Role of CYP2D6 pharmacogenetics in the revolving door condition of patients with psychiatric ilnesses.

D. Seripa, F. Panza, M. Lozupone, E. Stella, A. Daniele, C. Gravina, M. Urbano, M. La Montagna, P. Bisceglia. G. Miscio, L. Di Mauro, A. Greco, G. Logroscino, A. Bellomo.

[1]Complex Structure of Geriatrics, Department of Medical Sciences, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG); [2]Neurodegenerative Diseases Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari "Aldo Moro"; [3]Neurodegenerative Diseases Unit, Department of Clinical Research in Neurology, University of Bari "Aldo Moro" at "Pia Fondazione Card. G. Panico", Tricase (LE); [4]Psychiatric Unit, Department of Clinical and Experimental Medicine, University of Foggia; [5]Institute of Neurology, Catholic University of Sacred Heart, Rome; [6]Laboratory of Clinical Chemistry, Department of Clinical Pathology, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo (FG).

BACKGROUND AND AIMS

Psychiatric illnesses are recurrent disorders requiring a number of medications for their treatment, mostly substrates of Cytochrome P450 (CYP) 2D6. Adverse drug reactions (ADRs) and therapeutic failures (TFs) are frequently observed in these patients, contributing to the revolving door (RD) condition, a periodical hospital readmissions increasing costs for patient management. Inter-individual differences in CYP2D6 enzymatic activity are responsible of ADRs and TFs to CYP2D6-metabolized drugs. Objective of the present study was to evaluate CYP2D6 genotypes in RD patients attending a psychiatric setting.

METHODS

A controlled-series of sixteen consecutive RD cases diagnosed according to the DSM-IV-TR criteria were enrolled in the study and investigated for CYP2D6 gene polymorphisms. The RD condition was defined for those patients having a minimum of four admissions, and 1) no admission or discharge period lasting for more than 1/4 of the observation period or 2) at least four admissions over the first 1/4 of the observation period [1]. To avoid bias in RD evaluation, i.e. any clinical or social needs that aggravate the disease or explain disease exacerbation [2] possibly miming/exacerbating the RD condition, the Camberwell Assessment of Need (CAN) rating scale [3] was administered to each patient. A CAN score < 10 is the threshold for a patient to be considered as having no significant clinical/social needs. Psychiatric symptoms evaluation was conducted using the 24-item Italian version of the Brief Psychiatric Rating Scale Expanded Version 4.0 (BPRS) [4,5]. A response to treatment was defined by a change in BPRS score ≥ 25% as evaluated at the beginning of (t_0) and at 1 week (t_1) of stable treatment (100% of medications adherence) according to the following formula: $\Delta BPRS = [(BPRSt_1 - BPRSt_0)/BPRSt_0] \times 100)$. A Δ BPRS score < 25% suggested a TF. Drug-induced extra-pyramidal symptoms were evaluated by means of the Simpson Angus Scale (SAS) [6]. An SAS score > 0.3 and/or drug-induced metabolic impairment with weight gain according to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) criteria [7] were considered as ADRs. The analysis of the sixteen CYP2D6 clinical relevant polymorphisms CYP2D6*2, CYP2D6*2A, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*9, CYP2D6*10, CYP2D6*12, CYP2D6*14, CYP2D6*17, CYP2D6*29, CYP2D6*41, CYP2D6*XN was made in blinded fashion by means of the INFINITI™ Analyzer (AutoGenomics, Inc., Carlsbad, CA, USA) using the INFINITI™ CYP4502D6-I Assay according to manufacturer instructions. All the CYP2D6 genotypes were interpreted according to the Home Page of The Human Cytochrome P450 (CYP) Allele Nomenclature Committee [8].

RESULTS

The analysis revealed three patients as extensive metabolizers (EM) (CYP2D6 genotype *1/*1), one patient as ultrarapid metabolizer (UM) (CYP2D6 genotype *2A/*1XN), and 12 patients as intermediate/poor metabolizers (IM/PM), i.e. carriers of alleles associated to a reduced enzyme activity (EA) (*2A, *4, *17, *41). Overall, 13/16 patients (≈80%) showed functional genetic variants influencing CYP2D6 EA. Response to treatment are summarized in Figure 1. Drug-CYP2D6 interactions determining the response to treatment are presented in Figure 2.

FIGURE 1

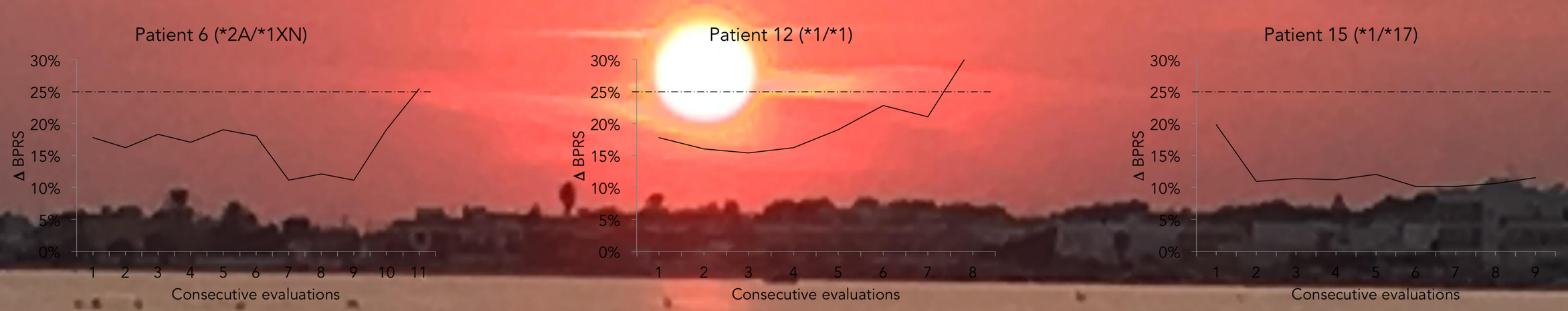
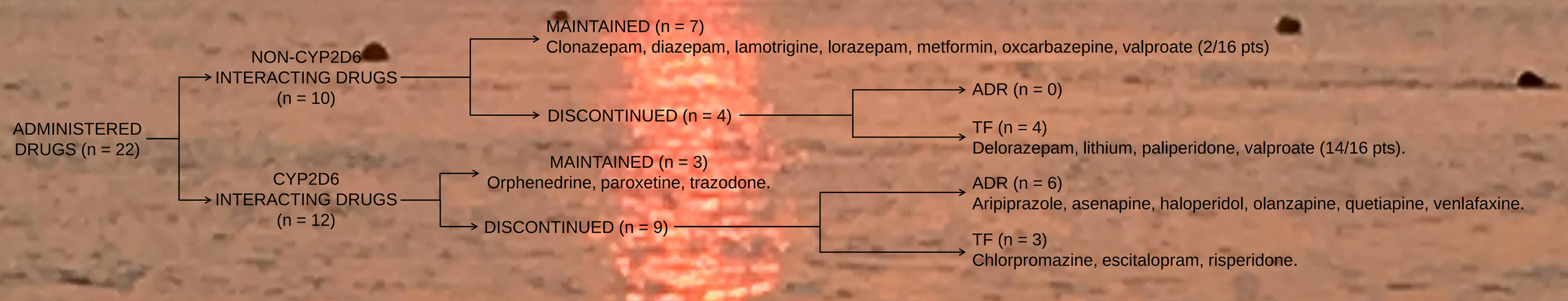


FIGURE 2



CONCLUSIONS

Excluding patients in whom the RD condition is influenced by social needs, the other patients are readmitted to the Hospital because to TFs/ADRs, both conditions resulting from defective CYP2D6 EA. Thus, CYP2D6 pharmacogenetics may influence prevalence and frequency of RD condition because to its role in the onset of TFs and ADRs. The analysis of CYP2D6 may be useful for the identification of RD patients at risk for TF/ADR that may be addressed towards alternative treatment, improving costs and patient quality of life in psychiatric settings. Further studies on the other main CYP2C9, 2C19 and CYP3A4 are needed to complete the genetic panel to be transferred in clinical practice.

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