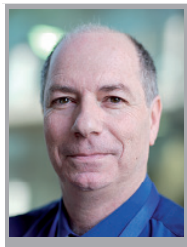
Pharmacogenetics education: 10 years of experience at Tel Aviv University

Lack of knowledge among clinicians regarding pharmacogenetics is often cited as one of the barriers delaying its clinical uptake, albeit there are many other, more crucial aspects that impede the implementation of pharmacogenetics into routine medical practice. Pharmacogenetics has been incorporated to the MD teaching curriculum at the Tel Aviv University Faculty of Medicine (Tel Aviv, Israel) since 2001 and offered as an elective class for graduate students since 2003. I share here my pharmacogenetics teaching experience over the past decade and look forward to 2020 when – hopefully – the use of pharmacogenetics tools will have become more established in routine clinical care.

KEYWORDS: continued medical education ▪ education ▪ pharmacogenetics ▪ pharmacogenomics



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Pharmacogenetics has a promising potential for improving drug safety and efficacy in many medical disciplines [1–4]. However, despite recent advances in our knowledge of human genetic variation and its relation to drug response, only a handful of pharmacogenetics tests are currently in use in the clinical setting. Many barriers to implementing pharmacogenetics in the clinic have been cited, above all, lack of knowledge regarding genotype–drug response phenotype correlations. Other often-cited barriers include scarcity of trials proving the utility and cost–effectiveness of its use; lack of earmarked funding; intellectual property rights issues; unclear regulatory framework; lack of enthusiasm of the private sector to develop pharmacogenetics tests for generic drugs; and lack of knowledge of healthcare professionals [5–9]. In this long and discouraging list, the last item may seem relatively minor. Nonetheless, without pharmacogenetics knowledge among clinicians – which ideally needs to be gained during their basic medical training, but can also be acquired through continued medical education training – they will be less likely to embrace pharmacogenetics tools even once such tools have become commercially available, validated in clinical trials, and made more affordable compared with current costs for pharmacogenetics tests. Indeed, in a recent survey of UK and Irish laboratories, lack of knowledge by clinicians was cited by the majority of responders as being among the key reasons for delayed uptake of pharmacogenetics testing [10].

It would be a pity if the scientific knowledge and proof of utility is made available for the use of certain pharmacogenetics-based diagnostics while their uptake is being impeded by lack of awareness and poor understanding of the principles of pharmacogenetics by healthcare professionals. There seems to be a consensus among clinical pharmacology educators that pharmacogenetics should be included in current MD training [10–16].

How it started: 2000

Having realized this need and potential 10 years ago, in 2000 I approached my colleague, Professor Moshe Rehavi, at that time the Chair of the Department of Physiology and Pharmacology at our Faculty of Medicine at Tel Aviv University (Tel Aviv, Israel) with a proposal to add pharmacogenetics to the pharmacology teaching curriculum of our MD students. Thanks to his support, this topic was incorporated into the second year pharmacology class curriculum of our MD students, starting in 2001. A slot of 4 h was allocated for teaching pharmacogenetics as part of this class toward the end of the second year, when the students are already familiar with basic principles of pharmacokinetics and pharmacodynamics, and have meanwhile completed their basic training in human genetics. Pharmacogenetics is included in the pharmacology final exam. By taking this move, our school of medicine has become one of the first to have incorporated this topic to their basic MD teaching curricula. In

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the subsequent year the education committee of our faculty approved an elective semester-long graduate class in pharmacogenetics, which I have been teaching since 2003.

Current update: 2010

A total of 10 years have passed in which our MD students at Tel Aviv received pharmacogenetics education as part of their second year pharmacology class. Students of the first few classes who received this training are already working as qualified clinicians. Meanwhile, the semester-long pharmacogenetics graduate class (30 h) has been popular with our students, with an average of 35 to 45 registered graduate students taking this elective class, which is given every second year and includes students' seminars on pharmacogenetics-related topics chosen from recently published studies [11]. Last year this graduate class included an international summer school at Tel Aviv University (see **Box 1**).

The task of teaching pharmacogenetics is demanding: in contrast to fields such as human anatomy or physiology, the knowledge of pharmacogenetics is rapidly evolving, thus topics discussed in class need to be updated each year. Thankfully, there have been many supportive colleagues who have helped with teaching materials and feedback (see acknowledgments). There is also a growing number of valuable online resources for pharmacogenetics teaching (**Box 1**).

Obviously the 4 h that were allocated to pharmacogenetics teaching for our MD students do not allow sufficient time for covering the field in depth, unlike the graduate class. Therefore, the first 2 h are devoted to presenting the students with a general introduction to the scope of human genetic variation and issues of variations in drug safety and efficacy among individual patients, while the latter 2 h are focused on specific examples.

The introductory section of the MD pharmacogenetics class includes background and facts on adverse drug reactions (ADRs), poor drug efficacy, and their relation to human genetic variation. The students are informed of the frequent relationship between ADRs and atypical drug pharmacokinetics, including those related to genetic polymorphism in drug-metabolizing enzymes, while making the point that most ADRs cannot be explained by genetics alone. The pioneering studies from the UK [17] and the US [18] on the high prevalence of ADRs as a primary reason for hospital admissions (being responsible for nearly 7% of all admissions) are presented. The class continues with general background on the large scope of common polymorphic alleles in humans. For example, students are informed that only approximately 3 million common SNPs were assumed back in 2003, when the Human Genome Project was concluded, while now over 11 million common SNPs have been recorded, with millions more less common SNPs and other polymorphic alleles, such as copy number variations, insertions and deletions, present in the human population, which may contribute to drug-response phenotypes.

The second half of the pharmacogenetics class for MD students (given on a separate day) continues with specific examples focused primarily on the genetic variation of cytochrome P450 (CYP) enzymes. The first examples are focused on prodrugs, such as codeine intoxication (owing to high morphine levels) in CYP2D6 ultra-rapid metabolizers; lack of tamoxifen efficacy in breast cancer patients who are CYP2D6 poor metabolizers; and lack of clopidogrel efficacy in cardiovascular disease patients who are CYP2C19 poor metabolizers. Examples of prodrugs seem to be most illustrative for introducing the topic of the genetic effects on drug response phenotype. Variations in drug response between members of different ethnic groups are also discussed, highlighting the very different frequencies of poor CYP2D6 metabolizers and poor CYP2C19 metabolizers among Europeans and Asians. Next, the students are given examples of polymorphic genes coding for second-phase drug-metabolizing enzymes, including azathioprine and TPMT; 5-fluorouracil and dihydropyrimidine dehydrogenase; irinotecan and *UGT1A1*28*. Further examples include warfarin and the *CYP2C9* and *VKORC1* polymorphisms; abacavir and *HLA-B*5701*; and omeprazole and *CYP2C19*. Over the years the examples are constantly updated. Thus, the relevance of *CYP2D6* genotyping for tamoxifen efficacy was introduced in 2007 while that of *CYP2C19* for clopidogrel efficacy was added in 2009.

A 2008 survey has found that most medical schools in the UK already include pharmacogenetics among the topics taught to MD students [19]. The survey found that, typically, between 2–8 h of pharmacogenetics teaching were included in the pharmacology curricula of UK medical schools. Attempts to survey medical schools on a global scale have failed owing to poor feedback [Newman W, University of Manchester, UK, Pers. Comm.].

Outlook for 2020

As knowledge regarding correlations of polymorphic genotypes and epigenetic markers with drug-response phenotype keeps expanding,

pharmacogenetics will definitely become part of the basic, as well as postgraduate medical training in an increasing number of medical disciplines. The examples used in teaching will focus primarily on those tests that make it to the marketplace. Hopefully, it will not be decades away until we see pharmacogenetics practiced in most large hospitals and clinics [20]. Teaching pharmacogenetics to healthcare professionals alone will not overcome the tough barriers facing its clinical uptake – but without such education the vision of personalized medicine shall not be realized.

Box 1. Online pharmacogenetics teaching resources.

- The Pharmacogenomics Knowledge Base
  www.pharmgkb.org
- Pharmacogenetics Research Network – Educational Materials
  www.nigms.nih.gov/Initiatives/PGRN/Education.htm
- NHS National Genetics Education and Development Centre
  www.geneticseducation.nhs.uk/teaching-genetics/pharmacogenetics.aspx
- American College of Clinical Pharmacology – online pharmacogenomics course
  http://user.accp1.org/index_new.html
- Pharmacogenetics for Every Nation Initiative (PGENI) education resources
  http://pgeni.unc.edu/resources/resources3.php
- Roche's education programme
  www.roche.com/research_and_development/r_d_overview/education.htm
- Minerva School on Pharmacogenetics: Improving the safety and efficacy of medicines
  www.tau.ac.il/medicine/minerva/
- Numerous lectures on pharmacogenetics are available on www.youtube.com

Acknowledgements

I am indebted to my teacher and colleague Professor Moshe Rehavi from our Faculty of Medicine at Tel Aviv University for his devoted support of my 2000 initiative to add the topic of pharmacogenetics to our school's MD teaching curriculum. I am grateful to many friends and colleagues whose help and support over the past decade have been instrumental for sustaining this goal (listed alphabetically): Russ Altman, Karen Avraham, Cathy Giacomini, David Goldstein, Dolores Ibarreta, Julie Johnson, Julia Kirchheiner, Klaus Lindpaintner, Gregory Livshits, Jeantine Lunshof, Howard McLeod, Arno Motulsky, William Newman, Katherine Payne and Munir Pirmohamed, and to numerous additional colleagues who have kindly provided teaching materials, suggestions and feedback over the 10 years since having embarked on this journey.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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