



editorial

Psychiatric Bulletin (2009), **33**, 361–363. doi: 10.1192/pb.bp.108.019497

RENATO D. ALARCÓN

Pharmacogenomic perspectives on the management of mood disorders

SUMMARY

Psychiatric pharmacogenomics is a relatively young field of clinical practice, focused on the identification of genetic profiles determining varieties of metabolic patterns that, in turn, assist in the choice of appropriate medications and their corresponding doses. In psychiatry, the mood disorders area has been the most active in trying to

advance knowledge and expertise in pharmacogenomics. The cytochrome P450 system (particularly 2D6 and 2C19 enzymes and their respective codifying genes) and, more recently, serotonin transporter and receptor gene tests are among the most utilised and promising. In spite of encouraging findings, however, there are still many questions related to preciseness,

scope, ethnic variations, diagnostic implications, 'non-biological' factors, and ethic considerations. The need of algorithms, follow-up studies, and assessment of financial impact, all listed here, require continuous and systematic research. It will not only add to the excitement of pharmacogenomics, but also to the creation of cogent evidence of its benefits.

Pharmacogenetics and pharmacogenomics

The extraordinary advances in neurobiological research throughout the past three or four decades reflect, primarily, the growth of basic sciences such as genetics and its impact on fields as different as biochemistry, neuroimaging or diagnosis. From the very complex tree of human genetics, rooted in the delineation of the human genome,^{1,2} branches such as pharmacogenetics focused on the role of inheritance in the individual variations of response to xenobiotics, and pharmacogenomics or the study of idiosyncratic responses to pharmacological compounds or drug/body interactions of hereditary basis. Pharmacogenomics evaluates drug absorption, distribution and excretion, kinetic and dynamic processes of proven clinical utility. The developments in both areas offer invaluable promises, as well as significant challenges to the eventual improvement of the clinical treatment of all patients.

Psychiatric pharmacogenomics

Psychiatric pharmacogenomics is probably the youngest and also one of the most exciting subfields unfolding in the past decade. Its main appeal is the possibility of reaching a truly 'individualised' or 'personalised' pharmacological treatment, based on the identification of a genotype or genetic profile that, by outlining the metabolic process of individual compounds through specific enzymes, codified by specific genes, would determine the choice of the most specific kind, and most

appropriate dose of medications for the diagnosed condition.³ Prediction (and, therefore, prevention) of secondary effects is not a small added benefit. And it so happens that the clinical area where psychopharmacogenomics has had its most active and fertile grounds is that of mood disorders, particularly depression and all its clinical variations.⁴

Genotype testing

That genetic variations in drug metabolising enzymes are an important factor in the differential response to medications by individuals and groups of patients, is a well-known fact in clinical practice. Several medical specialties, particularly oncology, have well-established rules of use of pharmacogenomic tests for the prescription of various medications. The cytochrome P450 (CYP) system, particularly the 2D6 enzyme and its respective gene, became the first 'biological marker' in this process by the end of the past decade.^{5,6} Other enzymes in the same system (2C19 and 2C9) have been identified as, together, metabolising a vast majority of psychotropic medications, particularly antidepressants, from the old tricyclics to the newest selective serotonin reuptake inhibitors (SSRIs). Testing the 'target genes', their number and types of copies or alleles, results in the determination of poor or slow, intermediate, normal (or extensive) and rapid/ultrarapid metaboliser patterns (pharmacokinetic phenotypes) for individual patients.^{7,8} The US Food and Drug Administration has approved 2D6 and 2C19



editorial

genotype testing, opening the door for pharmacotherapy decisions that will, doubtlessly, improve clinical outcomes.

More recently, serotonin transporter and receptor gene tests have been implemented, thus broadening the scope of pharmacogenomic applications. The short (s) and long (l) alleles of the serotonin transporter gene (*5-HTTR*) have different physiological consequences: the former is seemingly associated with poor response to some antidepressants and drug-triggered manic symptoms in individuals with bipolar disorder; the latter with a more favourable response to antidepressants and to lithium. In turn, the serotonin-2A receptor gene seems to also be associated with greater binding potential and better response to citalopram.⁹ Still in the pipeline of new genes under study are tests for glutamate, glucocorticoid, and interleukin receptors with potential predictive value for clinical response, tolerance, and ethnic variations.¹⁰

This brief review only touches the surface of a set of findings in a field that is flourishing at a frenetic pace. Its cultivators already speak of the 'pharmacogenomic revolution' and its sequel of 'true individualised treatment, true personalised medicine', pharmacotherapy based on a rational and scientifically based dictum. The picture is at times dazzling indeed, yet the claims sound reasonable and reachable despite their loudness. On the other hand, an equally reasonable question is whether the field is open, clean, objection-free, sound and totally predictable. The answer, at this point, may be a cautious 'No, not yet'. Some of the reasons (grouped in four areas) follow.

Laboratory studies

- Pharmacogenomic testing is not as precise as a mathematical formula. Clinicians using it on a more or less regular basis have observed divergent clinical responses to doses chosen on the basis of similar P450 or serotonin gene findings. The possible explanation is that metabolic processes and their outcomes are not only determined by genetic profiles or enzyme endowments; factors such as age, gender, diet, endocrine status, physical health and level of stress, play a complementary but decisive role.¹¹
- There are more enzymes (and their corresponding genes) than the number identified so far, besides the large number of polymorphisms (many of them still unidentified).¹² On the positive side, the so-called genome-wide associations currently allow the testing of more than 300 single-nucleotide polymorphisms per patient. Greater numbers from larger samples may detect more common susceptibility variants for psychiatric disorders and pharmacological responses.¹³
- Some substrates can also operate as inhibitors of their metabolising enzymes; such competitive inhibition may depend on factors such as affinity, dose, or others similar to those mentioned above. Yet, in cases, the substrates may be 'non-competitive inhibitors'.¹⁴

Clinical studies

- Follow-up studies are still scarce, samples may not be numerous as yet, even though individual reports

abound and are a growing set. Comparisons with placebo users need to be made.

- There are already known ethnic differences in genetic profiles: African and African-American populations as a group may have higher proportions of slow CYP2D6 metabolisers than White people; similarly, poor metabolisers predominate among Caribbean Hispanics when compared with Mexican Americans, both being subgroups of the Hispanic or Latino ethnic class.¹¹
- The diagnostic implications of pharmacogenomic approaches to treatment are still to be examined, for instance, negative links with level of stress,¹² and the impact of linkage disequilibrium.¹⁵ Pharmacogenomics adds a new dimension to the conventional characterisation of clinical entities, particularly those of the mood or bipolar spectra.¹⁶

Financial considerations

- The pharmaceutical industry's response to pharmacogenomic testing in psychiatry has been ambiguous at best; some minimise the usefulness of this type of information for fear that the market for their products will be segmented or reduced.
- The medical economic benefits of testing are still being debated. Nevertheless, in the USA, insurance companies seem to be willing to cover the testing in cases of repeated failures to traditional pharmacological management, or in the presence of severe side-effects with seemingly low doses of antidepressants.

Other factors

'Non-biological factors' such as expectations, adherence, placebo response, and clinician-patient relationship, some or all of them being culturally determined factors, continue to play an important role in shaping the strictly pharmacological response.^{15,16} Ethical considerations, crucial and strong in any genetics-based procedure or intervention, ought to be refined.¹⁷ Issues such as full disclosure, confidentiality, research use, and the implications of testing *vis-à-vis* insurance coverage, respect for human dignity, documentation, and overall clinical management in extreme cases (i.e. deleted or inactive polymorphisms) need to be clarified.

Conclusions

Despite these reservations, very few doubt that psychiatric pharmacogenomics is here to stay. The public health significance of mood disorders in general and depression in particular demands testing and other procedures aimed at optimising a rational, truly individualised management. Support of clinical research in this field will come if for no other reasons than pressures from a better informed public, and increased information and knowledge on the side of mental health and other health professionals. There is already work in progress on the elaboration of more precise algorithms and dose adjustments.^{18,19}



Clinical indications will move from the current focus on slow and ultrarapid metabolisers to a more universal application of the tests to everybody, particularly patients with first episodes of depression. The creation of large data banks, family studies, adequate follow-up, and preventive interventions will assist in providing cogent, research-based evidence. These are, indeed, exciting times.

Declaration of interest

None.

References

- Charney DS, Nestler EJ. *Neurobiology of Mental Illness* (3rd ed). Oxford University Press, 2009.
- LaPorte JL, Ren-Patterson RF, Murphy DL, Kalueff AV. Refining psychiatric genetics: from 'mouse psychiatry' to understanding complex human disorders. *Behav Pharmacol* 2008; **19**: 377–84.
- Mrazek DA. Current application of clinical genetic testing for psychiatric practice. *Minn Med* 2007; **90**: 42–3.
- Bertilsson L, Dahl ML, Tybring G. Pharmacogenetics of antidepressants: clinical aspects. *Acta Psychiatr Scand* 1997; **391** (suppl): 14–21.
- Weinshilboum R. Inheritance and drug response. *New Engl J Med* 2003; **348**: 529–37.
- Ingelman-Sundberg M. Human drug metabolizing cytochrome P450 enzymes: properties and polymorphisms. *Arch Psycho-pharmacol* 2004; **369**: 89–104.
- Black JL, O'Kane DJ, Mrazek DA. The impact of CYP allelic variations on antidepressant metabolism: a review. *Expert Opin Drug Metab Toxicol* 2007; **3**: 21–3.
- Kirchheiner J, Bauer S, Menoke I, Rohde W, Prang V, Meisel C, et al. CYP 2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand* 2001; **104**: 173–92.
- McMahon SJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genetics* 2006; **78**: 804–14.
- Serretti A, Kato M, Kennedy JL. Pharmacogenetic studies in depression: a proposal for methodological guidelines. *Pharmacogenomics J* 2008; **8**: 90–100.
- Smith M. Ethnopsychopharmacology. In *Cultural Psychiatry for Clinicians: A Handbook for Working with Diverse Patients* (ed R Lim): 271–98. American Psychiatric Press, 2006.
- Mandelli M, Marino E, Pirovano A, Calati R, Zanardi R, Colombo C, et al. Interaction between SERTPR and stressful life events on response to antidepressant treatment. *Eur Neuropsychopharmacol* 2009; **19**: 64–7.
- Psychiatric GWAS Consortium Coordinating Committee. Genomewide association studies: history, rationale and prospects for psychiatric disorders. *Am J Psychiatry* 2009; **166**: 540–56.
- Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP 2D6): clinical consequences, evolutionary aspects, and functional diversity. *Pharmacogenomics J* 2005; **5**: 6–13.
- Kato M, Zanardi R, Rossini D, De Ronchi D, Okugawa G, Takekita Y, et al. 5HT2A gene variants influence specific and different aspects of antidepressant response in Japanese and Italian mood disorder patients. *Psychiat Res* 2009; **117**: 97–105.
- Alarcón RD, Mrazek DA. Farmacogenómica osiquiátrica: actualización y perspectivas. In *Genética y Farmacogenómica en Psiquiatría* (ed H Silva): 59–79. C&C Ediciones SONEPSYN, 2007.
- Novoa F. Desafíos éticos en la investigación y aplicación clínica de la genética. In *Genética y Farmacogenómica en Psiquiatría* (ed H Silva): 121–37. C&C Ediciones SONEPSYN, 2007.
- Kirchheiner J, Seeringer A. Clinical implications of pharmacogenetics of cytochrome P450 drug metabolizing enzymes. *Biochem Biophys Acta* 2007; **1770**: 489–494.
- Kung S, Winner JG, Alarcón RD, Shinozaki G, Frye M, Mrazek DA, et al. Patients' and clinicians' satisfaction with pharmacogenomic testing for depressed inpatients at the Mayo Clinic Mood Disorders Unit. Poster Presentation, Annual Meeting, American Psychiatric Association, San Francisco, California, 16–21 May 2009.

Renato D. Alarcón Professor of Psychiatry, Mayo Clinic, College of Medicine. Medical Director, Mood Disorders Unit, Mayo Psychiatry and Psychology Treatment Center, Rochester, Minnesota 55905, USA, email: alarcon.renato@mayo.edu