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Cytochrome P450 genotype and aggressive behavior on selective serotonin reuptake inhibitors

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We would like to thank the respondents for their interest in our work. We agree that our findings based on reporting at the pharmacovigilance center are based on a small cohort, and thus should be interpreted with caution. The purpose of our study was to demonstrate whether CYP2D6 and CYP2C19 genotypes could indeed be associated with reporting of aggressive behavior on selective serotonin reuptake inhibitors (SSRIs), as was suggested by Lucire et al. [3].

In our study, 18 patients out of 50 wanted to cooperate, yielding an overall response rate of 36%. Since the total number of cases was assembled during a 5-year surveillance, we feel this is a respectable number seeing that extreme aggression on SSRIs is not a very frequent event.

In the 18 patients, we were not able to confirm that patients who experienced and reported aggression during use of SSRIs had a significant higher incidence of variant alleles for CYP2D6 and CYP2C19 isoenzymes, predicted decreased metabolism. In fact, we did not detect a single CYP2D6 or CYP2C19 poor metabolizer (PM). Based on an incidence of 18 cases and a PM frequency of 5–10%, we would have expected 0–2 CYP2D6 PMs in case of an identical frequency between cases and controls, which is actually the null hypothesis. By contrast, our research hypothesis, considering a strong correlation between CYP2D6 predicted phenotype and risk on aggressive behavior, implies that this proportion of CYP2D6 PM should have been higher among cases and thus generating an expected number of CYP2D6 PMs >2 in this group. With an outcome of 0 CYP2D6 PMs and no significant difference in percentage PM/intermediate metabolizer (IM) between cases and controls, the hypothesis that CYP2D6 deficiency would play a role in the risk on aggressive behavior was not substantiated in our group of 18 people. We do not stretch our conclusion to the general population as the respondents claim; we merely indicate that we could not find confirmation of this hypothesis in our study group. This implies that if there is any relation between CYP2D6/CYP2C19 deficiency with aggressive behavior on SSRIs, it has a low-effect size.

Our results are undeniably based on a small number of patients that implies, as stated in your letter, a low statistical power and by such, a relatively high type II error (nonrejection of the null hypothesis when it is actually false). However, the purpose of our study was not to exclude any correlation between CYP2D6/CYP2C19 genotype and aggression, but to investigate if a suggested correlation would exist on a clinically relevant level. With a sample...
size of 117 (18 cases, 99 controls), with 80% power, and a two sided \( \alpha \) of 0.05, we are able to detect a 3- to 4-fold increase of CYP2D6 PMs in the cases (32–41%) compared with controls (5–10%).

According to the respondents, the chance of finding 0 CYP2D6 PMs in our study is 15–40%. That calculation is based on the Poisson distribution (P[no event] = \( [1-P(event)]^n \)), in which the PM percentage in the general population was used (5–10%). This is, however, in contradiction with the research hypothesis of a higher PM percentage in patients showing aggressive behavior on SSRIs. The probability of finding 0 PMs should be found on a higher percentage of PM in the cases (P[event]). Based on the aforementioned percentage of 32–41% of PM among cases, according to the Poisson distribution, the chance of finding 0 PMs in this group is 0.5918–0.6818 = 0.0075–0.097%. We acknowledge that this hypothetical proportion of 32–41% is quite substantial and is solely based on our study design. However, even if indeed the PM percentage among cases is lower than the percentage our design allowed to detect, it would still be higher than 5–10%. Consequently, the chance of finding 0 CYP2D6 PMs would still have been considerably lower than 15–40%.

The article of Lucire, which is mentioned, indeed has more subjects. However, these are mainly akathisia patients. Akathisia is known to be associated with suicide and homicide, but is not identical to aggressive behavior. When focussing only on those subjects with aggressive behavior in the article of Lucire et al., the total number of patients in their study is 10. Therefore, our study with 18 patients is still the largest study in this field. A more serious aspect is the fact that Lucire et al. take into account the CYP2C9 genotype, and weigh this as heavy as a CYP2D6 and/or CYP2C19 genotype [3]. Seeing the contribution of CYPs to metabolism of SSRIs, CYP2C9 is of very little importance and thus should not be considered at all. This, we feel, is a serious flaw in this particular study. Furthermore, although a significant increased percentage of variant allele carriers was observed among cases by Lucire et al., this is not an universally accepted method of phenotype clustering. Namely, a person with one variant allele (for example, genotype CYP2D6*1/*9) is not translated into a functionally compromised enzyme activity, and is regarded as a CYP2D6 normal metabolizer [4]. Therefore, our comparison of PM/IM with extensive metabolizer (EM)/ultra rapid metabolizer (UM) is more biologically plausible and is also universally accepted.

We thank the respondents for their suggestion to look at CYP3A4 genetic polymorphisms. Yet, since there are no dosing guidelines for SSRIs based on CYP3A4 status, together with the low frequency of CYP3A4 SNPs (5% for CYP3A4*22, the other SNPs <1%), we did not include this genotype. After publication, we did genotype for CYP3A4*22 and found only one individual to be CYP3A4*1/*22. This patient was prescribed fluvoxamine, a drug in which CYP3A4 is not involved. We therefore conclude that the CYP3A4 genotype did not play a major role in our group.

A complicating factor is whether violent behavior can be simply defined as an adverse drug reaction (ADR) of SSRIs, and indeed if it is related to the plasma concentration. Only in that case, there would be a role for CYP polymorphisms. The demonstration that aggressive behavior on SSRIs is dose dependent is, in our knowledge, lacking, making a role of CYP450 polymorphisms as contributing to this effect less likely. Aggressive behavior can have many causes and a wide range of factors may play a role, including environment, a patient’s social and medical history, comedication, interpersonal relations, genetics, neurochemistry and endocrine function, and substance abuse. Table 1 does not include comedication [2]. Unfortunately, this was not known. Indeed, phenoconversion is a potential contributor. Our paper, however, addressed the influence of genetic polymorphisms itself. Additional studies may take comedication into account, although the amount of inhibition on every enzyme and drug is also a difficult assumption. In this study no information about other possible causes or blood levels of SSRIs was available. Future confirmatory studies should include these other factors and use aggression scales to define this complex behavior in a more specialized manner.

The outcome of this study has potential impact on criminal court cases, as mentioned by the respondents. It is for this particular reason that this study is important. In court cases, the genotype of a single individual is implicated to explain aggressive behavior on SSRIs. It is especially here that studies are needed to verify to what degree this conclusion is justified, especially taking into consideration that 90% of the population will have at least one particular genetic variant when analysing six genes [5]. Based on our results on 18 cases, we do not see confirmation of the hypothesis that genotype for CYP2D6 and CYP2C19, the two most important enzymes contributing to SSRI metabolism and aggressive behavior are related. Although small, our study is scientifically valid and supported by statistical analysis.
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