Practical implications of pharmacogenetics in antidepressant treatment

The case of amitriptyline

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Metabolism, a key player in the dose-exposure-response chain, is a focus of promising genetically-oriented investigations underpinning the usefulness of genetic testing in the pharmacokinetic field. Several pharmaceutical companies are today integrating pharmacogenetic aspects in product labels and actionable genotype-guided dosing recommendations are available. Conversely, many questions related to the implementation of personalised psychiatric therapy remain unanswered.

Is genotyping apt to determine the metaboliser status of patients receiving treatment for depression and translate biomarkers into personalised medicine *?*

Can pharmacogenetics support the re-evaluation of tricyclic antidepressants with respect to effectiveness and safety, compared to newer, more expensive drugs *?*

Should there be harmonisation at International, European and National level, in terms of what pharmacogenomic information is listed in drug labels *?*

What *makes* **PHARMACOGENETICS** *in* **PSYCHIARTY** intriguing **?**

Clinical scenario

A significant percentage of patients do not benefit from **antidepressant treatment** and those who do, may incur severe side-effects.[1]

The implicated long-term disability impacts on compliance, hospitalisations and healthcare costs. A 50-fold **inter-individual variation** in plasma levels is reported for drugs like amitriptyline[2] and since polypharmacy is common in psychiatry, **interactions** represent an additional concern.

Tricyclic antidepressants (TCAs) are often overlooked on claims of poor tolerability, although cheaper with a potential efficacy advantage. Much of the data available on TCAs derives from an era when genotyping studies were mostly unheard of. Research findings point towards a potential link between outcomes of **amitriptyline** therapy and the highly polymorphic ***CYP2D6*** and ***CYP2C19***.[3] These two genes regulate the metabolism of approximately 25% of all prescription drugs[4] implying that the result of one pharmacogenetic test is likely to be useful for a number of treatments.

Regulatory context

The **FDA**-approved **drug label** for amitriptyline states that *CYP2D6* poor metabolizers may have higher plasma concentrations of TCAs, and suggests monitoring of plasma levels if this drug is co-administrered with a *CYP2D6* inhibitor.[5] There is the duty to guide in **interpretation** of this data so as to translate into actual **patient benefit**. It is understood that at the **EU** level, simple addition of information into the label is considered impractical.

For most medicinal products, genetic polymorphism consequences were noted **after registration**. To improve efficacy, avoid serious side-effects and promote cost effectiveness, genomically guided research should ideally not neglect **currently marketed drugs** but rather be undertaken to **update the SmPC** during the life cycle of the products. Prospective studies may not always be feasible due to older drugs having been replaced as first-line therapy, the need for large sample populations, and the lacking business incentive. **Confirmatory evidence** from case control studies, observational or epidemiological studies may serve as independent verification.[6]

Analytical perspective

Genotyping data is often used to deduce **enzyme hydroxylation capacity** which may at times be misinterpreted as the **metabolic phenotype**.[7] The **ratio** between **parent drug** and relevant **metabolites** may allow better understanding of potential correlations between genetics, enzyme functionality and clinical outcomes. In the case of TCAs, it is relevant to note, for example, that **tricyclic hydroxy-metabolites**, like hydroxy-amitriptyline, are often excluded from therapeutic drug monitoring even though these are associated with cardiotoxicity.[8]

Different **DNA extraction kits** allow comparison of blood vs saliva as source of DNA while distinct **drug metabolism assays** present the strengths and weaknesses of **laboratory-based vs point-of-care** technologies.[9] *CYP2D6* is a good example where comprehensive analytics are essential to avoid flawed conclusions in view of the large number of polymorphisms to be analysed and the occurrence of copy number variations.

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Research in this field may 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. The 'ordinary' patient may, indeed, be uncommon.

OBJECTIVES

- Investigate the incidence and impact of genetic polymorphisms in patients receiving treatment for depression in Malta
- Determine allele frequencies of both *CYP2D6* and *CYP2C19* and examine potential additive effects which would support combined dosing recommendations
- Evaluate genotype-phenotype association in relation to metaboliser status, measured blood drug/metabolite concentrations and clinical outcome
- Assess feasibility and clinician perception of pharmacogenetic-guided individualisation of treatment for depression, compared to the current standard of psychiatric care
- Analyse effect of regulatory initiatives in supporting the implementation of pharmacogenomics in drug surveillance and clinical practice
- Pharmacoeconomic analysis of routine genotyping and worth of engineering point-of-care tests

STUDY DESIGN

Psychiatric outpatients receiving amitriptyline for depression • Free and informed consent • Blood, saliva and/or buccal cell samples • Depression and side-effects rating scales • Extensive genotyping and blood drug/metabolite monitoring • Results interpreted in line with gene/drug clinical practice guidelines • Potential recommendations, if any, for treatment plan revision • Clinical outcomes observed on patient follow-up •

Retrospective Analysis

Past hospitalisations related to depression or adverse events from its treatment and the antidepressant switching strategies adopted.

Standard of Care

Drugs with pharmacogenetic recommendations being prescribed at one time and the dose differences with respect to metaboliser status.
Are non-extensive metabolizers being prescribed regular doses or are physicians empirically identifying patients with aberrant metabolism?

Prospective Correlations

The total range of variables encountered is included in the statistical analysis, combining both genetics and environmental factors such as age and age of onset, lifestyle, comorbidities, and comedications with special focus on concomitant CYP inhibitors, in attempt of explaining an appreciable percentage of variation.

Further Observations

Comparison of genotyping techniques, clinician disposition in implementing pharmacogenetic-guided recommendations, and the implications of the evolving regulatory context, particularly referral procedures assessed by the European Medicines Agency and review of pharmacogenomic data in national authorisations.

References

1. Porcelli S, Drago A, Fabbri C, Gibiino S, Calati R, Serretti A. Pharmacogenetics of antidepressant response. *J Psychiatry Neurosci* 2011;36(2):87-113.
2. Schenk PW, Van Fessem MAC, Verploegh-Van Rij S, Mathot RAA, Van Gelder T, Vulto AG, et al. Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of depressed patients. *Mol Psychiatry* 2008;13:597-605.
3. 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.
4. Jain KK. Applications of AmpliChip CYP450. *Mol Diagn* 2005;9(3):119-27.
5. Sandoz Inc. (2016). Amitriptyline hydrochloride [drug label]. Princeton, NJ: Sandoz Inc.
6. European Medicines Agency scientific guidelines on pharmacogenomics. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&mid.
7. LLerena A, Peñas-Lledó EM. Metabolic phenotype prediction from genotyping data: a bottleneck for the implementation of pharmacogenetics in drug development and clinical practice. *Drug Metab Pers Ther* 2015;30(3):143-5.
8. 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* 2016 Accepted Author Manuscript. doi:10.1002/cpt.597.
9. Wirth F, Zahra G, Xuereb RG, Barbara C, Fenech A, Azzopardi LM. Comparison of a rapid point-of-care and two laboratory-based *CYP2C19*2* genotyping assays for personalisation of antiplatelet therapy. *Int J Clin Pharm* 2016:38(2):414-20.