Amitriptyline revisited

Pharmacogenetic implications in antidepressant treatment

Luana Mifsud Buhagiar[1,a], Anton Grech[2], 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] Medicines Authority, Malta Life Sciences Park, San Ġwann, Malta

Department of Pharmacy

University of Malta

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

INTRODUCTION

An interesting lead of pharmacogenomics 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. **Tricyclic antidepressants** (TCAs) are often overlooked in **psychiatry** on claims of poor tolerability, although cheaper with a potential efficacy advantage. Most data available on TCAs derives from an era when genotyping studies were not available.[1]

AIMS

To assess whether genotyping is apt to translate **biomarkers** into **individualised treatment** with amitriptyline and whether **harmonized labelling** that allows **interpretation of pharmacogenetic data** can support in exploiting the benefit of a relatively inexpensive antidepressant.

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 ***Clinical Protocol*** outlined.

Regulatory

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. 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. Proportional Reporting Ratio (PRR), a signal detection tool in EudraVigilance, is 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.

Patients

- **diagnosed with depression and receiving amitriptyline**
- **contacted for meeting with Independent Specialist, if interested to learn more about the study**

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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 depression and side-effects**
- **taking of buccal swab and blood sample**

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Experimental testing

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

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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

There is the need to guide in interpreting pharmacogenetic 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 the Clinical Pharmacogenetics Implementation Consortium.

CONCLUSION

Research in this field should yield significant benefits for both the patient and the economy by helping change our focus from merely trying to find the best treatment for the typical patient or opting for resource intensive trial-and-error regimens to **targeted personalised patient therapy**. Redefining drug use by pharmacogenetic evaluations is the challenge this study is seeking to address.

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