postulated as a "low affinity–higher capacity" metabolizing enzyme, and its influence is mainly manifested in smokers. So, not only of clozapine, but also of other classical and atypical antipsychotics, smoking may decrease the plasma levels. This enzyme induction is most extensively expressed in carriers of the CYP1A2*1F (−163C>A) polymorphism.

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## Statement of Interest

None to declare.

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