The role of pharmacogenetics in rediscovering old drugs

Spotlight on amitriptyline

Luana Mifsud Buhagiar[1,a], Anton Grech[2], Marilyn Casha[3], Anthony Serracino Inglott[1,a], Godfrey LaFerla[3].
[1] Department of Pharmacy, [2] Department of Psychiatry, [3] Department of Surgery
Faculty of Medicine and Surgery, University of Malta, Msida, Malta
[a] Malta Medicines Authority, Malta Life Sciences Park, San Ġwann, Malta

Department of Pharmacy

University of Malta

Email: luana.mifsud-buhagiar.06@um.edu.mt

INTRODUCTION

Tricyclic antidepressants (TCAs) are often overlooked in **clinical practice** on claims of poor tolerability, notwithstanding their potential advantages in **efficacy** and **pharmacoeconomics**. Most data available on TCAs derives from an era when genotyping studies were not available.[1] While still being used in **psychiatry**, prescribing trends of amitriptyline are increasing in the context of **pain management**. The effect of *CYP2D6* and *CYP2C19* **polymorphisms** on individual amitriptyline and metabolites exposure may predispose to **adverse events** or **treatment failure**.[2]

OBJECTIVES

The purpose of this research is to investigate whether genotyping is apt to translate biomarkers into **personalised treatment** with amitriptyline and whether harmonized labelling that allows interpretation of **pharmacogenetic data** can support in exploiting the benefit of an established, inexpensive drug.

METHODOLOGY

This exploratory research is designed to integrate **analytical**, **clinical** and **regulatory** aspects.

Analytical

HPLC determination of the **metabolite to parent drug concentration ratio** is employed to understand potential **correlations** between genetics and metabolic phenotype. Method development is underway, optimizing sample preparation and chromatographic conditions for the simultaneous analysis of amitriptyline and metabolites of interest. By directly measuring blood levels, the influence of **genetics and the environment**, such as comorbidities and comedications, can be considered together.

Testing the highly polymorphic ***CYP2D6*** and ***CYP2C19*** concurrently allows observation of potential additive effects. Comprehensive **genotyping** kits are utilised to avoid flawed conclusions in view of the large number of **polymorphisms** and the occurrence of copy number variations.

Clinical

The University Research Ethics Committee granted ethical approval to conduct the study as per the outlined **Clinical Protocol**

Regulatory

Implications of the evolving regulatory context are investigated by looking into the level of **harmonization** in pharmacogenomic guidelines and labelling reached at national, European and international level. Signals of disproportionate reporting (SDRs) tools in the EudraVigilance Data Analysis System, are exploited to evaluate the extent to which a particular adverse event is reported for individuals taking amitriptyline, and assess the potential link to metaboliser status and blood levels.

Cohort

- **Patients being prescribed amitriptyline and attending outpatient clinics at the local state hospital are contacted, if interested to learn more about the study**

↓

Ancillary appointment

- **Meeting with Independent Specialist to certify their capability to give free and informed consent**
- **Data collection via medical records and rating scales for side-effects and response**
- **Taking of buccal swab and blood sample**

↓

Experimental testing

- **gDNA extraction followed by genotyping of *CYP2D6* and *CYP2C19***
- **HPLC-determination of blood drug concentration levels**

↓

Scheduled appointment

- **Clinician provided with results and recommendations, if any, in line with gene-drug clinical practice guidelines[2]**
- **Potential treatment plan revision**

↓ *no recommendations; or recommendations not implemented; or recommendations implemented*

Follow-up

- **Monitoring of clinical outcomes**

RESULTS

For most medicinal products, genetic polymorphism consequences were noted after registration. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), in recent assessments, has supported the addition of pharmacogenetic warnings in the **Summary of Product Characteristics** (SmPC) of drugs whose metabolism is subject to genetic polymorphism. There is the duty to guide in interpreting this data so that it can **translate into patient benefit**. Proposals from this study are put forward to the Pharmacogenomics Working Party of the EMA and to international consortia dedicated to the clinical implementation of pharmacogenetics.

DISCUSSION

An intriguing lead of pharmacogenetics is whether drug potential could be maximized through **reattribution of medical purpose** for drugs in which the **balance between efficacy and toxicity** has been difficult to strike in the general population. **Redefining drug use by pharmacogenetic evaluations**, curtailing resource intensive trial-and-error regimens, is the challenge this study is seeking to address.

Acknowledgement *The research work is partially funded by the ENDEAVOUR Scholarships Scheme.*

References

1. Steimer W, Zöpf K, Amelunxen SV, Pfeiffer H, Bachofer J, Popp J, et al. Amitriptyline or not, that is the question: Pharmacogenetic testing of *CYP2D6* and *CYP2C19* identifies patients with low or high risk for side effects in amitriptyline therapy. *Clin Chem* 2005;51(2):376-85.
2. Hicks KJ, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants: 2016 Update. *Clin Pharmacol Ther* doi:10.1002/cpt.597.