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On naturalistic pharmacogenetic studies: reply from the authors

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).

We appreciate the insightful and constructive comments regarding our published work [1] linking length of psychiatric hospitalization for treatment of major depressive disorder (MDD) to *CYP2D6* gene functional status, as forwarded in letters to the editor by LLerena *et al.* [2] and Duconge *et al.* [3]. Our research approach compared the patient outcome of length of hospitalization in patients with absent or low functional status with patients with normal or high functional status, as determined by *CYP2D6* genotype status. We discovered that subnormal metabolizers had a longer hospitalization by 2 days.

The contributors of the letters praised our study for having carried the research to examine possible relationships between *CYP2D6* genotype test result and patient outcomes in a naturalistic setting. Such an approach necessarily decreases experimental control and runs the risk of having limitations. The contributors therefore rightfully identified study design issues and analytical considerations that warrant caution in generalizing the results.

Duconge *et al.* raised concern that the quasi-experimental design employed in our observational study and the ethnic diversity of the patients limits the generalizability of the results. Indeed, our design allowed patients from distinctly different ethnogeographic backgrounds or from a mixed ethnic background, and with or without a variety of other psychiatric diagnoses in addition to the diagnosis of MDD, to enter the study. Such heterogeneity may influence the length of hospitalization outcome. We acknowledge that our naturalistic study approach prevented the control of such factors and that such factors may affect the length of hospitalization. LLerena *et al.* raised concerns about possible bias in frequencies of *CYP2D6* alleles owing to the selection of patients at a single treatment center and about the confounding effects of

comedications and psychopathology, including severity of suicidal tendency. We agree with these authors, and in fact had included these limitations in the 'Perspective on clinical complexities' section in the Discussion section of the paper. In addition, the relationship raised by LLerena *et al.* between pharmacokinetic pathways and neurotransmitter levels is certainly noteworthy and will require consideration in future research.

Economic pressures to safely reduce length of hospitalization while avoiding readmission within 30 days pertain to all major psychiatric diagnoses including MDD. Our study findings suggest that *CYP2D6* genotype-guided prescribing in patients with MDD may have the potential to reduce healthcare costs.

A recently published study from Denmark demonstrated pharmacogenetic–economic relationships in patients with schizophrenia. Herbild *et al.* tested patients for variants in *CYP2D6* and *CYP2C19* and randomly assigned them to two groups [4]. One group was treated using pharmacogenetic-guided data on these genes and the other without such information. Pharmacogenetic-guided treatment consisted of informing psychiatrists about the genotype of the patients. Depending on a patient's genotype, the treating psychiatrist was recommended to follow a specific treatment approach outlined in a set of clinical guidelines. Total costs of treatment for 1 year in the PGx group (mean: US\$23,361) were 76% of those compared with the control group (mean: US\$27,350; trend; $p = 0.072$). The study also found that extreme metabolizers (poor and ultrarapid) prescribed with pharmacogenetic guidance had reduced costs of pharmaceuticals (53%) compared with nonextreme metabolizers. From our paper and this Danish study, the evidence continues to mount that pharmacogenetics matters both clinically and economically.

In summary, we are grateful for the cross-disciplinary interest evident from these authors

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and the scientific community at large, as we seek to advance personalized care for the mentally ill. We look forward to translating pharmacogenetics to the standard of care in psychiatry.

Disclaimer

This work is the opinion of the authors and does not represent the views of Future Medicine or its employees.

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