Replication of the pharmacogenetic effect of rs678849 on buprenorphine efficacy in African-Americans with opioid use disorder

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Opioid use disorder (OUD) includes dependence on heroin and prescription opioid analgesics. Methadone and buprenorphine are two commonly used medications for OUD treatment. Buprenorphine is a partial agonist of the mu-opioid receptor (MOR), while methadone is a full agonist. Buprenorphine is also an antagonist at the kappa-opioid receptor and is frequently compounded with the MOR antagonist naloxone to prevent injection use. We identified a pharmacogenetic marker in African-Americans (n=77) who participated in a 24-week, randomized, open-label trial of methadone or buprenorphine/naloxone for the treatment of OUD. An intronic variant (rs678849) in the delta-opioid receptor gene (*OPRD1*) was associated with the percentage of opioid-positive urine drug screens in both treatment groups. The effect of rs678849 genotype on buprenorphine, but not methadone, efficacy was replicated in an independent population of African-Americans (n=79). A meta-analysis of urine drug screen results for week 17-24 was performed, since that period represents the last two months of treatment in the original trial. African-American buprenorphine patients with the C/C genotype at rs678849 had opioid positive urine samples 56.3% of the time, compared to 30.7% for patients carrying the T allele ($p < 0.0001$). Patients were also grouped as either “responders” or “non-responders” for further analysis. Responders were retained in treatment until at least week 17 and submitted <50% opioid positive urines in weeks 17-24 of treatment. Only 28.1% of African-American buprenorphine patients with the C/C genotype met responder criteria, compared to 61.5% of T allele carriers ($p = 0.0012$). Luciferase assays in BE(2)C neuroblastoma cells further suggest that the C allele of rs678849 is functioning as a silencer region, while the T allele is not. In total, these findings indicate that rs678849 is a functional pharmacogenetic locus and that genotyping of the variant may improve outcomes in African-Americans with OUD by identifying the most efficacious pharmacotherapy.