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CYP2D6 genetic polymorphism and psychiatry patients' hospitalization period

A letter in response to: Ruaño G, Szarek BL, Villagra D *et al.* Length of psychiatric hospitalization is correlated with *CYP2D6* functional status in inpatients with major depressive disorder. *Biomarkers Med.* 7(3), 429–439 (2013).

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The article by Ruaño *et al.* analyzes whether *CYP2D6* has an effect on length of hospital stay (LOS) in inpatients with major depressive disorder [1]. The aim is of interest because cost–effectiveness studies must be performed for the clinical implementation of pharmacogenetics [2,3]. The reported findings showed longer hospital stays in individuals carrying *CYP2D6* alleles associated with deficient enzyme function (metabolic reserve <2) compared with metabolizers with normal or increased function (metabolic reserve ≥2; 7.8 vs 5.7 days, respectively; $p = 0.002$). The interpretation of these results is discussed below.

Point 1

A quantitative 'drug metabolic reserve index' was calculated based on each individual's *CYP2D6* genotype. In other words, a numeric value was assigned to *CYP2D6* alleles according to a 'theoretical' functional value: 0 to *CYP2D6* alleles *4, *4XN, *5, *6, *7, *8, *11, *12, *14 and *15; 0.5 to alleles *9, *10, *17 and *41; 1 to alleles *1 and *2; 1.5 and *2a; and 2 to the duplication/multiplication of alleles *1 and *2. Scores on the drug metabolic reserve index ranged from 0 to 3 in the population, and individuals were categorized into those with a score <2 ($n = 66$) and individuals with a score ≥2 ($n = 83$). The former category clustered all individuals with genotypes related to null or reduced enzyme activity, whereas the latter category comprised those with genotypes signaling normal or increased *CYP2D6* enzyme activity. However, the frequency of poor metabolizers or ultrarapid metabolizers is not clearly stated, and whether this population is different from others in the literature needs to be clarified. It seems that it is biased, showing a higher percentage of individuals carrying alleles related to deficient activity. The study of a population of psychiatric patients under pharmacological treatment might be linked to under- or over-representation of phenotypes potentially related to adverse drug reactions, lack

of efficacy or compliance [4,5]. In addition, the functional classification of *CYP2D6* activity from genotype should be discussed, since it is based on a theoretical enzyme activity value that is in turn the result of a theoretical value given to each allele. Therefore, this classification may be biased by the existence of some overlap between these theoretically defined groups. The only phenotype group that it is accurately defined by genotype is that of poor metabolizers carrying two alleles with a value of 0. However, there may be people without enzyme activity carrying copies of active genes as a result of *CYP2D6* inhibition during treatment [6]. In addition, other defined *CYP2D6* metabolism indices ('metabolic alteration' and 'allele alteration') were calculated, but were not discussed in relation to length of hospitalization.

Point 2

On the other hand, the authors partially acknowledged observational design as a main limitation of the study, including patients exposed to a variety of treatments. In spite of this type of design, several factors that were not controlled could have been analyzed. In keeping with that fact, it is reported that almost all patients were treated with antidepressants during hospitalization (98%), but that approximately 63% also received antipsychotics, and a smaller proportion anticonvulsants. Despite the fact that they stated that lack of control of the number of medications, individuals could have been classified into those under polypharmacy and those not. It appears that approximately 57% of the patients could have been under polypharmacy of antidepressants and/or antipsychotics and/or anticonvulsants during the hospitalization period. Because polypharmacy may increase the probability of adverse events, which are related to longer hospital stays, this factor should be analyzed in future studies [7]. Furthermore, future studies addressing this question should establish whether or not there are differences between patients taking

CYP2D6 substrates and those that are under treatment with other substrates, as well as the number of CYP2D6 substrates and the relevance of this metabolic path for each drug. These last aspects were calculated for the present study but were not analyzed later. This is a major point for discussion, since it is the main hypothesis of the study. LOS should be related to the *CYP2D6* genotype only in those taking CYP2D6 substrates. In addition, LOS should be related to genotype controlling for number of CYP2D6 substrates and drug dosage [7,8], since in a naturalistic study dosages should have already been empirically adjusted to the actual CYP2D6 hydroxylation capacity. Moreover, the relationship between genotypes and drug dosage could help to understand the nature of the association found with LOS [3,4].

Point 3

Besides the implication of CYP2D6 in drug metabolism, the potential relationship with psychopathology must be discussed [9,10]. It is highlighted that almost all patients (93%) were suicidal, and most had received psychotropic treatment for major depressive disorder prior to admission. Since severity of suicide, as well as suicidal attempt [11,12] and completion [13], have all been related to increased CYP2D6 enzyme activity regardless of drug treatment, this factor could have also affected present findings. Furthermore, was the history of drug treatment (lack of efficacy or intoxication prior to admission) taken into account to understand LOS? It might be expected

that poor metabolizers were hospitalized owing to drug intoxication and needed a longer stay in hospital to get back to normal.

Point 4

Other important demographic and clinical factors, such as ethnic background and comorbid psychiatric diagnoses, were very heterogeneous in the population and could also influence findings [10]. Consistently, LOS might be better explained by ethnicity [3,14].

While all these factors should be controlled in future naturalistic studies, the present study is of enormous value for the development of pharmacogenetics in clinical practice.

Disclaimer

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