Editorial comment

How to dose a psychotropic drug: beyond therapeutic drug monitoring to genotyping the patient

An editorial comment to Davies S et al. “Characterization of zuclopenthixol metabolism in vitro and therapeutic monitoring studies” (1)

The study of Davies et al. (1) published in this issue of the Acta Psychiatrica Scandinavica characterizes the drug metabolism pathways for a first-generation antipsychotic zuclopenthixol that is still in widespread use in many countries, both because it is relatively inexpensive and because it is available in a long-acting depot injection. Davies et al. (1) show that zuclopenthixol is inactivated essentially completely by only two enzymes, CYP 2D6 and CYP 3A4, that can be profoundly influenced by drugs and by inheritance. The impact of this finding will be to cause revisions in the dosing and drug interaction recommendations for this agent in future prescribing guidelines and books including those of this editorialist (2). The report of Davies et al. (1) may even encourage others to look more carefully at the neglected drug metabolism pathways for older psychotropic drugs, particularly those in continued use today. First-generation antipsychotics were all developed prior to the careful characterization of cytochrome P 450 (CYP) drug metabolizing enzymes and their genes. The result is that clinicians have often been ‘flying blind’ to the impact that drug interactions or hereditary variations in drug metabolism could have on dosing of many first-generation antipsychotics. Although the newer second-generation ‘atypical’ antipsychotics are much better characterized in terms of their drug interactions (3), many older psychotropic agents still suffer from incomplete information about how they are metabolized, and thus how to dose them, particularly in patients receiving concomitant medications, who have unusually severe side effects, or who do not respond to standard doses.

Is it enough to characterize the metabolism of the drug?

Characterizing the drug is only half of the story for finding the dose of a psychotropic drug. The missing half of the story is to characterize the patient. That is, dosing guidelines for new and old drugs alike are usually formulated on the basis of characterizing a drug’s metabolism combined with the results of randomized clinical trials. However, this is no longer adequate. The standard of care in psychopharmacology increasingly demands that not only should the drug’s metabolism be characterized but so should the genotypes and the phenotypes of the patient. This is especially true for patients in whom standard doses are not tolerated or are not effective, or who receive concomitant medications. Antipsychotics in fact may be a special example of this need to characterize the genotype of the patient because doses of antipsychotics suggested by clinical trials generally fail to predict the doses used in clinical practice (4–6). In the absence of rational information about how to dose patients when they do not respond as expected to a psychotropic drug, clinicians have had to rely on empiric results from clinical use (4–6). Now that it is possible both to genotype patients’ CYP 450 metabolic enzymes and to phenotype their actual metabolic pattern by therapeutic drug monitoring, there may be additional tools to help patients who are either excluded from clinical trials or are outliers in clinical practice: namely, those who are apparently treatment resistant or treatment intolerant.

Is genotyping ready for prime time in psychiatry?

Several CYP 450 genotypes can be now tested by various commercial laboratories, especially 2D6, 2C9, and 2C19 (7). These genotypes can partially predict those patients who will require low doses or high doses of certain psychotropic agents by indicating whether a patient is a poor metabolizer or an extensive metabolizer of those agents respectively. However, only therapeutic drug monitoring of the actual concentrations of the drug itself can
fully characterize a patient’s phenotype and explain unexpected side effects at standard doses (and thus the need to administer low doses), or the unexpected lack of side effects and lack of efficacy at standard doses (and thus the need to administer high doses), because of genotype, drug interactions, or to detect problems with drug absorption or noncompliance. However, neither genotyping nor therapeutic drug monitoring are extensively employed in psychiatry. Is it time to do this for patients who fail to respond or fail to tolerate a psychotropic drug? Is it even time to do this for all patients about to be treated with any psychotropic drug? How about testing for the various proposed genotypes that may predict who will respond to a given psychotropic drug (7, 8)? Or are all of these just expensive research tools not understood well enough and therefore not valuable enough to enter the standard of care of clinical practice in psychiatry?

The way forward

Just as it is no longer acceptable to use drugs in clinical practice whose metabolic patterns are unknown, so is it now unacceptable to use drugs in patients whose genotypes and phenotypes are unknown, especially for those who do not tolerate or do not respond to a drug as expected. Such patients are often the most expensive and time-consuming problems in a psychiatrist’s practice and having additional information while following the exploding literature on how to apply new genotyping tests in clinical practice should already be the standard of care for such patients. However, much is yet to be learned and there are potential misinformation perils with early adaptation of tests in clinical practice. It can be slippery if rewarding on the cutting edge of translation of new science into clinical practice, but the time for thoughtful genotyping of complex patients is now.

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References