Multiple adverse drug reactions and genetic polymorphism testing
A case report with negative result
Ana Lucía Arellano, MD\textsuperscript{a,b}, Marta Martin-Subero, MD\textsuperscript{c,d}, Mar Monerris, MD, PhD\textsuperscript{e}, Adrián Llerena, MD, PhD\textsuperscript{f}, Magí Farré, MD, PhD\textsuperscript{a,b}, Eva Montané, MD, PhD\textsuperscript{a,b,*}

Abstract
Rationale: Defects in drug metabolic pathways could explain why some patients have a history of multiple adverse drug reactions (ADR); therefore we aimed to analyze genetic polymorphisms in a patient with multiple ADR related to drugs with a common hepatic metabolic pathway through CYP2D6.

Patient concerns: We report a patient with psychosis and hypertension related to amitriptyline, tramadol, and duloxetine within a 2-year period.

Interventions and Outcomes: A pharmacogenetic test was performed to assess the causative role of the CYP2D6 enzyme, but did not demonstrate a metabolic deficiency.

Lessons: Although negative results in the reported case, typing for cytochrome P450 isoenzyme polymorphisms could be a useful diagnostic tool in some patients with a history of multiple ADR.

Abbreviations: ADR = adverse drug reactions, EM = extensive metabolizer, IM = intermediate metabolizer, MDIS = multiple drug intolerance syndrome, PM = poor metabolizer, ULM = ultrarapid metabolizer.

Keywords: adverse drug reactions, CYP2D6, drug metabolism, genetic polymorphism, multiple drug intolerance syndrome

1. Introduction
The multiple drug intolerance syndrome (MDIS) is characterized by adverse drug reactions (ADR) to more than 2 chemically unrelated drugs, with or without a known immunologic or other mechanism responsible.\textsuperscript{1,2} Its estimated prevalence varies from 2.1\% to 4.9\% of patients with any history of an ADR, and is more likely in females with anxiety and patients with other comorbidities.\textsuperscript{3,4} The management of these patients can be difficult, because reliance on medication avoidance may limit optimal first-line therapy. The pathogenic of MDIS is complex and not well understood.\textsuperscript{5} Our hypothesis is that patients with CYP450 enzyme genetic polymorphisms could present with MDIS, if drugs they used share this common metabolic pathway and the ADR are related to drug mechanism of action. To our knowledge, there is little data describing an association between the metabolic pathways of medications and clinically apparent MDIS. We describe a case of MDIS with intolerance to 4 different nervous system drugs manifested by episodes of drug-associated psychosis, hypertension, and skin eruption.

2. Case description
The patient reported here is a 56-year-old Caucasian female with only a medical history of neuropathic pain due to T2-T3 transverse myelitis in treatment with multiple analgesic drugs in the outpatient Pain Clinic. She started treatment with amitriptyline 10mg/d, and between 1 and 2 weeks later, she presented transitory episodes of visual hallucinations, and amitriptyline was switched to gabapentin (1200mg/d) ceasing the hallucinations. Almost a year later, because the pain persisted, tramadol (100mg/d) was added to the treatment. One month later, the visual hallucinations reappeared accompanied by delusional ideation, leading to a decrease in the dose of tramadol to 50mg/d. Thereafter, to control the neuropathic pain, the dose of gabapentin was increased (2200mg/d). Two months later, she developed a generalized skin rash with itching. Gabapentin was suspected to be the responsible drug; the dose was reduced to its previous of 1200mg/d. The rash progressively disappeared within 2 weeks. The hallucinations and paranoia persisted for almost a year and the patient had to take a sick leave from work. At that moment, the patient was evaluated by a psychiatrist who diagnosed a drug-induced psychotic disorder that required treatment with olanzapine, and tramadol was stopped as it was suspected to be related to the psychosis. Her pain was then controlled with gabapentin 1500mg/d and acetaminophen 1g...
TID. One month later, because of anxiety and depression, the psychiatrist prescribed duloxetine (30 mg/d). Two days later, she was admitted to the emergency room for symptomatic hypertension (blood pressure up to 166/105 mm Hg) that normalized with captopril. Duloxetine was switched to escitalopram without new ADR and afterward stopped. The psychosis disappeared after withdrawal of tramadol and temporary treatment with olanzapine. Currently, the pain is controlled with gabapentin and acetaminophen, and the hypertension with enalapril. This case was reported to the Spanish Pharmacovigilance System.

All the ADR (psychosis, hypertension, and skin eruption) fulfill the criteria of causality: a plausible time between exposure to drugs and onset of symptoms, the disappearance of these symptoms following the withdrawal of the drugs and the evidence in the literature associating the reactions to the drugs. After applying the Naranjo’s ADR probability algorithm, the score was 5 points (probable causal association) for tramadol-induced psychosis, for duloxetine-induced hypertension, and for gabapentin-induced skin rash; and the score was 4 points (possible causal association) for amitriptyline-induced psychosis (Table 1).

Neuropsychiatric effects of tramadol and amitriptyline, as well as cardiovascular effects of duloxetine could be explained by their own mechanism of action through binding to opioid receptors and/or increasing neurotransmitters such as norepinephrine (type A adverse reactions). Unfortunately plasma concentrations of drugs were not available in this patient. Because a common hepatic metabolic pathway through CYP2D6 was shared by those drugs, a poor metabolism of the CYP2D6 isoenzyme was suspected. Therefore, some of the most common alleles for CYP2D6 in Spanish population (∗2, ∗3, ∗4, ∗6, ∗10, ∗35, and ∗41) were analyzed by real-time PCR using TaqMan assays (Table 1), after the informed consent was signed by the patient. The PCR conditions were a 10-minute pre-incubation at 95°C to activate the Taq DNA polymerase, followed by 40 cycles of denaturation at 92°C for 15 seconds and then by primer annealing and extension for 1 minute at 60°C. Moreover, CYP2D6 ∗5 and CYP2D6 ∗6 multiplications were analyzed by XL-PCR as described in detail elsewhere. In addition, CYP2C9 and CYP2C19 genes were also assessed using TaqMan assays (Table 2). The amplification conditions were the same as for CYP2D6 alleles. The results of the pharmacogenetic test revealed that the patient was homozygous for all the 3 isoenzymes (wild type).

### 3. Discussion

As a result, no metabolic deficiencies for CYP2D6 were confirmed in the pharmacogenetic test. The main reason that could explain those results could be the limited assessed alleles in the pharmacogenetic test. Other reasons could be the fact that other factors influencing the pharmacokinetic of the drug, such as drug transporters, would be implicated in the occurrence of ADR. One out of every 15 persons treated with drugs at standard doses may have either no therapeutic response or an exaggerated response to the pharmacological treatment leading to an ADR. Some of this variability could be explained by CYP450 enzymes genetic polymorphisms. The different allelic variants translate into 4 major enzyme hydroxylation capacity groups: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultrarapid metabolizer (UM). About 7% to 10% of European Caucasian population is PMs, and about 5% of Spaniards are UMs. In those cases, the pharmacogenetic test can elucidate the problem related to the therapeutic response. Recently, a Pharmacogenetic Decision

### Table 1

| Characteristics of the adverse drug reactions (ADR). | Involved drug | Drug metabolic pathway | Naranjo algorithm score | ADR treatment |
|-----------------------------------------------------|---------------|------------------------|------------------------|--------------|
| Psychosis                                           | Amitriptyline | CYP2D6, CYP2C19        | 4 (possible)           | —            |
| Hypertension                                        | Duloxetine    | CYP2D6, CYP3A4         | 5 (probable)           | Olanzapine   |
| Skin eruption                                       | Gabapentin    | Not hepatic metabolism | 5 (probable)           | —            |

### Table 2

| CYP2D6, CYP2C19, and CYP2C9 alleles studied in this patient. | Allele | SNP ID | Genetic polymorphism | Enzyme activity | TaqMan SNP genotyping assay |
|-------------------------------------------------------------|--------|--------|----------------------|----------------|--------------------------|
| CYP2D6                                                      | ∗2     | rs1080885 | −1584C>G             | Normal         | C_32407252_30            |
|                                                            | ∗3     | rs35742886 | 2549delA             | Null           | C_32407232_50            |
|                                                            | ∗4     | rs1065852; rs3892097 | 100C>T, 1846G>A | Null           | C_11484460_40; C_27102431_D0 |
|                                                            | ∗5     | rs5030655 | 1707delT             | Null           | —                        |
|                                                            | ∗6     | rs1065852 | 100C>T               | Reduced        | C_32407243_20            |
|                                                            | ∗10    | rs1065852 | 100C>T               | Reduced        | C_11484460_40            |
|                                                            | ∗35    | rs1080885; | −1584C>G; 31G>A      | Normal         | C_32407252_30; C_27102444_80 |
|                                                            | ∗41    | rs769258  | 2688G>A              | Reduced        | C_27102444_80            |
|                                                            | ∗17/19  |          | —                    | Enhanced       | —                        |
| CYP2C9                                                     | ∗2     | rs1798653 | 430C>T               | Reduced        | C_25625805_10            |
|                                                            | ∗3     | rs1057910 | 1075A>C              | Very reduced   | C_27104902_10            |
|                                                            | ∗6     | rsC32287221 | 8184delA         | Null           | C_32287221_20            |
| CYP2C19                                                    | ∗2     | rs4244285 | 681G>A               | Null           | C_25986767_70            |
|                                                            | ∗4     | rs28399504 | 1A>G                | Null           | C_30634136_10            |
Algorithm designed to simplify the decision-making of clinicians about when to perform a pharmacogenetic test has been proposed, and it can be useful for selecting the right patient that could benefit from it.

The CYP2D6 is a highly polymorphic isoenzyme with >100 allelic variants and subvariants described. There are ethnic differences in allele frequencies. About 7% of white persons and 2% to 7% of black persons are PM of CYP2D6. This enzyme is known to metabolize as many as 25% of commonly prescribed drugs, such as antidepressants, antipsychotics, analgesics, cough suppressants, beta adrenergic blocking agents, antiarrhythmics, and antiemetics. PM of analgesics, cough suppressants, beta adrenergic blocking agents, enzyme is known to metabolize as many as 25% of commonly prescribed drugs, such as antidepressants, antipsychotics, and antihypertensive medications.

The patient had drug metabolizing deficiencies for CYP2D6, CYP2C19, and CYP2C9, suggesting that adverse events were drug induced.

4. Conclusion

Although pharmacogenetic testing did not demonstrate a metabolic deficiency in the reported case; we suggest that typing for cytochrome P450 isoenzyme polymorphisms could be a useful diagnostic tool in some patients with a history of multiple ADR, helping physicians to manage pain or other conditions with a better safety profile drug.

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