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Association between gene variants and response to buprenorphine maintenance treatment ☆

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ABSTRACT

A variety of studies were addressed to differentiate responders and non-responders to substitution treatment among heroin dependent patients, without conclusive findings. In particular, preliminary pharmacogenetic findings have been reported to predict treatment effectiveness in mental health and substance use disorders. Aim of the present study was to investigate the possible association of buprenorphine (BUP) treatment outcome with gene variants that may affect kappa-opioid receptors and dopamine system function. One hundred and seven heroin addicts (West European, Caucasians) who underwent buprenorphine maintenance treatment were genotyped and classified into two groups (A and B) on the basis of treatment outcome. Non-responders to buprenorphine (group B) have been identified taking into account early drop out, continuous use of heroin, severe behavioral or psychiatric problems, misbehavior and diversion during the 6 months treatment period. No difference was evidenced between responders and non-responders to BUP in the frequency of kappa opioid receptor (OPRK1) 36G > T SNP. The frequency of dopamine transporter (DAT) gene polymorphism (SLC6A3/DAT1), allele 10, was evidently much higher in "non-responder" than in "responder" individuals (64.9% vs. 55.93%) whereas the frequency of the category of other alleles (6, 7 and 11) was higher in responder than in non-responder individuals (11.02% vs. 2.13% respectively). On one hand, the hypothesis that possible gene-related changes in kappa-opioid receptor could consistently affect buprenorphine pharmacological action and clinical effectiveness was not confirmed in our study, at least in relation to the single nucleotide polymorphism 36G > T. On the other hand, the possibility that gene-related dopamine changes could have reduced BUP effectiveness and impaired maintenance treatment outcome was cautiously supported by our findings. DAT1 gene variants such as allele 10, previously reported in association with personality and behavioral problems, would have influenced the effects of BUP-induced dopamine release, modulated through mu and kappa opioid receptors, and probably the related reinforcing capacity of the drug.

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1. Introduction

Different individual responses to long-acting opiates maintenance treatment are commonly observed among heroin addicts in the clinical setting. A substantial group of patients whose urinalysis results indicate a continued regular use of opiates during substitution treatment has been repeatedly evidenced in methadone and buprenorphine maintenance programs (Mattick et al., 2003; Petitjean et al., 2001; Strain et al., 1996). In spite of numerous attempts to differentiate responders and non-responders to substitution treatment, conclusive findings are still not available. "Responders" and "non-responders" were found not to differ significantly on measures of psychosocial problem severity in any other area, nor did they differ in their treatment service utilization (Belding et al., 1998). Although a trend indicating more treatment attrition for participants with personality disorders was revealed in previous studies on methadone maintenance patients, also psychiatric comorbidity seems to be unrelated to retention in treatment and outcome measures (Bovasso and Cacciola, 2003).

Both for methadone and buprenorphine, high doses have been demonstrated to increase responder rate, in comparison with low doses (Strain et al., 1999), without any reference to patient characteristics.

Many years ago, a pilot trial of treatment with buprenorphine (a mixed mu opioid agonist/kappa opioid antagonist) suggested that

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positive response to treatment may identify a subgroup of untreated addicts whose levels of psychosocial functioning are intermediate between those for whom methadone (a pure agonist) or naltrexone (a pure antagonist) are used (Resnick et al., 1991). In contrast, our recent findings indicated that buprenorphine was more effective in opioid-dependent patients affected by depression, probably due to its action as kappa opioid-receptors antagonist, counteracting dysphoria, negativism and anxiety (Gerra et al., 2004, 2006). Accordingly, other authors reported that psychometric measures of depression, together with high level of psychopathology, low disinhibition and boredom susceptibility correlated with a good response to buprenorphine substitution treatment (Poirier et al., 2004).

Following pharmacogenomic evidence, applied to predicting treatment effectiveness in psychiatry (Basile et al., 2002), the relationship between substitution treatment outcomes and gene variants has been investigated in some preliminary studies, with uncertain findings. In particular, the results obtained seem to indicate that dopamine receptor (DRD2) gene polymorphisms (allele A1) may be used as predictors of heroin use and subsequent methadone treatment outcome (Lawford et al., 2000), but this possibility was not confirmed by more recent studies for both methadone and buprenorphine responses (Barratt et al., 2006).

On the other hand, the short-term effects of levo-methadone have been found to be significantly affected by a polymorphism (OPRM1 118A > G) affecting mu-opioid receptors (Lötsch et al., 2006), again suggesting a possible pharmacogenetic approach to predicting addiction treatment outcome.

In the present study, we decided to investigate the possible association of buprenorphine treatment outcome with gene variants that may affect opioid receptors function and dopamine turnover, possibly involved in the pharmacological action of the drug.

Taking into account the specific pharmacological profile of buprenorphine, with a complex action including partial agonist effects on mu opioid receptors and antagonist effects on kappa opioid receptors (Robinson, 2002), we evaluated in particular whether treatment outcome was influenced by the kappa opioid receptor (OPRK1) single nucleotide polymorphism, which was previously found associated to heroin addiction (Yuferov et al., 2004; Gerra et al., 2007).

In addition, considering the coexistence of kappa-opioid receptors and dopamine transporter (DAT) on neuron terminations in the *nucleus accumbens* and the well known inhibitory role exerted by kappa-opioid receptors system on dopamine rewarding pathways (Svingos et al., 2001), we decided to investigate the possible relationship between buprenorphine outcome and gene variants (Vanderberg et al., 1992) affecting DAT availability (Kelada et al, 2005).

Aim of the study was to identify gene variants possibly associated with the outcome of buprenorphine maintenance treatment. Our hypothesis was that a possible dysfunction of kappa opioid receptors system and/or dopaminergic system may reduce the effectiveness of buprenorphine in a subgroup of patients.

To this purpose, the frequencies of kappa opioid receptor (OPRK1) single nucleotide polymorphism 36G > T and dopamine transporter (SLC6A3/DAT1) polymorphism have been evaluated in two groups of heroin addicted patients that significantly differed for their response to pharmacological therapy with buprenorphine.

2. Methods

2.1. Subjects

One hundred and seven (107) heroin dependent subjects, 80.8% males and 19.2% females, aged 21–41 years ($M \pm$ S.D. = 32.8 ± 10.9 years), with a history of heroin alone dependence of 4–7 years (5.9 ± 1.9), entered the study, after informed written consent. They were consecutive admissions to the buprenorphine treatment program of six (6) public health services for outpatient addiction treatment. The six centers were equally distributed in northern, central and southern regions of Italy, representing almost all the areas of Italian population. The patients were not paid for their participation and accepted to enter the study as volunteers. Daily intake of heroin ranged from 1.5 to 2.0 g. of street heroin (18% pure heroin). The main criteria for patient selection included heroin dependence (diagnosed utilizing DSM IV interview), current urine drug screening positive for morphine metabolites, urine drug screening positive for morphine metabolites in previous records and availability to take buprenorphine. Previous continuous consumption of other drugs of abuse and psychotropic agents, or excessive alcohol intake, with alcohol dependence, was accurately evaluated: poly-abusers were not admitted to participate in the study.

Exclusion criteria included multiple substance dependence, severe chronic liver or renal diseases or other chronic severe somatic disorders, endocrinopathies, immunopathies, and, in particular, HIV disease. All subjects were Caucasian Italians. After the complete description of the study to the subjects, written informed consent was obtained.

2.2. Socio-demographic characteristics

The data collection strategy routinely utilized in the Centers involved in the study consisted of a form for the outpatient program counselors to complete for each patient who entered substitution treatment with buprenorphine. The patients form requested the following information: patient identification; socio-demographic characteristics; previous treatment; employment status; highest school grade completed; quality of interpersonal relationships; marital status; legal problems; commitments; alcohol related problem; perception of alcohol as a current problem.

2.3. Psychiatric assessments

Heroin dependent subjects were submitted to structured interviews and a diagnostic evaluation by a trained psychiatrist, utilizing the Structured Clinical Interview (SCID) for axis I disorders (Spitzer et al., 1990, Italian Version: Clinical Interview structured for the DSM-III-R by Fava et al., 1993) and the Structured Interview for DSM IV Personality Disorders (SIDP) for axis II disorders (Pfohl et al., 1989: Italian Version by Maffei et al., 1997).

2.4. Buprenorphine treatment

The same treatment protocol was applied in all the centers participating in the study, following clinical criteria that are usually utilized in Italian Public Health System Services for Addiction Treatment. Stable dosage of buprenorphine was reached during the first week of treatment: the patients treated with buprenorphine received a first dose of 2 mg, 8 h after the last injection of heroin; then they received another 2 or 4 mg of buprenorphine, in absence of withdrawal symptoms, during the first day. Additional buprenorphine doses were administered to rapidly reach high doses: in some cases, first day buprenorphine was limited to 2 mg because withdrawal symptoms were clearly buprenorphine-induced. Flexible dosing schedule was applied in the first 3 months of treatment, but rarely in the following 3 months, for clinical reasons: after obtaining an agreement with the patients about appropriate doses, they were asked to evaluate their own behavioral reactions to stable doses for at least another 3 months, without focusing continuously on medication. The decision about doses was independent from the inclusion in the observational protocol. Buprenorphine was administered daily in the outpatient center for 81% of the patients and three times a week for 19% of the patients. Weekly take home buprenorphine was not permitted in the first six months of treatment. All patients were submitted to twice a week urinalyses for illicit and non-prescribed drugs use monitoring. The "three times a week" schedule of buprenorphine administration was not used as a behavioral privilege, but independently from negative urines.

All patients attended weekly individual counseling meetings and behavioral therapy sessions in combination with pharmacological treatment.

2.5. Treatment response evaluation

On the basis of their response to buprenorphine substitution treatment during the first six months the patients were included in one of two groups, responders (group A) and non-responders (group B). Non-responders to buprenorphine were selected taking into account the following criteria: (1) early drop out from buprenorphine treatment and relapse to heroin (within the first 12 weeks); (2) continuous use of heroin during the treatment period (33% or more of urinalyses positive for morphine or cocaine metabolites); (3) severe behavioral or psychiatric problems in coincidence with buprenorphine treatment (aggressiveness episodes, severe mood problems, depression, delusions) with consequent switch to methadone or drug-free treatment; and (4) misbehavior concerning buprenorphine assumption (simulation of the assumption, diversion) and program discontinuation.

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