*mibefradil* was found to inhibit CYP3A4, and CYP2D6, resulting in increases of the concomittantly used other drugs to dangerous levels. When first marketed, the package label warned against concurrent use with astemizole, cisapride, and terfenadine. After a few months, statins (lovastatin, simvastatin) were added to this list of drugs that must not be coadministered with mibefradil (42).

## d. Naturally Occurring Genetic Variations That Influence Drug–Drug Interactions

Genetic variations that influence drug–drug interactions exist naturally in the human population. The most frequent source of concern is variation in the expression and activity of isozymes of cytochrome P450 and, in particular, the isozymes that are:

- CYP2D6;
- CYP2C19;
- CYP2C9.

CYP2D6 is responsible for catabolizing about 25% of drugs that are antidepressants, antiarrhythmias, and tamoxifen (43). To provide an example of people with CYP2D6 variants that are expressed at abnormally low levels, Schultz discloses that, "Caucasians are more likely than people of Asian and African ancestry to have abnormally low levels of ... CYP2D6" (44). A danger arising from the variability of expression in one or more of the cytochrome P450 isozymes is that some patients will exhibit, as a consequence, unexpected drug–drug interactions that have an adverse influence on efficacy or safety of either drug.

## e. Drug–Drug Interactions Involving Fluoxetine and Atomoxetine

The following illustrates the situation where a patient is given *fluoxetine* and *atomoxetine*. Each of these drugs may be used alone, or in combination with each other, for treating depression (45). Fluoxetine (Prozac®) inhibits CYP2D6. When administered, fluoxetine's inhibition of CYP2D6 provokes increases in concentrations of various drugs that would otherwise have been oxidized by CYP2D6. These oxidized drugs include atomoxetine (Strattera®). But for people who naturally fail to express CYP2D6, administered fluoxetine cannot inhibit CYP2D6 (because there does not exist any CYP2D6), and as a consequence any administered fluoxetine will not influence the levels of atomexetine (46).

## f. Atomoxetine's Package Insert Warns That Fluoxetine Increases Levels of Atomexetine in the Body

The package insert for atomoxetine warns that fluoxetine will increase amoxetine levels

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[43]Samer CF, et al. Applications of CYP450 testing in the clinical setting. Mol. Diagn. Ther. 2013;17:165–84.

[44]Schultz J. FDA Guidelines on race and ethnicity: obstacle or remedy? J. Natl. Cancer Inst. 2003;95:425–6.

[45]Kratochvil CD, et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety syndromes. J. Am. Acad. Child Adolesc. Psychiatry. 2005;44:915–24.

[46]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Drug interaction studies—study design, data analysis, implications for dosing, and labeling recommendations; February 2012 (75 pp.).